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EDITORIAL

Osteoarthritis, an old wine in a new bottle!

Sathish Muthu

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Abstract

Osteoarthritis (OA) is the most common form of arthritis that has a major impact on patient morbidity and health care services. Despite its prevalence and impact, we do not have any effective management strategy to prevent or control their manifestations. Several decades of pharmacological development have failed to deliver a disease-modifying solution to OA. This editorial article outlines the lacunae in the research efforts of the past, the challenges that we are facing at present, and the exciting opportunities we have in the future for the management of OA. OA research has to be made more personalized concerning the phenotypic and endotypic disease variants. To begin with, robust disease classification criteria need to be defined for early OA, and biomarkers to detect such early diseases to aid in patient stratification. We also need to refine our clinical research design to make them more objective to meet the demands of the patient and the regulatory agencies. Embracing the current technologies such as artificial intelligence along with the use of genomic profiling from the omics platforms, the future of OA is more promising in developing appropriate management of OA.

Key Words: Osteoarthritis; Management; Phenotypes; Endotypes; Theratypes

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Core Tip: We analyzed the current landscape of management of osteoarthritis (OA) and identified the challenges we are facing to develop an effective management strategy for OA at present and commented on the exciting opportunities available in the future. We also detailed the patient stratification based on the phonotypic and endotypic disease variants. We suggest that by embracing the current technologies such as artificial intelligence, and genomic profiling of patients, personalized management of OA is amenable with predictable results tailored for individual patient needs.

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INTRODUCTION

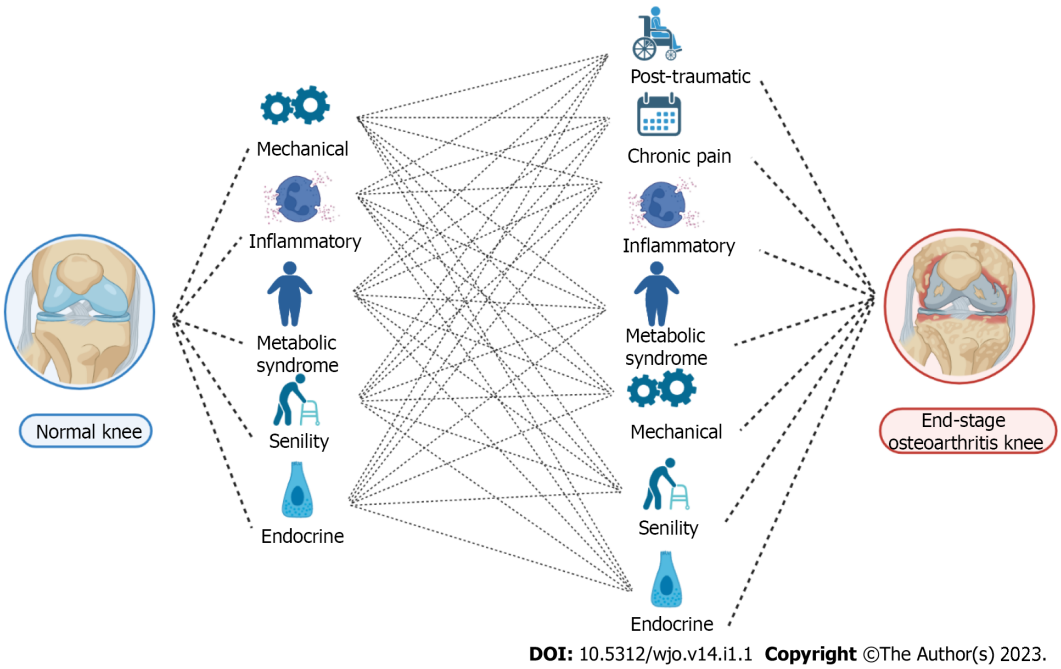
Osteoarthritis (OA) remains the most common form of arthritis causing a huge burden on the health care system[1]. The prevalence of the disease keeps on increasing due to the aging population compounded by the increasing obesity epidemic. But we do not find comparable progress in disease control and its management options[2]. Over the past 3 decades, all the pharmacological ventures to develop a disease-modifying OA drug (DMOADS) have resulted in disappointing results making OA a "graveyard of drug development"[3]. Any drug that is being developed for OA cannot impact the structure of the joint as seen by radiographs and this has been the key reason for failure in the past decades of drug development for OA[4]. The clear expectations of the regulatory agencies such as the United States Food and Drug Administration for any DMOADs involve establishing the impact of the drugs on the subjective patient feeling, improvement in their function, and prolonged joint survival following the treatment[5].

OA PHENOTYPES

OA is now being understood as a multifaceted heterogeneous disease with multiple causative factors, clinical phenotypes, and molecular endotypes[6]. The clinical phenotypes in OA refer to the cluster of visible properties such as associated mechanical deformities that individualize the disease expression in a certain group of patients[7]. Similarly, a comprehensive set of such visible parameters including age, sex, race, disease duration, symptoms, and radiological features such as joint space narrowing, osteophytes, and subchondral sclerosis needs to be utilized to characterize the patient's response to the treatment outcomes. The various phenotypes proposed for OA include chronic pain phenotype, inflammatory phenotype, metabolic syndrome phenotype, mechanical overload phenotype, minimal joint disease phenotype, senescent phenotype, endocrine phenotype, and sarcopenic phenotype as shown in Figure 1[6,8,9]. Prospective studies are needed to validate the efficacy of these phenotypic subtype-based management methods to surpass or prevent symptoms at an early stage before progressive and irreversible changes occur[10].

OA ENDOTYPES

While the clinical phenotypes describe the presenting features of the OA individual, endotypes refer to the compilation of disease mechanisms that explains the disease expression in the group of patients. In OA, the disease expression is mostly based on a few typical endotypes such as inflammatory endotype, metabolic syndrome endotype, senescent endotype, endocrine endotype, and senescent endotype with characteristic biomarkers in serum and synovial fluid of the joint[6]. The biomarkers used in defining a characteristic endotype involve cartilage matrix destruction markers, proteases, subchondral bone matrix destruction markers, signaling markers, synovial inflammatory markers, and systemic inflammatory markers[11,12]. Hence a typical OA endotype may present as various OA phenotypes and on the contrary, every OA phenotype may have an overlap with various OA endotypes as illustrated in Figure 1 before presenting as an end-stage disease. Angelini *et al*[11] in their endotypic stratification based on clustering of biochemical marker data was proved to potentially drive the stratification of the clinical studies and contribute to precision medicine strategies for OA progression in the future.



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Figure 1 Illustration of the interplay between the various endotypes and phenotypes proposed in osteoarthritis.

CURRENT CHALLENGES

Having identified OA to be a multifactorial, heterogenous, multi-dimensional complex disease, the challenges before us to develop DMOADs include the introduction of the OA phenotypes and endotypes into clinical study designs to test the efficacy of biomarkers and newly developed DMOADs. Although we have various newer ortho-rheumatological tools to grade joint degeneration[13], we do not have a defined early disease identification and categorization tool to embark on the enrolment of patients in clinical studies. We do not have the necessary genetic and polyomic tools to stratify patients into therapeutic subgroups to test their efficacy. However, by harmonizing the data collection from the clinical studies in OA, true stratification of the patients by clinical data from all the interventional and observational studies provides the future to predict the response to treatment[14]. Current research has identified various key biomarkers such as oncostatin M, a cytokine from the interleukin-6 family, and metabolite of C-reactive protein was identified as candidate biomarkers to stratify the patients of inflammatory subtype[12]. However, the list is not sufficient to comprehensively enlist all the OA subtypes into their appropriate phenotypic and endotypic subclassification to tailor their clinical management algorithms.

FUTURE RESEARCH PERSPECTIVES

Before the development of therapeutic DMOADs, measures to develop a robust early classification criterion for OA need to be established. The other main focus of future research in OA involves identifying the key biomarkers that would enable the categorization of OA patients into individual subtypes for optimal management. This involves studying the disease at a molecular level in the early stages without evident radiographic changes which enables us to distinguish between the molecular endotypes and corresponding phenotypes before all the phenotypes coalesce into a final common presentation as classical end-stage OA as shown in Figure 1.

Further, research on the key biomarkers that differentiate between the different subgroups of OA needs to be identified. The current platforms (*e.g.*, omics techniques) help in the assessment of a panel of markers to find their relationship with a particular phenotype rather than just a few markers tested in the conventional methods. The ideal substrate suitable for such categorization might be the local biochemical markers (*e.g.*, synovial fluid) that better distinguishes the molecular endotypes free from the systemic sources with noise such as comorbidities. With the identified phenotypic and endotypic markers in OA, we can identify the potential theratypes in OA where predicted treatment responses could be contemplated based on their endotypic categorization.

CONCLUSION

Tailoring an effective early management strategy for OA involves the development of early disease identification methods, and disease stratification algorithms based on the distinctive phenotypic and endotypic expression in the individuals using their molecular signature patterns. The future of OA management is focussed more on prevention and early identification of disease process rather than redemption of the joint from an end-stage disease.

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MINIREVIEWS

Update on surgical procedures for carpal tunnel syndrome: What is the current evidence and practice? What are the future research directions?

Valerio Pace, Fabrizio Marzano, Giacomo Placella

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Abstract

Carpal tunnel syndrome (CTS) is a multifactorial compression neuropathy. It is reported to be very common and rising globally. CTS's treatment varies from conservative measures to surgical treatments. Surgery has shown to be an effective method for more severe cases. However few unclear aspects and room for further research and improvements still remains. We performed a narrative literature review on the most up to date progress and innovation in terms of surgical treatments for CTS. The simple algorithm of leaving the choice of the surgical method to surgeons' preference and experience (together with consideration of patients' related factors) seem to be the best available option, which is supported by the most recent metanalysis and systematic reviews. We suggest that surgeons (unless in presence of precise indications towards endoscopic release) should tend to perform a minimally invasive open approach release, favoring the advantage of a better neurovascular structures visualization (and a consequent higher chance to perform a complete release with long term relief of symptoms) instead of favoring an early reduction (in the first postoperative days) of immobilization and pain. Research towards a universally accepted standardization should be aimed for by the researchers, who have failed to date to sufficiently limit bias and limitations.

Key Words: Carpal tunnel; Carpal tunnel release; Transverse ligament; Endoscopic release; Open release

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Core Tip: After reviewing the most up to date literature, it could be said that evidence of superiority of one technique over the others is lacking from a high level of evidence point of view. Specific advantages and disadvantages of surgical methods can however be taken into account when choosing among treatments. The simple algorithm of leaving the choice of the surgical method to surgeons' preference and experience (together with consideration of patients' related factors) seem to be the best available option, which is supported by the most recent metanalysis and systematic reviews.

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INTRODUCTION

Carpal tunnel syndrome (CTS) is a multifactorial neuropathy caused by compression of the median nerve at the carpal tunnel. Its symptoms include pain, tingling or numbness affecting mainly the thumb, index and middle finger (sometimes the ring finger is also involved), with this sensation that could travel up the arm; hand weakness (mainly the thumb's pinching muscles).

The incidence of CTS in the general population is thought to be about 3%-4%; although it could reach 8% in the working population. Figures vary quite significantly among continents and countries, but unequivocally the trends suggest the CTS incidence and subsequent surgical management are rising globally[1-3].

The majority of cases seem to be idiopathic. Other causes such as fractures, infections and systemic diseases should also be taken into account. In fact the primary diseases should be properly assessed and treated, together with CTS in order to achieve complete resolution of symptoms[1-4].

The diagnosis is made with accurate history taking and clinical examination, supported by electromyography (EMG) and nerve conduction studies. Ultrasound has been used to aid diagnosis. Most people with mild to moderate symptoms are initially treated non-operatively. However surgery is thought to provide more effective and durable symptom relief, especially for the most severe cases[4].

Various surgical methods have been proposed and studied, with contradictory results. In fact little agreement on the best surgical procedure to treat CTS has been reached. Most of studies are characterized by significant limitations, which do not allow the clinicians to achieve a consensus on the matter [4,5].

Our aim is to present an update on surgical procedures for carpal tunnel syndrome, highlighting what the current evidence is, with advantages and limitations of the studied surgical methods. The final goal is to provide the most up to date scientific information in order to help the clinicians to maintain good practice with decisions based on the highest possible level of evidence.

DIAGNOSIS

Accurate physical examination is warranted (after full history taking). It should include Tinel sign and Phalen sign, which are commonly utilized to reveal median nerve compression at the carpus. Durkan's compression test could also be used, but it is not useful to discriminate between symptomatic patients with and without EMG disturbances. The closed fist test is specific in these situations. Two-point discrimination is considered positive if greater than 4 mm. EMG shows that the median nerve transmission rate decreases and the latency period extends beyond normal values. Ultrasounds are sometimes used to aid diagnosis[4-7].

SURGICAL MANAGEMENT

Surgical management is recommended after failure of conservative measures (splinting, physiotherapy, manual therapy, steroid injections, platelet-rich plasma injections, Kinesio taping, neurodynamic techniques, gabapentin, therapeutic ultrasound, and extracorporeal shockwave therapy) for mild and moderate cases of CTS, or for the most severe cases (numbness in the hand, atrophy of the hand muscles, restricted hand function). No high-grade clinical evidence currently supports specific surgical

indications. Surgery should be aimed at reduce the compression on the median nerve at the carpus, at the level of the transverse ligament. The cause of CTS should also be clearly identified, as the primary disease should be treated and resolved as well. However most of cases are thought to be idiopathic. For those cases, a carpal tunnel release is indicated[4,6-8].

SURGICAL PROCEDURES

The first reported surgically treated cases of CTS we could found in the literature are the ones presented by Herbert Galloway in 1924. Since then, surgical methods have become more and more common. Many surgical options have been studied and proposed, but in the end the main open uncertainty is about the choice between open surgery and endoscopic assisted surgery. Ultrasound guided methods have also been developed[6-9].

Open carpal tunnel release

Surgeons could use a traditional incision or a mini-incision. The landmarks for the traditional incision are the radial border of the hypothenar muscle, where the incision should be started and extended proximally till the distal wrist crease. 5 cm is the most common length of the incision, but it can be further extended to better visualize the structures. The mini-incision techniques include a transverse incision of about 2 cm on the ulnar side of the wrist stripes or a longitudinal incision starting from the mid-palm and ending at the most proximal portion of the palm. The main issues when using the two latter options are increased complexity, scar pain and increased chance of incomplete transverse ligament release. Other options such as double mini-incisions or other slightly different longitudinal incision options have been presented with promising results. Many studies have proved that all mini-incision technique are safe and provide good results[6,10,11].

After skin incision, the surgeon should go through the palmar fat and fascia, trough which the flexor retinaculum should be visualized. When adequately exposed, it should be completely split longitudinally, with decompression and visualization of the median nerve. Wound closure (skin stitches) and a wound dressing are the last surgical steps. Some authors have presented a method of open release through a small incision using a set of specially designed instruments, retaining advantages of observing the pathology under direct vision and avoiding complications of hazardous injuries to important structures. The instruments consist of a thin metal guide with a groove in the center to accommodate an angled knife holder. The procedure has been performed since 1997 with no complications[10,11].

Open carpal tunnel release (OCTR) has been reported to be a safe procedure overall. Only few cases of wound infections are reported. Scar formation on the palm could also be a complication, especially for traditional size incisions. The palmar nerve branch of the median nerve could also be damaged inadvertently during surgical exposure, as it arises at the distal part of the forearm palmarly and it divides into a medial and lateral branch, passing superficial to the flexor retinaculum of the hand. Another nerve that might be injured is the recurrent motor nerve branch of the median nerve, which normally supplies the thenar muscles. His injury might significantly affect the thumb function[9,11,12].

Endoscopic carpal tunnel release

Single-portal and two-portal endoscopic carpal tunnel release (ECTR) have been reported. The first was introduced in 1986 by Okutsu *et al*[13] who started using the aid of endoscopy to perform carpal ligament release. This technique was used and modified by several other authors in the years, such as Agee and Linvatec[14].

Agee used an entry portal between the palmaris longus and the flexor carpi ulnaris at the level of the proximal wrist striatum. The palmaris longus tendon is then exposed after soft tissue dissection. The endoscope is then placed at the level of the ulnar side of the transverse ligament through the portal, and the ligament is cut from distal to proximal. Not good visualization of the neurovascular structures is the main issue of this approach[14-17].

Linvatec introduced a similar single-portal technique. The main characteristic and difference compared to the previous described technique is that the transverse ligament is cut from proximal to distal[14-17].

Among the two-portal ECTR, the Chow technique is the most widely used method. The first portal is made similarly to Agee method's entry portal, whilst the second portal is made in the palm surface (0.5-0.75 ncm in length) on the bisect line of the angle formed from the distal border of the fully abducted thumb and the third web space and approximately 1 cm proximal to the junction of these lines[18,19].

The surgeon should than push the sleeve till it enters into carpal tunnel from the entry portal and exits through the exit portal with the flexor tendon sliding. Cutting tools are then inserted into the sleeve and surgeons can cut the transverse ligament bilaterally under endoscopic monitoring[18,19].

It is thought that two-portal techniques allow a better visualization of the neurovascular structures and therefore they carry the lowest risk of complications and the higher chance to completely cut the transverse ligament. On the other hand, given the quite distal incision of the Chow technique, we must

say that the risk of injury to the arcus volaris superficialis is higher than in other endoscopic techniques, together with a higher risk of excessive palmar scar formation[15,16,18,19].

Comparison among surgical procedures

A huge amount of work has been carried out and lots of papers published on the matter. Several reviews and metanalysis are also available. From the most up to date evidence it seems that no significant differences exist among the different surgical methods. However it must be said that relevant limitations often bias the results[12,15-17].

Results related to differences among mini-incision and traditional incision surgery are various and contradictory. There are studies reporting good outcomes and lower complication rates with mini-incision techniques. Undoubtedly a smaller approach results in less invasive surgery and this could contribute to better esthetic results both on the short and long run, with potential better patients' satisfaction. However symptoms resolution on the long run is the main objective of the performed surgery, and it is unclear whether open surgery could allow better results due to better visualization of the structures and reduced revision surgery rate. Similar results among mini and conventional approach have also been reported[19-24].

Despite what one could hypothesize regarding potential benefits of endoscopic procedures *vs* open surgery in terms of complication rate, operative time and outcomes and patients' satisfaction, overall data do not clearly highlight such advantages. Moreover most of papers present similar results. More evidence is present with regards to postoperative hand pain and recovery time, in favor of endoscopy procedures, allowing a quicker return to work and his consequent reduction of costs and resources. In fact open surgery (particularly the traditional approach) may prolong the immobilization time and augment postoperative pain and the risk for hypertrophic or hypersensitive scar formation. However the better visualization of the neurovascular structures allowed by the open procedures makes the latter safer from this point of view. However it must be said that most noted nerve injuries were transient, and patients still achieved full recovery after surgery. It should be taken as a worrying sign that often the choice between open and endoscopic surgery is left to surgeons' preference and experience, together with patients' related factors. It seems that a lack of universally accepted evidence on one of the most common syndromes and related surgical management still exist[15,16,20-23].

Among the endoscopic techniques, the majority of the studies have focused their attention on the two-portal technique, whilst fewer studies have reported the results of the Agee's technique. The latter is claimed to be used for his potentials of reducing the higher complication rates of the Chow's technique reported by some authors. Better results in terms of recovery time and return to work has been reported in favor of the single-portal techniques. However the utilization of just one portal could cause a not perfect visualization of the structures (including the transverse ligament), and this could lead to incomplete ligament section and the consequent recurrence of symptoms and the need of revision surgery[22-27].

Intuitively one could relate the endoscopic techniques to mini-incision techniques, as they are based on the same objectives (a smaller approach able to provide good or even better results). In fact surgeons utilizing these techniques aim to a better appearance of the scar (and less complications related to scarring processes) and a quicker recovery, with better patients' satisfaction and acceptance of the procedure. However insufficient evidence with regards of comparison between the two techniques is still present[26-29].

A mention to ultrasound-guided percutaneous carpal tunnel release is needed. Several authors have performed carpal tunnel release with such modality, reporting good results and claiming that it could be an effective treatment for CTS. However the overall level of evidence has been reported by review and metanalysis to be very low, with several studies with at least moderate risk of bias. A low complication rate and fast recovery have often been reported after such procedures[29-32].

Another special mention should be given to epineurotomy and flexor tenosynovectomy. They are often considered as a useful adjunct to the basic surgical procedure, but their indications are still controversial. It seems that tenosynovectomy is only recommended for patients with rheumatic disease (or inflammatory risk factors), or patients undergoing chronic hemodialysis. The intraoperative finding of excessive or abnormal synovial tissues makes a tenosynovectomy also indicated[33-37] Table 1.

CONCLUSION

There has been controversy regarding the superiority of ECTR over OCTR in the last decades. Many original articles have been published on this issue; moreover, several meta-analyses have compared ECTR with OCTR as treatment options for CTS, but relevant bias and limitations have commonly been reported. Therefore a universal consensus has not been achieved yet, even if CTS is a very common pathology and his surgery is routinely and widely performed[26,27].

Over the years the wrist anatomy knowledge has improved and various surgical instruments and methods have been studied and presented. Sufficient effectiveness has always been reported, but a high quality evidence is lacking.

Table 1 Advantages of surgical options (risk of hypertrophic or hypersensitive scar formation should be considered secondary, despite temporary discomfort for the patients)

Advantages of open release	Advantages of endosopic release
Good outcomes	Good outcomes
Low complication rates	Low complication rate (slightly better the open release)
Mini-incision: best approach and better patients' satisfaction	Better esthetic results (much smaller scars)
Reduced revision surgery rate	Reduced risk for hypertrophic or hypersensitive scar formation
Better visualization of structures	Reduced postoperative hand pain
Safest approach for neurovascular structures	Reduced recovery time
Possibility to use a mini-incision approach	Quicker return to work
Possibility to perform epineurotomy and flexor tenosynovectomy	Reduced costs and resources

Many studies determined that ECTR was superior to OCTR in terms of higher satisfaction rates, improved key pinch strengths, earlier recovery times, and fewer scar-related complications. This suggests that patients with CTS can be effectively managed with ECTR; however, the possibility of transient nerve injury should be considered. However most of studies are characterized by significant limitations, which do not allow the clinicians to achieve a consensus on the matter. Clear and high level of evidence advantages of one technique over the others have not been provided yet, and sufficient results seem to be provided with any of the studied methods[4,5,26-29,38].

We believe that the lack of high level of evidence regarding the surgical techniques should be taken as a worrying sign, especially because clear evidence is most of the time provided for the most common diseases and related management options. In fact it seems that often the choice between open and endoscopic surgery is left to surgeons' preference and experience, together with patients' related factors. To date, this simple algorithm has shown to be able to provide the best results. Surgeons should refrain from attempting potentially less invasive procedures if not familiar with the technique, as the risks of arming would outweigh the potential better results.

Relevant authors tend to strongly recommend their proposed technique, commonly providing evidence of excellent results and elements in favor of their method over the other ones. However when it comes to systematic reviews and metanalysis, data suggest that relevant bias and limitations do not allow standardization and do not provide sufficient evidence of the superiority of a technique over the others.

We suggest that surgeons (unless in presence of precise indications towards endoscopic release) should tend to perform a minimally invasive open approach release, favoring the advantage of a better neurovascular structures visualization (and a consequent higher chance to perform a complete release with long term relief of symptoms) instead of favoring an early reduction (in the first postoperative days) of immobilization and pain. Moreover, in view of higher chances to obtain long term symptoms relief, the risk of hypertrophic or hypersensitive scar formation should be considered secondary, despite temporary discomfort for the patients Table 1.

We believe there is room for further research evidence, possibly high level of evidence works (level 1 or 2) which should separately study specific aspects and provide detailed and clear advantages and disadvantages of every single treatment option. Cohorts should be sufficiently big and bias reduced to the minimum. The problem of the current heterogeneity should also be overcomed.

CTS is becoming more and more common, as is its surgical management. This constitutes a significant economic burden for societies. All surgical techniques have provided satisfactory results and have been proven to be effective options. After reviewing the most up to date literature, it could be said that evidence of superiority of one technique over the others is lacking from a high level of evidence point of view. Specific advantages and disadvantages of surgical methods can however be taken into account when choosing among treatments. The simple algorithm of leaving the choice of the surgical method to surgeons' preference and experience (together with consideration of patients' related factors) seem to be the best available option, which is supported by the most recent metanalysis and systematic reviews. Research towards a universally accepted standardization should be aimed for by the authors, who have failed to date to sufficiently limit bias and limitations.

FOOTNOTES

Author contributions: Pace V, Marzano F, and Placella G designed the article, performed research and literature review, analyzed data and wrote the review.

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MINIREVIEWS

Polydactyly: Clinical and molecular manifestations

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Abstract

Polydactyly is a malformation during the development of the human limb, which is characterized by the presence of more than the normal number of fingers or toes. It is considered to be one of the most common inherited hand disorders. It can be divided into two major groups: Non-syndromic polydactyly or syndromic polydactyly. According to the anatomical location of the duplicated digits, polydactyly can be generally subdivided into pre-, post-axial, and mesoaxial forms. Non-syndromic polydactyly is often inherited with an autosomal dominant trait and defects during the procedure of anterior-posterior patterning of limb development are incriminated for the final phenotype of the malformation. There are several forms of polydactyly, including hand and foot extra digit manifestations. The deformity affects upper limbs with a higher frequency than the lower, and the left foot is more often involved than the right. The treatment is always surgical. Since the clinical presentation is highly diverse, the treatment combines single or multiple surgical operations, depending on the type of polydactyly. The research attention that congenital limb deformities have recently attracted has resulted in broadening the list of isolated gene mutations associated with the disorders. Next generation sequencing technologies have contributed to the correlation of phenotype and genetic profile of the multiple polydactyly manifestations and have helped in early diagnosis and screening of most non-syndromic and syndromic disorders.

Key Words: Polydactyly; Gene; Syndromic; Non-syndromic; Preaxial; Postaxial

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Core Tip: The molecular basis of hand and foot polydactyly, syndromic or non- syndromic, is diverse. There are several phenotypes of the disorder which are correlated to a specific molecular profile and other whose molecular basis is still unclear. We summarize and provide an overview of gene mutations that cause hand and foot polydactyly as an isolated disorder or as part of a syndrome and present the clinical manifestations that they cause.

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INTRODUCTION

Non-syndromic (Table 1) or syndromic polydactyly (Table 2) is often inherited with an autosomal dominant trait with variable penetrance[1]. It is related with a disturbance of the anterior–posterior axial development procedure of the limb[2] and is classified into preaxial, axial (central), and postaxial polydactyly[3]. Preaxial polydactyly is defined as an extra digit affecting the radial/tibial digits while postaxial involves the ulnar/peroneal digits. The rare type of axial (central) polydactyly refers to the duplication of three central hand or foot digits. Mirror-image polydactyly and Haas-type polysyndactyly are rare and distinct types, not fitting to the three categories[4].

Many specific phenotypes, including all types of hand and foot polydactyly, have been identified and correlated to gene mutations[5].

Since polydactyly is often a part of a syndrome, the ability to identify the potential syndromes associated with this anomaly is very important for the clinician. Additionally, it is important to distinguish between syndromic and non-syndromic cases for reasons of genetic counselling. In this paper, we review the recent progress in the molecular genetics, including clinical and molecular manifestations of disorders, and present some representative syndromes including polydactyly as a phenotype.

CLINICAL AND MOLECULAR MANIFESTATIONS OF NON-SYNDROMIC HAND AND FOOT POLYDACTYLY

Preaxial polydactyly

The preaxial form of polydactyly is the second most common phenotype behind the postaxial with a reported prevalence of approximately 0.8 to 2.3 in 10000 live births. It is characterized by an extra digit on the tibial/radial side of limb (Figure 1). The following classification has been suggested:

Preaxial polydactyly type I, which is thumb polydactyly (*OMIM 174400*)[6]—characterized by duplication of one or more skeletal elements of a biphalangeal thumb.

Preaxial polydactyly type II, which is polydactyly of a triphalangeal thumb (*OMIM 174500*).

Preaxial polydactyly type III, which is polydactyly of the index finger, characterized by the presence of one or two triphalangeal digits (*OMIM 174600*).

Preaxial polydactyly type IV and syndactyly of various degrees involving the middle and ring finger/second and third toe (*OMIM 174700*) or hallux polydactyly (*OMIM 601759*)[7].

Preaxial polydactyly type I: Thumb polydactyly is usually observed in unilateral form. In bilateral cases, hands are more often affected and the left hand is also more often affected than the right. It follows an autosomal dominant inheritance model[7]. However, a recent study in a Pakistani family has revealed a rare autosomal recessive form of preaxial polydactyly, linked to a novel variant (c.1517T>A; p. Leu506Gln) in the *GLI1* gene on chromosome 12q13.3[8].

The most commonly used classification is Wassel classification which divides thumb duplication into six subtypes according to the level and the extent of duplication (partial or complete)[9]. Hallux polydactyly is known to exist as a predominant presentation or an isolated disorder. The incidence of hallux duplication is 2.4/100000 as compared to thumb polydactyly incidence in South America, which is 1.65/10000.

Preaxial type I polydactyly is caused by sequence variants in the sonic hedgehog (*SHH*) enhancer, called zone of polarizing activity (*ZPA*) regulatory sequence (*ZRS*), which is regulated by *LMBR1* gene.

Table 1 Mutated genes isolated in non-syndromic polydactyly

Preaxial	Central	Postaxial	Complex
CEP290	*CPLANE1*	*GLI3*	*MIPOL1*
RPGRIP1		*ZNF141*	*PITX1*
TMEM216		*DACH1*	*LMBR1*
FBN1		*GLI1*	
CEP164			
MEGF8			
LMBR1			
ZRS			
GLI3			
ZNF141			
STKLD1			
GLI1			
KIAA0586			
EVC			
HES1			

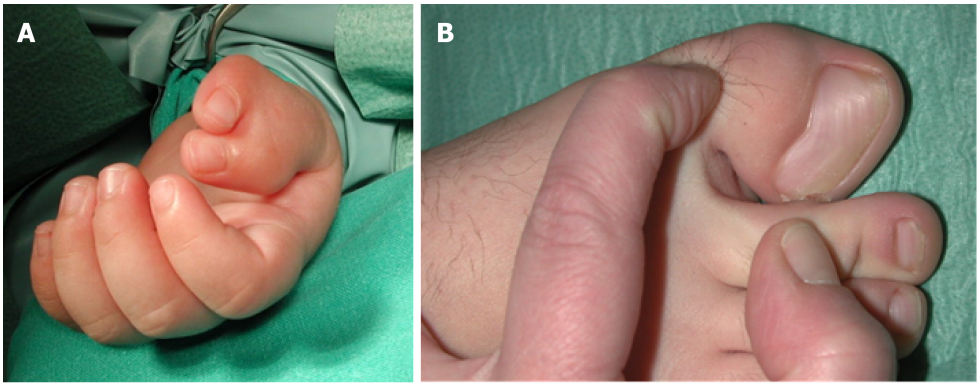
Table 2 Mutated genes isolated in syndromic polydactyly

Syndrome	Mutated gene(s)
Bardet-Biedl	*CCDC28B, ARL6, MKS1, BBS8, SDCCAG8, LZTFL1, WDPCP, BBS4, BBS12, TMEM67, BBS1, BBS2, BBS6, BBS10, BBS9, BBS7, BBS5, CEP290, TRIM32, BBIP1, ALMS1, MKKS*
McKusick-Kaufman	*MKKS*
Carpenter	*P4HB, RAB23*
Saethre-Chotzen	*TWIST1, FGFR2*
Poland syndrome	-
Greig cephalopolysyndactyly	*GLI3*
Short-rib polydactyly	*ATD1, LBN, DYNC2H1, IFT81*
Pallister-Hall	*GLI3*
Triphalangeal thumb-polydactyly	*LMBR1*
Smith-Lemli-Opitz	*DHCR7*

Mutations in *CEP290, RPGRIP1, TMEM216, FBN1, CEP1*, and *MEGF8* genes have been isolated and suspected to play a role in Wassel III and Wassel IV manifestations[10]. Recently, a mutation in *STKLD1* gene, located on chromosome 9q34.2, was found and correlated with the disease phenotype in all members of the studied family[11]. Another molecular study of the *SHH/GLI* signaling axis, identified *HES1* gene as a downstream modifier which can cause preaxial polydactyly[12].

Next generation sequence analysis in a large four-generation family with isolated preaxial polydactyly revealed a new *ZRS* mutation (g.101779T>A) which can cause the disease phenotype[13]. Another recent genetic analysis of 20 Chinese patients with preaxial polydactyly identified two novel mutations in *GLI3* gene (c.G2844A) and in *EVC* gene (c.1409_1410del). Mutations in *KIAA0586* gene, which are related with ciliopathies (*OMIM 610178*), were also detected[14].

Preaxial polydactyly type II: Preaxial polydactyly type II is characterized by the presence of a usually opposable triphalangeal thumb with or without additional duplication of one or more skeletal components of the thumb. The thumb appearance can differ widely in shape or it can be deviated in the radio-ulnar plane. It can also be associated with Holt-Oram syndrome and Fanconi anemia. *LMBR1* and its related pathways *Wnt/Notch* and *Hedgehog* play a significant role in the development of the disorder. The disease gene locus was mapped to chromosome 7q36[15]. Mutations in the *SHH* regulatory factor



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Figure 1 Preaxial polydactyly. A: Preaxial/radial hand polydactyly phenotype; B: Preaxial/tibial foot polydactyly phenotype.

were also reported[16]. Two mutations, a 739A>G transition near the 5- end of the *ZRS* and a 621C>G mutation in the *ZRS* of the *LMBR1* gene, were identified[17]. Triphalangeal thumb-polysyndactyly can manifest as a syndrome. It is an isolated limb deformity characterized by pre- and postaxial polysyndactyly of hands and feet. Mutations in *ZRS* have been identified[18,19].

Preaxial polydactyly type III: Preaxial polydactyly type III is an autosomal dominant disorder which is characterized by a malformation of fingers, where the thumb is replaced by one or two triphalangeal digits with dermatoglyphic pattern specific for the index finger. It can occur unilaterally and bilaterally. No responsible gene has been identified[20].

Preaxial polydactyly type IV: Preaxial polydactyly type IV is an autosomal dominant disorder which can be described as mild duplication of the thumb, syndactyly that affects the third and fourth hand/foot fingers/toes, duplication of the first or second toes, and toes syndactyly. There are patients who have only foot malformations. *GLI3* gene mutations are associated with the disorder. Genetic analysis in two families with the phenotype were found heterozygous for p.L1216PfsX31 and p.R290X mutations in the *GLI3* gene[21].

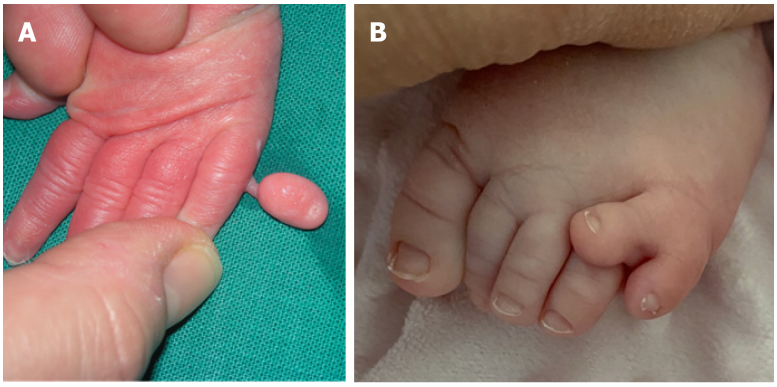
Postaxial polydactyly

Postaxial polydactyly is a frequent congenital hand malformation characterized by fifth digit duplications in hands and/or feet (Figure 2). Its prevalence is estimated between 1/630 and 1/3300 in Caucasian race and between 1/100 and 1/300 in Black race. Two phenotypic categories have been described: Type A, the extra digit is well formed and articulates with the fifth or an extra metacarpal; Type B, there is a rudimentary extra fifth digit which is usually represented by an extra skin tag. Both types can be inherited by autosomal dominant or recessive trait[22]. There are six subcategories of type A postaxial polydactyly.

Postaxial polydactyly type A1: In postaxial polydactyly type A1, the extra digit is well-formed and articulates with the fifth or a sixth metacarpal/metatarsal. Genetic analysis in an Indian family resulted in the identification of association of *GLI3* gene mutations with the phenotype[23]. It was mapped to 7pl5-q11.23. Mutation in the C- and the N-terminal or the zinc finger domain of the *GLI3* gene causes isolated postaxial polydactyly type A1 and is also linked to Greig cephalopolysyndactyly syndrome, while a mutation in the post-zinc finger region is incriminated for Pallister–Hall syndrome[24]. A recent genetic study in a Chinese family with isolated postaxial polydactyly revealed a new mutation of *GLI3* (c.1180C>TT, p.P394fs18x)[25]. A *DACH1* gene mutation was identified in a patient with bilateral postaxial polydactyly who was subjected to whole exome sequencing[26]. New mutations of the *GLI1* gene have been incriminated for postaxial polydactyly according to a novel study which aims to help in prevention of the disorder[27].

Postaxial polydactyly type A2: It consists of Type A polydactyly phenotypes with an extra digit well-formed. A genetic study of an Indian kindred revealed disease gene locus of postaxial polydactyly type A2 (*OMIM 602085*) which was mapped to 13q21-q32[28]. The underlying gene for the disorder has not been identified.

Postaxial polydactyly type A3: It manifests with polydactyly phenotypes Type A/B in hands and feet. Genetic analysis of a Chinese family discovered incomplete penetrance of the phenotype and identified the disease gene locus which was mapped to 19p13.2-p13.1[29]. There is not an identified gene responsible for the disorder.



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Figure 2 Postaxial polydactyly. A: Postaxial/ulnar hand polydactyly phenotype; B: Postaxial/fibular foot polydactyly phenotype.

Postaxial polydactyly type A4: It is characterized by polydactyly phenotypes Type A/B in hands and feet and two to three finger/toe syndactyly. The disease locus (*OMIM 608562*) was mapped to 7q21-q34 by genetic analysis in a Dutch family with an autosomal dominant inheritance of the phenotype[30]. Until now there is no candidate gene for this manifestation.

Postaxial polydactyly type A5: It is characterized by polydactyly of hands and feet, minor syndactyly, and five to six metacarpal synostoses. Two Indian families and a Sicilian family were identified to have this type of autosomal recessive postaxial polydactyly[31]. Postaxial polydactyly type A5 (*OMIM 263450*) was mapped to 13q13.3- 13q21.2 region. The underlying gene for this phenotype has not yet been identified.

Postaxial polydactyly type A6: The phenotype is characterized by an extra functionally developed digit in hands and/or feet. Mutations in the *ZNF141* gene are considered to cause postaxial polydactyly type A6 (*OMIM 615226*). Exome sequencing in a Pakistani family resulted in showing autosomal recessive inheritance of A6 phenotype. The *ZNF141* gene consists of four exons[32]. The final protein is expressed in many different tissues and it is still unclear whether it plays a role in embryogenesis[33].

Postaxial polydactyly type B: It is the most common type of polydactyly. There is a vestigial nonfunctional, partially formed, ulnar (or fibular) digit with no bony attachments, attached by a narrow neurovascular pedicle to the lateral aspect of the hand or foot[25]. *GLI3* gene mutations are associated with this often manifestation.

Central polydactyly

Central polydactyly (*OMIM 174200*) is a very rare phenotype which is characterized by duplication of one of the three middle digits of the hand and foot. It can be an isolated defect or can be accompanied with other anomalies. The most often manifestation of hand central polydactyly is duplication of the fourth digit[3]. Foot central polydactyly is very rare and the second toe is most commonly duplicated [34]. Central polydactyly is related to split-foot malformation with mesoaxial polydactyly and Holzgreve syndrome. *CPLANE1* is the only known gene which is associated with central polydactyly.

Complex types

Mirror image polydactyly: This rare non-syndromic limb malformation (*OMIM 135750*) presents with mirror-image hand or foot polydactyly. The malformation can be unilateral, bilateral, and very rarely tetramelic. It can be associated with other congenital anomalies or can present isolated. *MIPOL1* and *PITX1* gene mutations have been identified and incriminated for this disorder. A recent German study in a patient with the phenotype showed a heterozygous deletion of 4.9 Mb on 5q31 including *PITX1*[35].

Haas-type polysyndactyly: Haas-type polysyndactyly (*OMIM 186200*) is characterized by complete cutaneous syndactyly of all hand fingers and occasionally foot toes are affected. It frequently presents with polydactyly with six digits and six metacarpals. It is inherited with an autosomal dominant trait. It is usually classified as syndactyly type IV. The locus for Haas-type polysyndactyly was mapped on 7q36 by linkage and haplotype analysis of a Chinese family[36]. Mutations of the *ZRS* region of *LMBR1* gene and other *ZRS* point mutations were found in families presenting with the clinical sings of Haas-type polysyndactyly according to two recent studies[37,38].

CLINICAL AND MOLECULAR MANIFESTATIONS OF SYNDROMIC HAND AND FOOT POLYDACTYLY

Bardet-Biedl syndrome

Bardet-Biedl syndrome (*OMIM 209900*) is an autosomal or digenic recessive disorder which can present with vision loss, obesity, hand and/or foot polydactyly, intellectual disabilities, and hypogonadism. Mutations in at least 20 genes have been identified and associated with the syndrome[39]: *CCDC28B*, *ARL6*, *MKS1*, *BBS8*, *SDCCAG8*, *LZTFL1*, *WDPCP*, *BBS4*, *BBS12*, *TMEM67*, *BBS1*, *BBS2*, *BBS6*, *BBS10*, *BBS9*, *BBS4*, *BBS7*, *CEP290*, *TRIM32*, *BBIP1*, *IFT27,* and *IFT172*genes are examples of them. A recent study in four Iranian children with a clinical diagnosis of Bardet-Biedl syndrome identified in three children one previously reported mutation in *BBS12* gene (c.265-266delTT, p.L89fs) and two newly detected mutations in *MKKS* (c.1196T>G, p.L399X) and *BBS7* gene (c.1636C>T, p.Q546X). A new mutation in *ALMS1* gene was isolated in the other child[40].

McKusick-Kaufman syndrome

McKusick-Kaufman syndrome's phenotype (*OMIM 236700*) consists of the following features: Genitourinary malformations (hydrometrocolpos, glanular hypospadias, and prominent scrotal raphe), postaxial hand and/or foot polydactyly, and rarely cardiac defects. *MKKS* gene mutations are associated with McKusick-Kaufman syndrome and they are inherited with an autosomal recessive trait [41].

Carpenter syndrome

Carpenter syndrome (*OMIM 201000*) is characterized by craniosynostosis, involving a pointed head (acrocephaly), syndactyly of certain fingers or toes, and polydactyly. It appears most commonly with foot polydactyly, rarely hand polydactyly and hand or toe cutaneous syndactyly. *RAB23* gene mutations are associated with the syndrome, which appears with autosomal recessive inheritance[42]. Recent molecular studies have identified two new mutations in *RAB23* gene (NM_001278668:c.T416C:p.Leu139-Pro and NM_016277.5:c.398+1G>A)[43] and a new mutation in *P4HB* gene [44].

Saethre-Chotzen syndrome

Saethre-Chotzen syndrome's phenotype (*OMIM 101400*) is characterized by premature closure of cranial sutures, hand syndactyly, and foot polydactyly. Foot polydactyly most often involves the first toe. *TWIST1* and *FGFR2* gene mutations are usually incriminated and inherited with an autosomal dominant trait[45].

Poland syndrome

Poland syndrome (*OMIM 173800*) involves underdeveloped pectoralis muscles on one side of chest wall and ipsilateral hand abnormalities, including short fingers and syndactyly (symbrachydactyly); however, there are rare cases of preaxial polydactyly manifestations in the literature[46]. Most cases of Poland syndrome are not related with a family history, and they are sporadic. Rarely it is inherited with an autosomal dominant trait through generations in families. There are no isolated gene mutations correlated with Poland syndrome.

Greig cephalopolysyndactyly syndrome

Greig cephalopolysyndactyly (*OMIM 175700*) syndrome is an autosomal dominant syndrome, which presents with hypertelorism, macrocephaly, and polydactyly. The polydactyly is most commonly preaxial of the feet and postaxial in the hands. Greig cephalopolysyndactyly is associated with *GLI3* mutations[47]. Recently, molecular studies have broadened the spectrum of known *GLI3* mutations correlated with the syndrome[48,49].

Pallister-Hall syndrome

Pallister-Hall syndrome (*OMIM 146510*) is a rare disorder which affects many parts of the body. Very often manifestation of the syndrome is postaxial polydactyly and cutaneous syndactyly of hands and toes. *GLI3* gene mutations are considered responsible for this autosomal dominant disorder[50].

Short-rib polydactyly

Jeune syndrome, Ellis-van Creveld syndrome, Saldino-Noonan syndrome, and Majewski syndrome are called short-rib polydactyly syndromes (*OMIM 613091*). They belong to a group of lethal congenital disorders characterized by shortening of the ribs and long bones, hand and/ or foot polydactyly, and a range of extraskeletal phenotypes. *ATD1* gene is considered to be responsible for Jeune syndrome. *LBN* gene mutations cause Ellis-van Creveld syndrome and individuals carrying *DYNC2H1* gene mutations can present with Saldino-Noonan and Majewski syndromes. Novel exome sequencing studies have isolated two new mutations in *DYNC2H1* gene (c.8077G>T and c.11741_11742delTT) and a new mutation in *IFT81* gene, causing malformation of the cilia[51,52]. Short-rib polydactyly syndromes are

usually inherited with an autosomal recessive trait[53].

Triphalangeal thumb-polydactyly syndrome

Triphalangeal thumb-polydactyly syndrome (*OMIM 173800*) consists of triphalangeal thumbs, pre- or post-axial polydactyly, and syndactyly. *LMBR1* gene is considered to be responsible for this manifestation. It is inherited with an autosomal dominant genetic trait. Typically, the syndrome presents with duplicated triphalangeal thumbs and typical phenotypic findings include duplicated triphalangeal thumbs and syndactyly between middle, ring, or little finger[54].

Smith-Lemli-Opitz syndrome

Smith-Lemli-Opitz syndrome (*OMIM 173800*) is a multi-malformation syndrome. The responsible gene for this syndrome is considered to be *DHCR7* gene and it is inherited with an autosomal recessive pattern[55]. Its phenotype contains foot syndactyly (usually of 2nd and 3rd toes) and postaxial hand polydactyly.

CONCLUSION

Genetic mechanisms which combine epigenetic and environmental factors play a significant role in foot and hand polydactyly manifestations[56]. Proper genotype-phenotype correlations might help in future genetic testing and enhance our knowledge about identified diseases and their associated genes. Recent genetic analysis techniques of extra foot or hand digit formation highlight the existence of nongradual transitions in phenotypes, suggesting a distinction between continuous and discontinuous variation in evolution. Genome sequencing will probably lead to the discovery of a number of new gene mutations responsible for non-syndromic or syndromic polydactyly. Clinical manifestation and genetic profile correlation of polydactyly types will be further established by use of bioinformatics analysis of gene mutations. Progress of prenatal diagnosis, which is still mostly postnatal, prenatal operative treatment planning, and potential future gene modification treatment will be enhanced and unknown molecular background of diseases, which is to date unclear, will be elucidated.

FOOTNOTES

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META-ANALYSIS

Comparative effectiveness of adipose-derived mesenchymal stromal cells in the management of knee osteoarthritis: A meta-analysis

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Abstract

BACKGROUND

Osteoarthritis (OA) is the most common joint disorder, is associated with an increasing socioeconomic impact owing to the ageing population.

AIM

To analyze and compare the efficacy and safety of bone-marrow-derived mesenchymal stromal cells (BM-MSCs) and adipose tissue-derived MSCs (AD-MSCs) in knee OA management from published randomized controlled trials (RCTs).

METHODS

Independent and duplicate electronic database searches were performed, including PubMed, EMBASE, Web of Science, and Cochrane Library, until August 2021 for RCTs that analyzed the efficacy and safety of AD-MSCs and BM-MSCs in the management of knee OA. The visual analog scale (VAS) score for pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, Tegner score, magnetic resonance observation of cartilage repair tissue score, knee osteoarthritis outcome score (KOOS), and adverse events were analyzed. Analysis was performed on the R-platform using OpenMeta (Analyst) software. Twenty-one studies, involving 936 patients, were included. Only one study compared the two MSC sources without patient randomization; hence, the results of all included studies from both sources were pooled, and a comparative critical analysis was performed.

RESULTS

At six months, both AD-MSCs and BM-MSCs showed significant VAS improvement ($P = 0.015$, $P = 0.012$); this was inconsistent at 1 year for BM-MSCs ($P < 0.001$, $P = 0.539$), and AD-MSCs outperformed BM-MSCs compared to controls in measures such as WOMAC ($P < 0.001$, $P = 0.541$), Lysholm scores ($P = 0.006$; $P = 0.933$), and KOOS ($P = 0.002$; $P = 0.012$). BM-MSC-related procedures caused significant adverse events ($P = 0.003$) compared to AD-MSCs ($P = 0.673$).

CONCLUSION

Adipose tissue is superior to bone marrow because of its safety and consistent efficacy in improving pain and functional outcomes. Future trials are urgently warranted to validate our findings and reach a consensus on the ideal source of MSCs for managing knee OA.

Key Words: Mesenchymal stromal cell; Adipose tissue-derived mesenchymal stromal cell; Bone-marrow derived mesenchymal stromal cell; Cartilage regeneration; Knee osteoarthritis; Meta-analysis; Efficacy; Safety

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Core Tip: With the ongoing rise in the exploration of the clinical efficacy of mesenchymal stromal cells (MSCs) in the management of osteoarthritis (OA), there is an imminent need to identify the ideal source of MSCs to be utilized. Our meta-analysis has brought out the lacunae in the literature for studies to evaluate the impact of the source of MSCs in the management of OA. From a single-arm meta-analysis of available studies on the two commonly used sources such as bone marrow (BM) and adipose tissue, we found the adipose tissue to be superior to BM concerning the safety and consistent efficacy in improving pain and functional outcomes. However, considering the paucity of evidence, we recommend future trials to validate our findings and reach a consensus on the ideal source of MSCs for managing knee OA.

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INTRODUCTION

Osteoarthritis (OA) of the knee is the world's leading cause of degenerative joint disease leading to

articular cartilage damage resulting in pain, stiffness, and loss of joint mobility[1]. Owing to the hypovascular and aneural nature, the articular cartilage has a decreased integrity for intrinsic repair mechanisms[2]. The management of OA knee aims to provide painless functional joint with a full range of motion. To minimize the morbidity in the surgical management of OA knee, regenerative and translational medicine has paved a way to manage the articular cartilage defects with orthobiological products due to the limited potential for redifferentiation of chondrocytes[3,4].

Cell-based therapy has revolutionized its usage in the area where disease-modifying pharmacological agents or biological therapies are unavailable to treat the disorders. Mesenchymal stromal cells (MSCs) have proven the benefits in the formation of articular cartilage in the OA knee[5,6]. There are various sources of MSCs available namely bone marrow (BM), adipose tissue, synovium, peripheral blood, placenta, menstrual fluid, and amniotic fluid where the regenerative potential of all these sources of MSCs varies[7]. Out of all these sources of MSCs, the most commonly used sources are BM and adipose tissue for cartilage regeneration.

Adipose tissue possesses higher stem cell yield than BM[8]. One gram of adipose tissue yields approximately 0.35-1 million MSCs whereas one gram of BM yields 500-50000 MSCs[9]. BM-derived MSCs (BM-MSCs) show early senescence during expansion than adipose-derived MSCs (AD-MSCs)[10]. Mohamed-Ahmed *et al*[11] have demonstrated that AD-MSCs continued to proliferate up to 21 d than BM-MSCs and AD-MSCs showed considerable chondrogenic capacity, but less than BM-MSCs. Im *et al*[12] stated that osteogenic and chondrogenic potentials of BM-MSCs and AD-MSCs differ. The difference in potentiality exponentiated when an equal amount of bioactive factors are seeded and AD-MSCs demonstrated inferior regenerative potential to differentiate into bone and cartilage when compared with BM-MSCs[12]. However, Jeyaraman *et al*[13] demonstrated the efficacy, safety, and superiority of AD-MSCs transplantation when compared to BM-MSCs in OA knee management. With the conflicting evidence in literature[14-16], we aim to critically analyze the clinical efficacy and patient safety in the use of BM-MSCs and AD-MSCs in the management of OA of the knee.

MATERIALS AND METHODS

We conducted this meta-analysis in accordance with the guidelines from the Back Review Group of Cochrane Collaboration[17] and we followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[18].

Search strategy

We conducted an independent and duplicate electronic literature search for studies evaluating the ideal source of MSC therapy for knee OA. The literature databased searched the relevant studies include: PubMed, EMBASE, Web of Science, Reference Citation Analysis, and the Cochrane Library up to August 2021. We did not apply any language or date restrictions to the search query. We used the following keywords in the search strategy "Knee Osteoarthritis", "Knee Degeneration", "Stem Cell Therapy" and "Mesenchymal Stromal Cells", "Bone marrow", "Adipose". We have presented a sample search strategy utilized for retrieving the relevant studies from one of the included databases in Supplementary Table 1. Apart from the above databases, we also searched to identify studies not identified in the primary search from the reference list of potential articles shortlisted. Based on the criteria identified as a priori for inclusion and exclusion of studies, eligible studies were identified and included for meta-analysis. In case of discrepancy among the reviewers in study selection, discussion was made until a consensus was obtained. PRISMA flow diagram of the selection of the studies included in the analysis is given in Figure 1.

Inclusion criteria

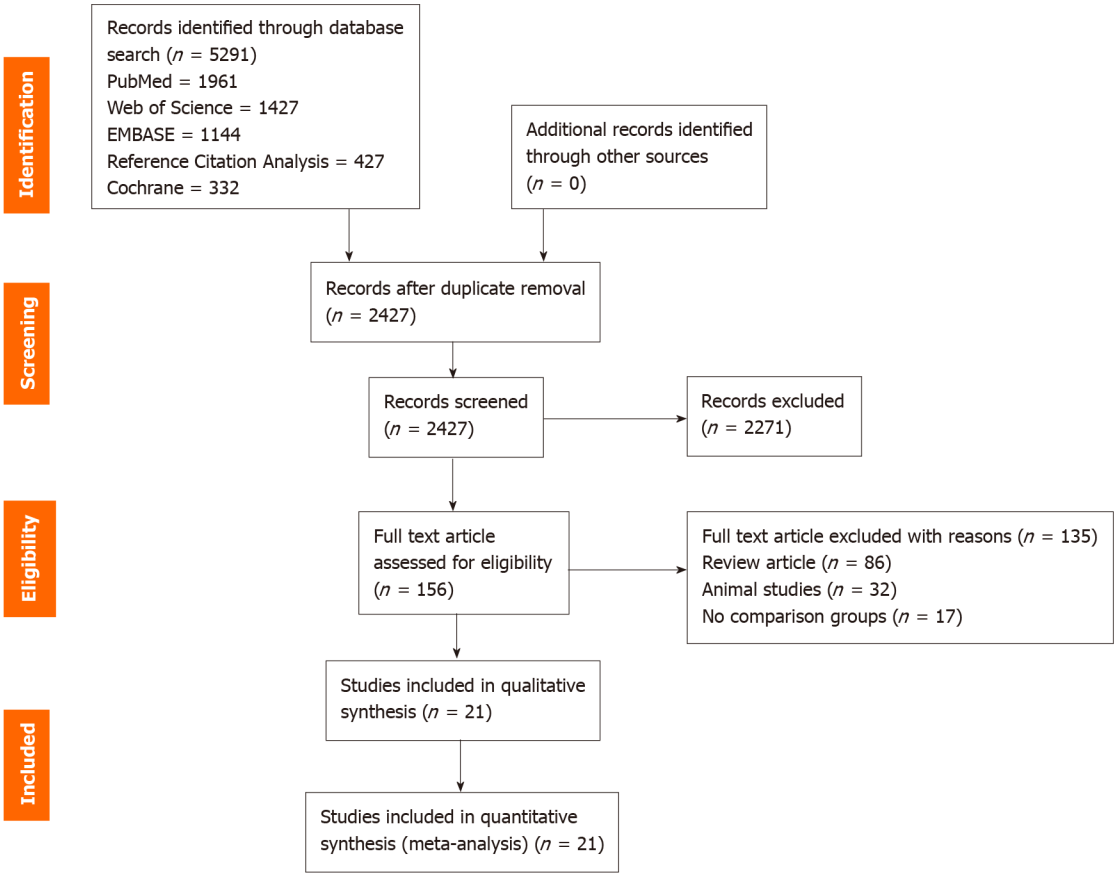
Studies were included for quantitative review if they met the following PICOS criteria: Population: Patients with OA of knee. Intervention: AD-MSC therapy. Comparator: BM-MSC therapy. Outcomes: Visual analog score (VAS) for Pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm Knee Scale (Lysholm), Magnetic resonance observation of cartilage repair tissue (MOCART) Score, knee osteoarthritis outcome score (KOOS), Tegner Activity Score (TAS) and reported adverse events. Study design: Randomized controlled trials.

Exclusion criteria

We excluded studies from analysis if they were of the following characteristics: (1) *In-vitro* studies involving stem cell therapy; (2) Studies of observational nature and interventional studies without appropriate comparison group; (3) Studies conduction animal models of knee OA investigating stem cell therapy; and (4) Review articles and *in-vitro* studies involving stem cell therapy.

Data extraction

We made an independent and duplication extraction of the following data from the included studies: (1) Study characteristics: Name of the author, publication year, country, total number of patients enrolled in



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Figure 1 PRISMA flow diagram of the included studies.

the study and level of evidence of the study; (2) Baseline characteristics: Age (mean with standard deviations), gender proportions of the individual groups, Kellgren Lawrence grades of OA, type of MSC source used in them, protocol of intervention utilised for both the groups, mean duration of follow-up of the study population and parameters used for assessment of clinical measures. We grouped studies utilizing BM based therapies involving BM concentrates and isolated expanded BM-MSCs into one group and another group involving studies using stromal vascular fraction (SVF) and isolated expanded AD-MSCs; (3) Efficacy outcomes: Pain outcomes using VAS, functional outcomes using WOMAC score, Lysholm score, KOOS, TAS, and radiological outcomes like MOCART score; (4) Safety outcomes: Reported adverse events; and (5) In case of any disagreement in data collection, discussion was made until a consensus was attained.

Risk of bias and quality assessment

We performed an independent and duplicate analysis of the methodological quality of the included studies by two reviewers based on the ROB2 tool of Cochrane Collaboration for randomized studies. The tool has five domains of bias assessment including randomization process followed in the studies, bias in application of the intended intervention, bias in the presentation of the study outcome data, bias in the measurement of measured outcome, and bias in reporting of results of the study[19].

Statistical analysis

We performed the analysis in the R platform using OpenMeta(Analyst) software[20]. We used risk ratio (RR) with 95% confidence interval (CI) for analysing dichotomous variable outcomes and weighted mean difference (WMD) with 95%CI for continuous variable outcomes. We analysed the heterogeneity observed in the results analysed using the I^2 test [21]. We used fixed-effects model to evaluate the outcomes if the value of $I^2 < 50\%$ and $P > 0.1$. We used random-effects model if the value of $I^2 > 50\%$ and $P < 0.1$. We considered a P-value < 0.05 to be significant. We performed sensitivity analyses in case of heterogeneity among the reported results from the studies included for analysis. We used Funnel plot, Egger regression test, and normal quantile plot to analyse the publication bias for the outcomes in the included studies.

RESULTS

Search results

Our initial electronic database screening yielded 4864 articles, which upon removal of the duplicate articles resulted in 2427 articles. We then performed title and abstract screening and shortlisted 156 eligible articles and excluded 2271 articles. We made a full-text review of the 156 articles qualified articles and excluded 135 of them for the reasons listed in the PRISMA flow diagram for study selection (Figure 1). Among the included studies, we found only one study by Estrada *et al*[22] to make a direct comparison of the adipose tissue and BM as a source of MSC and found no significant difference among the groups compared despite observing a significant improvement from the baseline. The study had a selective allocation of the subjects based on the stage of the disease and utilized adipose tissue-based cellular therapy for high-grade disease and BM-based therapy for intermediate grade disease and platelet-based therapy for early disease. To objectively evaluate the results of the study across all the grades of disease, we pooled the results of all the included studies of both sources and made a combined comparative quantitative analysis of all 21 included studies[22-42] with 936 patients. 9/21 studies[22,26,27,29,31,36-40] utilized MSC of adipogenic origin, of which 1 study utilized AD-MSC of allogenic source while rest 8 studies utilized AD-MSCs of autogenous source. 12/21 studies[22-25,28,30,32-35,41,42] utilized MSC of BM origin, of which 2 studies utilized BM-MSCs of allogenic sources, and the rest 10 studies utilized autogenous sources of BM-MSC. We did not note a standardised utilization of the dose of the MSCs transplanted in the included studies. We did not note uniformity among the included studies for the measures of outcomes assessment employed. We presented the general characteristics of the included studies in Table 1. The protocol of intervention used in the case and control groups along with the measures of outcome assessment were given in Table 2.

Quality assessment

We utilised RoB2 tool for the evaluation of the methodological quality of the included studies and presented in Figure 2. We did not note the included studies to have high risk of bias to warrant exclusion from the analysis.

Efficacy outcomes

Visual analog scale for pain: We analysed 7 studies[16,17,21,26-28,30], 5 studies[26,27,31,36,40], and 1 study[39] reporting the VAS outcome at 6, 12, and 24 mo respectively using adipose tissue as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant reduction in VAS score was noted compared to their controls at 6 mo [WMD = -13.414, 95%CI: (-24.175)-(-2.653), P < 0.015; Figure 3A], 12 mo [WMD = -21.498, 95%CI: (-33.819)-(-9.177), P < 0.001; Figure 3B), and 24 mo [WMD = -6.000, 95%CI: (-9.079)-(-2.921), P < 0.05; Figure 3C] compared to their controls as shown in Figure 3. Similarly, we analysed 5 studies[24,25,28,32,33], 4 studies[23,24,28,33], and 1 study[24] reporting the VAS outcome at 6, 12, and 24 mo respectively using BM as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant reduction in VAS score was noted compared to their controls at 6 mo [WMD = -11.028, 95%CI: (-19.605)-(-2.450), P < 0.012; Figure 3A), and 24 mo [WMD = -17.589, 95%CI: (-22.486)-(-12.692), P < 0.001; Figure 3C), with a drop in the pain control at 12 mo [WMD = -2.366, 95%CI: (-9.912)-5.180, P = 0.539; Figure 3B], period compared to their controls.

On critical analysis of the pain reduction potential of both the sources, it is noted as shown in Figure 4 that despite the inconsistency in the pain reduction at 12 mo with BM, we noted a rising trend curve in pain reduction which favors the therapy. Although both the sources were capable of significant pain reduction compared to their controls, adipose tissue demonstrated consistent results across all the time points. However, the inconsistencies in the results of BM could also be accounted to the heterogeneity in the studies included for analysis.

WOMAC score: We analyzed 6 studies[27,31,36,37,39,40], and 6 studies[27,31,36-39] reporting the WOMAC scores at 6, and 12 mo respectively using adipose tissue as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant reduction in WOMAC scores were noted compared to their controls at 6 mo [WMD = -21.317, 95%CI: (-27.146)-(-15.488), P < 0.001; Figure 3D], and 12 mo [WMD = -19.341, 95%CI: (-30.544)-(-8.138), P < 0.001; Figure 3E] compared to their controls as shown in Figure 3. Similarly, we analyzed 7 studies[24,25,28,32-35], and 6 studies[24,25,28,33-35] reporting the WOMAC outcome at 6, and 12 mo respectively using BM as the source of MSCs. There was a significant heterogeneity observed between the included studies (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, we did not note any significant reduction in WOMAC scores compared to their controls at 6 mo [WMD = -1.958, 95%CI: (-10.273)- 6.357, P = 0.644; Figure 3D], and 12 mo [WMD = -1.944, 95%CI: (-8.183)-4.294, P = 0.541; Figure 3E] compared to their controls.

Table 1 Characteristics of included studies

Sl. No	Ref.	Country	Nature of study	Kellgren Lawrence Grade	Sample size	Treatment/ control	Mean age (SD)		Male/female		MSC type	MSC source	Follow-up (mo)
							Treatment group	Control group	Treatment group	Control group			
1	Vega *et al*[23], 2015	Spain	RCT	II, III, IV	30	15/15	56.6 ± 9.24	57.3 ± 9.09	06/09	05/10	BM	Allo	12
2	Vangsness *et al*[24], 2014	United States	RCT	NR	55	36/19	44.6 ± 9.82	47.8 ± 8	25/11	13/06	BM	Allo	24
3	Garay-Mendoza *et al*[25], 2018	Mexico	RCT	NR	61	30/31	55.57 ± 12.02	59.32 ± 10.85	07/23	09/22	BM	Auto	6
4	Kuah *et al*[26], 2018	Australia	RCT	I, II, III	20	16/4	50.8 ± 7.29	55.0 ± 10.42	11/05	01/03	AD	Allo	12
5	Estrada *et al*[22], 2020	Argentina	RCT	I, II, III	89	60/29	61 ± 12	61 ± 12	NR	NR	BM / AD	Auto	12
6	Freitag *et al*[27], 2019	Australia	RCT	II, III	30	20/10	54.6 ± 6.3	51.5 ± 6.1	11/09	01/09	AD	Auto	12
7	Ruane *et al*[41], 2021	United States	RCT	I, II, III	32	17/15	58.06 ± 9.14	58.6 ± 8.05	09/08	10/05	BM	Auto	12
8	Lamo-Espinosa *et al*[28], 2016	Spain	RCT	II, III, IV	30	20/10	65.9	60.3	12/08	07/03	BM	Auto	12
9	Garza *et al*[29], 2020	United States	RCT	II, III	39	26/13	60.5 ± 7.9	57.1 ± 9.1	15/11	7/6	AD	Auto	12
10	Wong *et al*[30], 2013	Singapore	RCT	NR	56	28/28	53	49	15/13	14/14	BM	Auto	24
11	Lu *et al*[31], 2019	China	RCT	I, II, III	53	27/26	55.03 ± 9.19	59.64 ± 5.97	03/24	03/23	AD	Auto	12
12	Lv *et al*[42], 2015	Huang	RCT	I, II	80	40/40	55.9 ± 8.1	55.1 ± 6.8	14/26	13/27	BM	Auto	12
13	Emadedin *et al*[32], 2018	Iran	RCT	II, III, IV	43	19/24	51.7 ± 9.2	54.7 ± 5.3	12/07	15/09	BM	Auto	6
14	Gupta *et al*[33], 2016	India	RCT	II, III	60	40/20	58.10 ± 8.23	54.90 ± 8.27	12/28	4/16	BM	Allo	12
15	Bastos *et al*[34], 2020	Brazil	RCT	I, II, III, IV	47	30/17	55.7 ± 7.8	55.9 ± 13.4	15/15	09/08	BM	Auto	12
16	Wakitani *et al*[35], 2002	Japan		I, II	24	12/12	NR	NR	NR	NR	BM	Auto	16
17	Tran *et al*[36], 2019	Taiwan	RCT	II, III	33	15/18	58.2 ± 5.70	59.0 ± 6.04	03/12	05/13	AD	Auto	24
18	Lee *et al*[37], 2019	South Korea	RCT	II, III, IV	24	12/12	62.2 ± 6.5	63.2 ± 4.2	03/09	03/09	AD	Auto	6
19	Koh *et al*[38], 2012	South Korea	RCT	IV	50	25/25	54.2 ± 9.3	54.4 ± 11.3	08/17	08/17	AD	Auto	16
20	Koh *et al*[39], 2014	South Korea	RCT	I, II, III	44	23/21	52.3 ± 4.9	54.2 ± 2.9	06/17	05/16	AD	Auto	24
21	Hong *et al*[40], 2019	China	RCT	II, III	32	16/16	51 ± 5.95	53 ± 10.97	03/13	03/13	AD	Auto	12

AD: Adipose derived; Allo: Allogenic; Auto: Autologous; BM: Bone marrow; MSC: Mesenchymal stem cell; NR: Not reported; RCT: Randomized controlled trial; SD: Standard deviation.

On critical analysis of the WOMAC score reduction potential of both the sources, it is noted as shown in Figure 3 that most of the studies that utilized BM did not report any significant improvement compared to their controls, despite their heterogeneity in results at both 6 mo and 12 mo. Since the WOMAC score concentrates more on the functional efficiency of the intervention apart from pain reduction, adipose tissue stands superior to BM as a dependable source of MSC to give better functional results consistently across both time points.

Lysholm knee score: We analyzed 3 studies[36,36,38], and one study[39] reporting the lysholm score at 12, and 24 mo respectively using adipose tissue as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant improvement in scores was noted compared to their controls at 12 mo (WMD = 6.494, 95%CI: 1.889-11.100, P = 0.006; Figure 3F). However, at 24 mo, the improvement in scores was not sustained [WMD = 4.100, 95%CI: (-4.757)-12.9557, P = 0.757; Figure 3G] compared to their controls as shown in Figure 3. Similarly, we analyzed 3 studies[22, 24,30], and 2 studies[24,30] reporting Lysholm scores outcome at 12 and 24 mo respectively using BM as the source of MSCs. There was a significant heterogeneity observed between the included studies. (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, we did not note any significant improvement in Lysholm score compared to their controls at both 12 mo [WMD = 0.232, 95%CI: (-5.133)-5.597, P = 0.933; Figure 3F], and 24 mo [WMD = 4.412, 95%CI: (-0.801)-9.626, P = 0.097; Figure 3G] respectively. On critical analysis of the improvement of the Lysholm score of both the sources, it is noted only in studies utilizing adipose tissue as the source of MSC significant improvement in the functional outcomes is noted which is in corroboration with the WOMAC score results.

KOOS & MOCART Score

We analyzed the quality of life outcomes such as KOOS reported in 3 studies[22,27,39] using adipose tissue and 3 studies[22,34,41] utilizing BM as the source of MSCs. There was a significant heterogeneity observed between the included studies (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis across all time points. On analysis, significant improvement in scores was noted in both adipose tissue (WMD = 13.124, 95%CI: 4.745-21.502, P = 0.002; Figure 3H) and BM (WMD = 2.642, 95%CI: 0.587-4.698, P = 0.012; Figure 3H) as the sources compared to their controls, despite the inconsistencies noted earlier in the functional outcomes such as WOMAC or Lysholm scores.

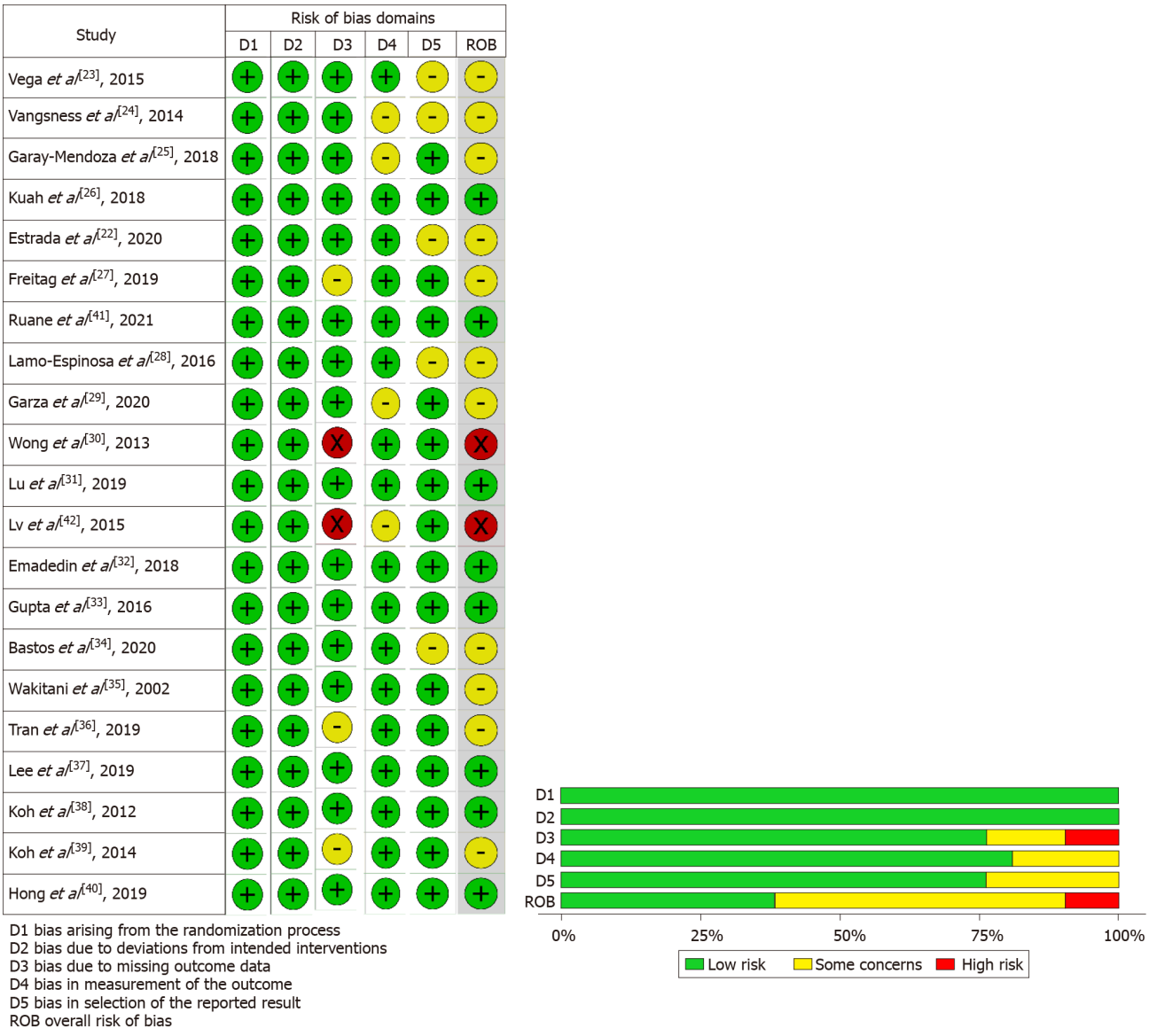
Similarly, we analyzed 2 studies that objectively analyzed the regenerate cartilage tissue using magnetic resonance imaging with MOCART score between the two sources[30,40]. There was a significant heterogeneity observed between the included studies (I^2 > 80%, P < 0.001). Hence, the random-effects model was used for analysis. We noted significant improvement in the MOCART scores at 12 mo in both the sources (WMD = 31.625, 95%CI: 7.481-55.769, P = 0.010; Figure 3I) compared to their controls. As shown in Figure 3, although both the sources had significantly improved KOOS and MOCART scores at 12 mo, the improvement noted with adipose tissues stands relatively high compared to the BM.

Table 2 Stem cell transplantation protocol of the included studies

Ref.	MSC type	MSC source	MSC preparation	MSC count (10^7 cells)	Treatment group intervention	Control group intervention	Outcome measures
Vega *et al*[23], 2015	BM	Allo	CE-BMMSC	4	sIA injection of MSC	sIA Injection of 60 mg HA	VAS, WOMAC
Vangsness *et al* [24], 2014	BM	Allo	CE-BMMSC	5/15	sIA injection of MSC + 20 mg HA	sIA Injection of 20 mg HA	VAS, Lysholm Score
Garay-Mendoza *et al*[25], 2018	BM	Auto	BMC	NA	600 μg/d G-CSF for 3 consecutive days before the procedure + sIA injection of MSC	Oral acetaminophen, 500 mg every 8 h for 6 mo	VAS, WOMAC
Kuah *et al*[26], 2018	AD	Allo	CE-ADMSC	0.39-0.67	sIA injection of MSC	Placebo sIA injection of cell culture media and cryopreservative	VAS, WOMAC, MRI assessment
Estrada *et al*[22], 2020	AD	Auto	BMC	NA	sIA injection of BM concentrate	sIA injection of PRP	IKDC, Lysholm Score, KOOS
Estrada *et al*[22], 2020	BM	Auto	SVF	NA	sIA injection of lipoaspirate	sIA injection of PRP	
Freitag *et al*[27], 2019	AD	Auto	CE-ADMSC	10	sIA injection of MSC ± 2 nd injection at 6 mo	Conservative management	VAS, WOMAC, KOOS, MRI assessment
Ruane *et al*[41], 2021	BM	Auto	BMC	NA	sIA injection of BM concentrate + PRP	Gel-One® Cross-Linked hyaluronate injection	VAS, KOOS
Lamo-Espinosa *et al*[28], 2016	BM	Auto	CE-BMMSC	1	sIA injection of MSC + 60 mg HA	sIA injection of 60 mg HA	VAS, WOMAC, MRI assessment
Garza *et al*[29], 2020	AD	Auto	SVF	NA	sIA injection of MSC	Placebo injection without cells	WOMAC, MRI assessment
Wong *et al*[30], 2013	BM	Auto	CE-BMMSC	1.46	HTO + microfracture + sIA injection of MSC + 20 mg HA	HTO + microfracture + sIA injection of 20 mg HA	Tegner Score, Lysholm Score
Lu *et al*[31], 2019	AD	Auto	CE-ADMSC	5	2 IA injection of MSC at 0, 3 wk and sham injection at 1, 2 wk	4 IA injection of 25 mg HA at 0, 1, 2, 3 wk	VAS, WOMAC
Lv *et al*[42], 2015	BM	Auto	CE-BMMSC	3.82	3 × monthly IA injection of MSC + 20 mg HA	sIA injection of 20 mg HA	Tegner Score, Lysholm Score
Emadedin *et al* [32], 2018	BM	Auto	CE-BMMSC	4	sIA injection of MSC	Placebo sIA injection of normal saline	VAS, WOMAC
Gupta *et al*[33], 2016	BM	Allo	CE-BMMSC	2.5-15	sIA injection of MSC + 20 mg HA	Placebo sIA injection of 20 mg HA	VAS, WOMAC, MRI assessment
Bastos *et al*[34], 2020	BM	Auto	CE-BMMSC	4	sIA injection of MSC in 10 mL of PRP	sIA injection of 4 mg dexamethasone	KOOS, MRI assessment
Wakitani *et al* [35], 2002	BM	Auto	CE-BMMSC	1	HTO + microfracture + sIA injection of MSC	HTO + microfracture + placebo injection	MRI assessment, HSS knee rating scale
Tran *et al*[36], 2019	AD	Auto	SVF	NA	Arthroscopic micro fracture + sIA injection of MSC	Arthroscopic micro fracture	WOMAC, MRI assessment
Lee *et al*[37], 2019	AD	Auto	CE-ADMSC	10	sIA injection of MSC	Placebo injection with normal saline	WOMAC, MRI assessment
Koh *et al*[38], 2012	AD	Auto	SVF	0.189	Arthroscopic debridement + sIA injection of MSC + PRP	Arthroscopic debridement + PRP	VAS, Tegner Score, Lysholm Score
Koh *et al*[39], 2014	AD	Auto	CE-ADMSC	0.411	HTO + sIA injection of MSC + PRP	HTO + PRP	VAS, Lysholm Score
Hong *et al*[40], 2019	AD	Auto	SVF	0.745	sIA injection of MSC	sIA injection of 40 mg HA	VAS, WOMAC, MRI assessment

AD: Adipose derived; Allo: Allogenic; Auto: Autologous; BM: Bone marrow; BMC: Bone marrow concentrate; CE-ADMSC: Culture expanded adipose

derived mesenchymal stem cell; CE-BMMSC: Culture expanded bone marrow mesenchymal stem cell; HA: Hyaluronic acid; HSS: Hospital for special surgeries; HTO: High tibial osteotomy; IA: Intra-articular; IKDC: International Knee Documentation Committee; KOOS: Knee Osteoarthritis Outcome Score; PRP: Platelet rich plasma; MRI: Magnetic resonance imaging; MSC: Mesenchymal stem cell; sIA: Single intra-articular; SVF: Stromal vascular fraction; VAS: Visual analog score; WOMAC: Western Ontario Mc-Master Universities Osteoarthritis index.



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Figure 2 Methodological quality and risk of bias assessment of all the included studies.

Safety

Seven studies involving 141 patients reported adverse effects with low heterogeneity among the included studies using adipose tissue as the source of MSC for knee OA. (I^2 = 0.0%, P = 0.968). Hence, a fixed-effects model was used for analysis. There was no significant increase in the adverse events compared to the controls (RR = 1.081, 95%CI: 0.754-1.549, P = 0.673; Figure 5).

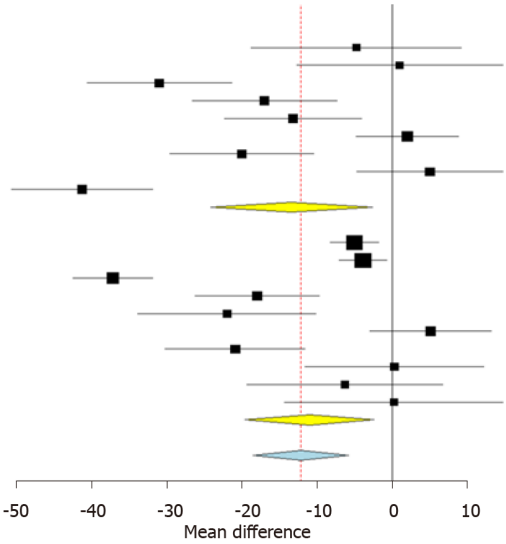
Seven studies involving 180 patients reported adverse effects with low heterogeneity among the included studies with AD-MSC (I^2 = 0.0%, P = 0.996). Hence, a fixed-effects model was used for analysis. There was no significant increase in the adverse events compared to the controls (RR = 1.072, 95%CI: 0.440-2.612, P = 0.876; Figure 5). No major serious adverse events with permanent effects such as death, tumor, or immune reaction to the intervention were noted during follow-up in either of the sources of MSCs.

Sensitivity analysis

We conducted sensitivity analysis whenever heterogeneity was noted in the outcomes analysed. The

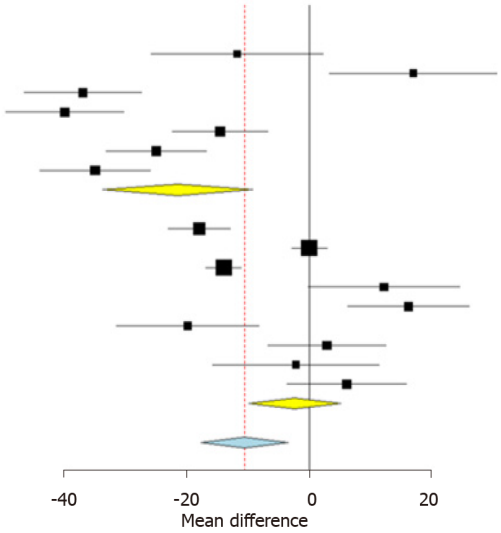
A

Study	Estimate (95%CI)
Kuah *et al*[26], 2018	-4.800 (-18.822, 9.222)
Kuah *et al*[26], 2018	1.000 (-12.696, 14.696)
Freitag *et al*[27], 2019	-31.000 (-40.642, -21.358)
Freitag *et al*[27], 2019	-17.000 (-40.642, -21.358)
Lu *et al*[31], 2019	-13.200 (-22.361, -4.039)
Tran *et al*[36], 2019	2.000 (-4.852, 8.852)
Lee *et al*[37], 2019	-20.000 (-29.602, -10.398)
Koh *et al*[38], 2012	5.000 (-4.705, 14.705)
Hong *et al*[40], 2019	-41.300 (-50.712, -31.888)
Subgroup adipose (I^2 = 90.89 %, P = 0.000)	-13.414 (-24.175, -2.653)
Vangsness *et al*[24], 2014	-5.000 (-8.223, -1.777)
Vangsness *et al*[24], 2014	-3.900 (-7.123, -0.677)
Garay-Mendoza *et al*[25], 2018	-37.200 (-42.518, -31.882)
Lamo-Espinosa *et al*[28], 2016	-18.000 (-26.269, -9.731)
Lamo-Espinosa *et al*[28], 2016	-22.000 (-33.841, -10.159)
Emadedin *et al*[32], 2018	5.100 (-2.996, 13.196)
Gupta *et al*[33], 2016	-20.900 (-30.218, -11.582)
Gupta *et al*[33], 2016	0.300 (-11.606, 12.206)
Gupta *et al*[33], 2016	-6.300 (-19.316, 6.716)
Gupta *et al*[33], 2016	0.200 (-14.309, 14. 709)
Subgroup bone marrow (I^2 = 94.17%, P = 0.000)	-11.028 (-19.605, -2.450)
Overall (I^2 = 92.68%, P = 0.000)	-12.160 (-18.539, -5.780)



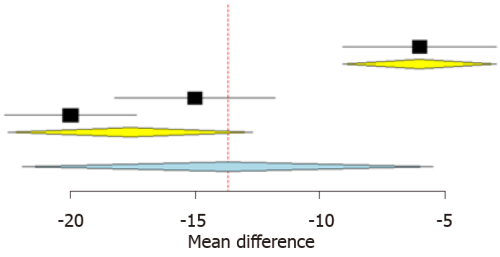
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Study	Estimate (95%CI)
Kuah *et al*[26], 2018	-11.800 (-25.822, 2.222)
Kuah *et al*[26], 2018	17.000 (3.304, 30.696)
Freitag *et al*[27], 2019	-37.000 (-46.642, -27.358)
Freitag *et al*[27], 2019	-40.000 (-49.642, -30.358)
Lu *et al*[31], 2019	-14.600 (-22.419, -6.781)
Tran *et al*[36], 2019	-25.000 (-33.223, -16.777)
Hong *et al*[40], 2019	-35.300 (-44.035, -25.965)
Subgroup adipose (I^2 = 90.93 %, P = 0.000)	-21.498 (-33.819, -9.177)
Vega *et al*[23], 2015	-18.000 (-23.061, -12.939)
Vangsness *et al*[24], 2014	-0.000 (-2.910, 2.910)
Vangsness *et al*[24], 2014	-14.000 (-16.910, -11.090)
Lamo-Espinosa *et al*[28], 2016	-12.200 (-0.218, -24.618)
Lamo-Espinosa *et al*[28], 2016	16.200 (6.255, 26.145)
Gupta *et al*[33], 2016	-19.900 (-31.528, -8.272)
Gupta *et al*[33], 2016	2.900 (-6.762, 12.562)
Gupta *et al*[33], 2016	-2.200 (-15.807, 11.407)
Gupta *et al*[33], 2016	6.100 (-3.680, 15.880)
Subgroup bone marrow (I^2 = 92.64%, P = 0.000)	-2.366 (-9.912, 5.180)
Overall (I^2 = 93.96%, P = 0.000)	-10.556 (-17.690, -3.422)



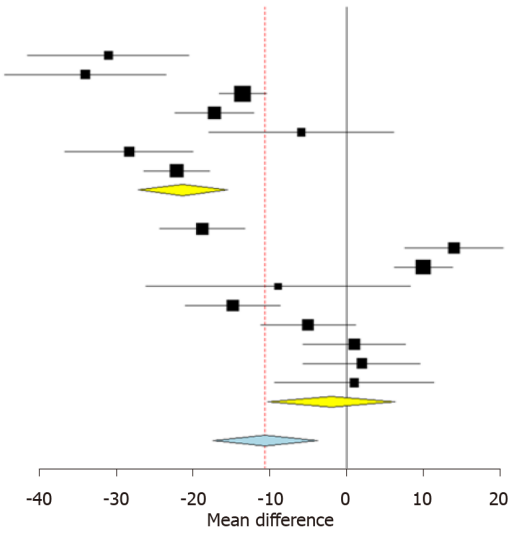
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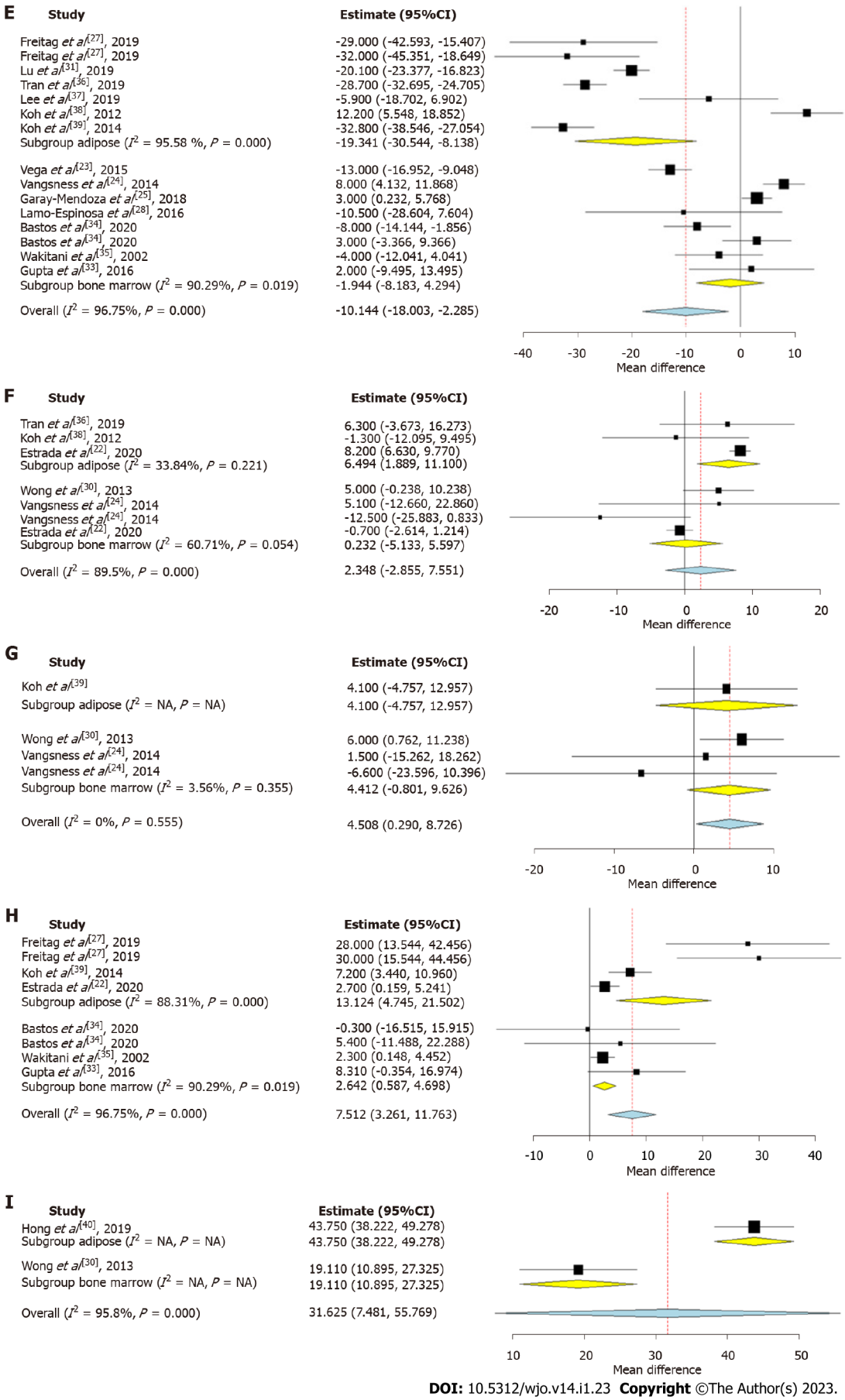
Study	Estimate (95%CI)
Koh *et al*[39], 2014	-6.000 (-9.079, -2.921)
Subgroup adipose (I^2 = NA, P = NA)	-6.000 (-9.079, -2.921)
Vangsness *et al*[24], 2014	-15.000 (-18.223, -11.777)
Vangsness *et al*[24], 2014	-20.000 (-22.641, 17.359)
Subgroup bone marrow (I^2 = 81.92%, P = 0.019)	-17.589 (-22.486, -12.692)
Overall (I^2 = 95.65%, P = 0.000)	-13.691 (-21.921, -5.461)



D

Study	Estimate (95%CI)
Freitag *et al*[27], 2019	-31.000 (-41.518, -20.482)
Freitag *et al*[27], 2019	-34.000 (-44.518, -23.482)
Lu *et al*[31], 2019	-13.500 (-16.555, -10.445)
Tran *et al*[36], 2019	-17.200 (-22.319, -12.081)
Lee *et al*[37], 2019	-5.880 (-17.909, 6.149)
Koh *et al*[38], 2012	-28.300 (-36.615, -19.985)
Hong *et al*[40], 2019	-22.100 (-26.356, -17.844)
Subgroup adipose (I^2 = 83.57 %, P = 0.000)	-21.317 (-27.146, -15.488)
Lv *et al*[42], 2015	-18.770 (-24.275, -13.265)
Vangsness *et al*[24], 2014	14.000 (7.625, 20.375)
Garay-Mendoza *et al*[25], 2018	10.000 (6.223, 13.777)
Lamo-Espinosa *et al*[28], 2016	-8.900 (-26.155, 8.355)
Emadedin *et al*[32], 2018	-14.800 (-20.974, -8.626)
Bastos *et al*[34], 2020	-5.000 (-11.161, 1.161)
Bastos *et al*[34], 2020	1.000 (-5.695, 7.695)
Wakitani *et al*[35], 2002	2.000 (-5.612, 9.612)
Gupta *et al*[33], 2016	1.000 (-9.390, 11.390)
Subgroup bone marrow (I^2 = 93.11%, P = 0.019)	-1.958 (-10.273, 6.357)
Overall (I^2 = 94.97%, P = 0.000)	-10.577 (-17.392, -3.763)





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Figure 3 Forest plot of the included studies comparing adipose tissue and bone marrow as a source of mesenchymal stromal cell therapy compared to their controls. A: Visual analog scale (VAS) at 6 mo; B: VAS at 12 mo; C: VAS at 24 mo; D: Western Ontario McMaster Universities

Osteoarthritis Index (WOMAC) at 6 mo; E: WOMAC at 12 mo; F: Lysholm at 12 mo; G: Lysholm at 24 mo; H: Knee osteoarthritis outcome score at 12 mo; I: Magnetic resonance observation of cartilage repair tissue score at 12 mo. CI: Confidence interval; NA: Not available.

results of the outcomes analysed such as VAS for pain, WOMAC, Lysholm, KOOS, MOCART, and adverse events were not significantly altered by sequentially omitting each study in the meta-analysis. We also did not note a change in the consistency of the results for the outcomes analysed upon changing the analysis to the random-effects model.

Publications bias

Publication bias was analyzed utilizing the funnel plot, normal quantile plot, and Egger's regression test for the meta-analysis performed. There was no evidence of publication bias by funnel plot and normal quantile plot as shown in Figure 6 or by Egger's regression test (P = 0.519). We noted symmetrical distribution of studies in the funnel plot and studies were found to lie close to the 95%CI and no significant heterogeneity was noted in the distribution of the studies about the axes, suggestive of minimal publication bias.

DISCUSSION

In the era of regenerative medicine, MSCs serve the ideal cell-based resort for treating cartilage disorders and provide a platform for regeneration. Various animal models have demonstrated the safety and efficacy of MSCs in cartilage regeneration. MSCs bridge a gap between pharmacological and surgical management of OA of the knee. MSCs offer a balanced equilibrium between pro-and anti-apoptotic, pro-and anti-inflammatory cytokines, and pro-and anti-angiogenic factors to maintain joint homeostasis which is required for cartilage regeneration. Though the reliability of cellular therapy for OA knee has been tested in various preclinical and clinical trials, they provide the readers with conflicting results in the source of MSCs to be used for cartilage regeneration. In literature, the ideal source of MSCs for cartilage regeneration is still under debate. The chondrogenesis among the available sources of MSCs is demonstrated in all the sources of MSCs. The most ideal chondrogenic MSC is still under question.

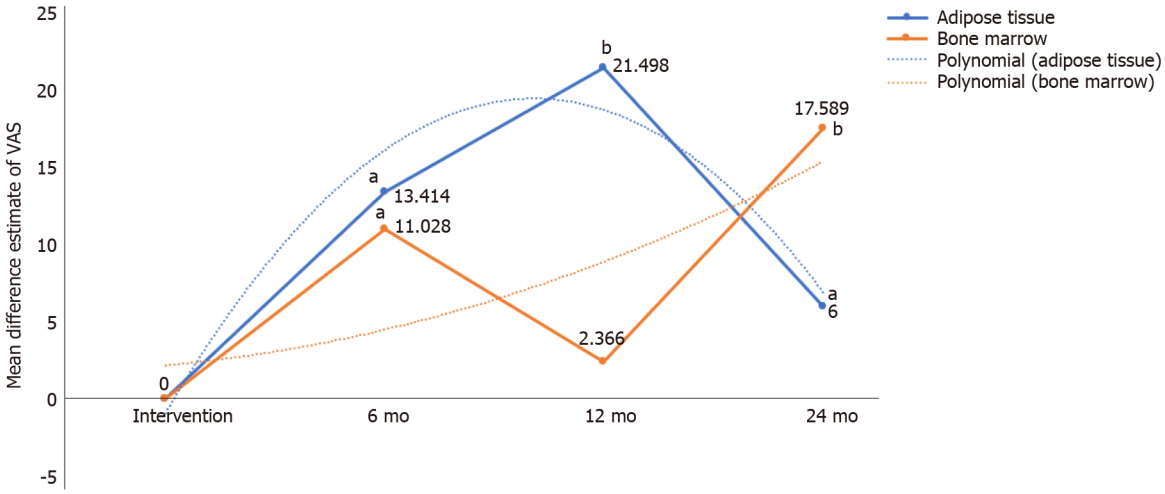
The efficacy of MSC in cartilage regeneration should withstand the biomechanical stress which has to be evaluated according to regulatory guidelines to demonstrate the role of cellular therapy for adoption across an expanding patient population. The reasons behind the less exploration of other sources of MSCs for chondrogenesis are inadequate standardization of isolation protocols to retrieve MSC from that particular source and the strict regulatory guidelines laid by the governing bodies. In this analysis, we tried to analyze whether BM-MSCs or AD-MSCs are the ideal sources for chondrogenesis. Among all the available sources of MSCs, extraction of MSCs from BM and adipose tissue pose minimal morbidity to the donor site while compared with other sources of MSCs. BM-MSC is the most popular source and widely used MSC for osseous and cartilage regeneration. The MSC count in BM appears to be less when compared with the MSC count in adipose tissue. Hence the source of MSC from where it is retrieved plays a major role in cartilage regeneration.

Although Estrada *et al*[22] in their study compared the two sources, they did not randomize the study participants to the interventions analyzed. Instead, they categorized the patients with severe disease to be allotted to adipose-based therapy while mild and moderate diseases to platelet- and BM-based therapy respectively. Hence one cannot objectively compare the efficacy of the two different sources, which necessitated us to undergo a pooled analysis of the studies using adipose tissue and BM as the source of MSCs in the management of knee OA and compared their results using minimum clinical importance difference (MCID) for the parameter concerned.

Main finding

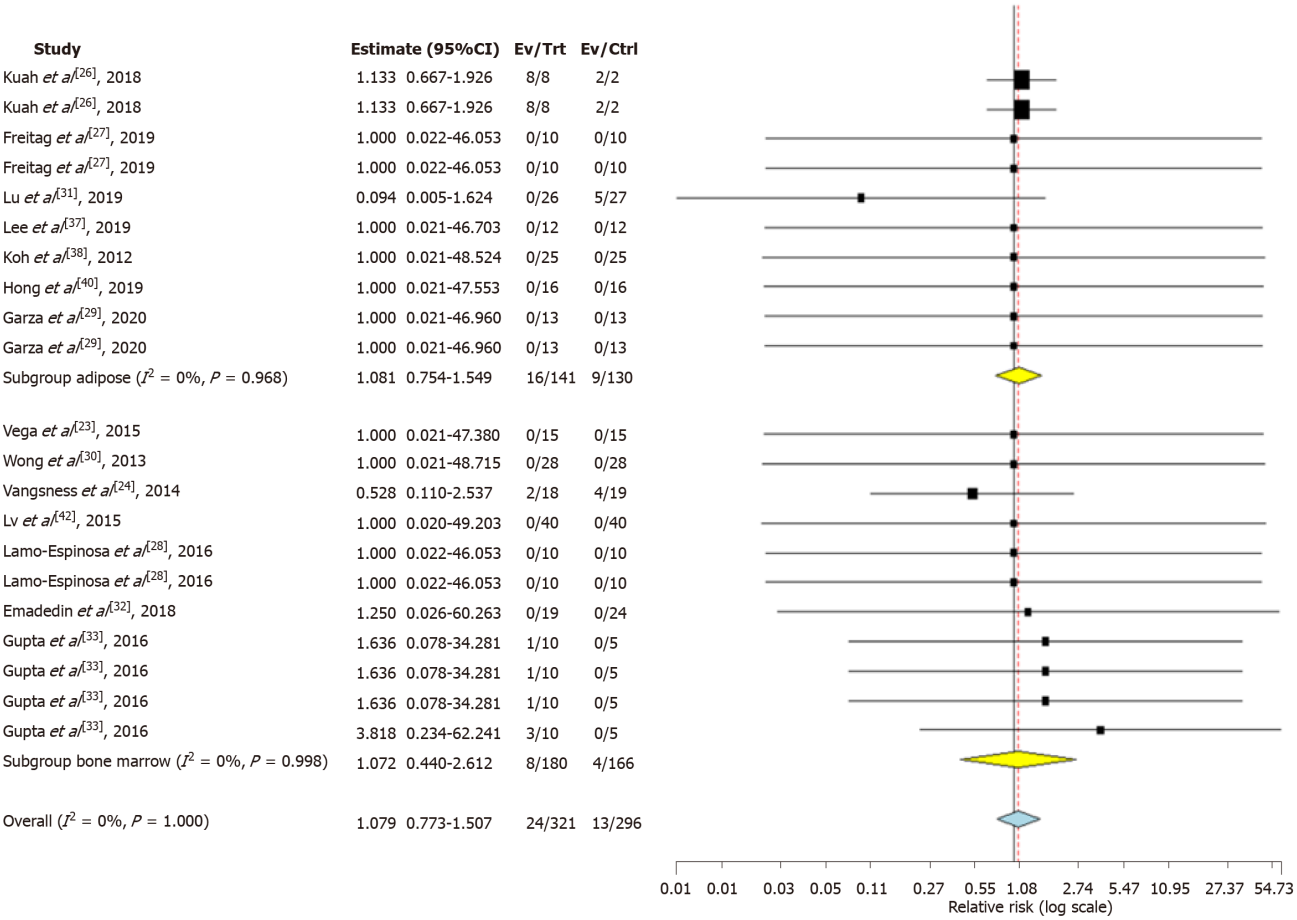
We comprehensively and critically reviewed all available literature to identify the ideal source of MSCs for knee OA and found that: AD-MSCs showed a statistically significant and consistent improvement in all functional outcome measures, such as the VAS score for pain, WOMAC, Lysholm, KOOS, and radiological outcome parameters such as MOCART at varied time intervals compared to their corresponding controls. In contrast, despite better improvement in the VAS score for pain in the long term (24 mo), BM, as a source of MSCs, did not show functional benefits when evaluated using the WOMAC and Lysholm. However, objective measures of quality of life using KOOS and radiological outcome parameters, such as MOCART, showed significant benefits compared to their corresponding controls.

On comparing the relative improvement in various analyzed parameters, such as the VAS score, WOMAC, Lysholm, KOOS, and MOCART, between the two sources adipose tissue outperformed BM, with the difference in their outcome parameters more than the MCID for the concerned parameter. The MCID used were 15 for VAS score, 10 for WOMAC, 25 for Lysholm, 15 for KOOS[43,44]. There were no significant adverse events with either MSC compared to their controls.



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Figure 4 Pain reduction potential of adipose tissue and bone marrow at various timepoints based on visual analog scale score. [a]*P* < 0.05; [b]*P* < 0.001. VAS: Visual analog scale.

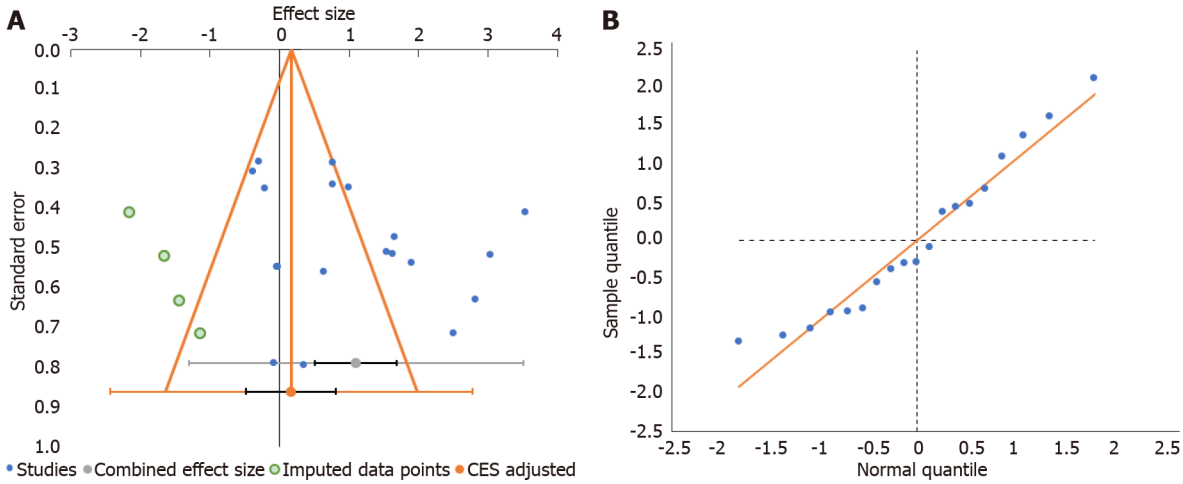


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Figure 5 Forest plot of the included studies comparing adverse events upon using adipose tissue and bone marrow as a source of mesenchymal stromal cell therapy compared to their controls. CI: Confidence interval.

MSC harvest

The source of MSC harvesting is an important factor in stem cell research. Although the BM-MSC harvesting method has been the most commonly used method of MSC harvesting, recent studies have pointed towards AD-MSC owing to their ease of extraction and lack of procedure-related morbidity [45]. Isolation of AD-MSCs from adipose tissue blocks is superior to liposuction[11]. There is a well-



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Figure 6 Publication bias assessment. A: Funnel plot; B: Quantile plot for the visual analog score outcome at 6 mo in the included studies. CES: Combined effect size.

documented procedure for harvesting a larger number of AD-MSCs under local anesthesia with minimal procedure-related patient morbidity[46]. Although there have been reports of fat embolism during AD-MSC harvesting, its incidence is very low. With appropriate techniques and skill, the incidence can be further reduced. The ease of access to fat sources and its minimally invasive approach, unlike access to BM, is sufficient to compel researchers to further explore AD-MSC harvesting techniques.

MSC yield

Pendleton *et al*[46] reported that AD-MSCs had a higher yield than BM-MSCs. Furthermore, a higher seeding density is necessary for the successful growth and expansion of BM-MSCs. Luna *et al*[47] recovered 1×10^6 adipocytes, 1×10^6 ASCs, 1×10^6 vascular endothelial cells, and 1×10^6 other cells from 1 g of adipose tissue. Adipose tissue contains up to 3% stem and progenitor cells in the uncultured SVF, containing 2500 times more stem cells than the BM source[48,49]. SVF mixture, a derivative of adipose tissue, contains 30% MSCs, 3% endothelial cells, and 14% endothelial precursor cells[50], whereas BM-MSCs contain 0.001% MSCs, 0.1% endothelial cells, and 2% endothelial precursor cells[51].

AD-MSCs demonstrate a consistently faster proliferation rate across multiple passages[46]. While the proliferation rate of MSCs from both sources was comparable on days 3 and 7, AD-MSCs continued to proliferate significantly up to day 21, and BM-MSCs attained a plateau from day 14. Similarly, significantly higher cellular metabolic activity was noted in AD-MSCs than in BM-MSCs on days 14 and 21, indicating a higher cellular yield of MSCs[46].

MSC differentiation potential

Although AD-MSCs are harvested with minimal morbidity and provide a better yield than BM-MSCs, the ultimate target of these MSCs in orthopedic research is their differentiation potential in chondrogenic and osteogenic lineages. Chondrogenic differentiation at the gene level, determined by real-time quantitative polymerase chain reaction, showed that the expression of the chondrogenic gene aggrecan varied in AD-MSCs and BM-MSCs from different donors. However, overall, the expression was significantly higher in BM-MSCs than in AD-MSCs. There was no remarkable difference in cartilaginous proteoglycan matrix formation between AD-MSCs and BM-MSCs[11]. The expression of Runx2, collagen type I, and alkaline phosphatase increases from day 7 to day 14 in both AD-MSCs and BM-MSCs, with significantly higher expression in BM-MSCs than in AD-MSCs[11].

Despite easier harvest and superior yield from adipose tissue, AD-MSCs fall short in terms of differentiation potential in chondrogenesis or osteogenesis compared to BM-MSCs. Therefore, research to enhance the necessary lineage differentiation characteristics of AD-MSCs is ongoing to reap the full benefits of its abundant availability and ease of harvesting because AD-MSCs have a more grounded immunomodulatory impact than BM-MSCs in altering the pathological milieu of the target site[52-54].

MSC storage

Short- and long-term storage of AD-MSCs was investigated. The storage of AD-MSCs decreases their cellular proliferative capacity over time[55]. Hence, it must be supplemented with 10% human serum or PRP in 0.9% saline solution at 4 °C for the first 2 h and not more than 4 h[56,57]. For long-term storage, AD-MSCs can be stored at -80 °C in liquid nitrogen for up to 6 mo[58,59]. In contrast, BM-MSCs have been stored for more than 10 years without losing their multipotency[60].

Future directives

With the evolution in the understanding of the biology of MSCs, there is a corresponding expanding horizon of their therapeutic possibilities with their properties towards induction of angiogenesis; regulation of immune response and inflammation; modulation of cell differentiation and proliferation; extracellular matrix formation; neuroprotective and neurotrophic effects; and anti-apoptotic, anti-tumor, and anti-microbial activities[61]. Apart from identifying the ideal source of MSCs for a particular scenario, the development of methods to identify their potency is needed for objective assessment of the individual MSCs concerned to account for individual variability, which might affect the therapeutic response[62]. The future of MSC-based therapies is driving towards a cell-free secretome-based therapy using MSC-derived exosomal vesicles that exert the necessary functional activities of MSCs, where the ideal required cellular characteristics of MSCs from multiple sources could be combined to obtain the maximum benefits of the individual MSC source[63].

Limitations

Our study had certain limitations. First, we could not find data on the blinding of the intervention to the participants in most of the included studies, which could invite room for bias on the part of patients or observers. Second, we noted heterogeneity among the majority of the analyzed outcomes, which could be due to the variability in the protocols followed for intervention in the included studies, as shown in Table 2. The heterogeneity could also be attributed to the inclusion of patients with a different spectrum of disease processes or difference in the control interventions utilized across the included studies. Therefore, we recommend a large multicenter trial with a standardized dosage and intervention protocol, evaluated using established outcome measures both in the short and long term, without any adjuvant procedures to further confirm our analysis results.

CONCLUSION

Our critical analysis of the literature showed that adipose tissue is superior to BM as a source of MSC because of its safety and consistent efficacy concerning improvement in pain and functional outcomes in managing knee OA. However, future trials of sufficient quality are warranted to validate our findings to arrive at a consensus on the ideal source of MSC for use in cellular therapy for knee OA.

ARTICLE HIGHLIGHTS

Research background

Mesenchymal stromal cell (MSC)-based therapies are being commonly utilized in the context of knee osteoarthritis (OA) with promising results. The commonly used sources of the MSC remain in the bone marrow (BM) and the adipose derived (AD).

Research motivation

Despite the prevalence of the use of MSCs of varying origins in the management of knee OA, the literature is not clear on the ideal source to focus on for future research.

Research objectives

In this study, we aim to compare the efficacy and safety of the two commonly used sources of MSCs namely BM and adipose tissue in the management of knee OA.

Research methods

We conducted a systematic review and meta-analysis of the randomized controlled trials (RCTs) in the literature identified from databases such as PubMed, EMBASE, Web of Science, and Cochrane Library until August 2021 that analyzed the efficacy and safety of AD and BM-MSCs in the management of knee OA. we used outcome parameters such as the visual analog scale (VAS) score for pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Lysholm score, Tegner score, magnetic resonance observation of cartilage repair tissue (MOCART) score, knee osteoarthritis outcome score (KOOS), and adverse events.

Research results

We identified twenty-one studies including 936 patients. Of all the studies included, only one study compared the two MSC sources without patient randomization; hence, the results of all included studies from both sources were pooled, and a comparative critical analysis was performed. At six months, both AD-MSCs and BM-MSCs showed significant VAS improvement (P = 0.015, P = 0.012); this was inconsistent at 1 year for BM-MSCs (P < 0.001, P = 0.539), and AD-MSCs outperformed BM-MSCs

compared to controls in measures such as WOMAC ($P < 0.001$, $P = 0.541$), Lysholm scores ($P = 0.006$; $P = 0.933$), and KOOS ($P = 0.002$; $P = 0.012$). BM-MSC-related procedures caused significant adverse events ($P = 0.003$) compared to AD-MSCs ($P = 0.673$).

Research conclusions

Our study identified adipose tissue to be superior to BM in terms of its safety and consistent efficacy in improving the pain and functional outcome parameters analyzed.

Research perspectives

We suggest for future RCTs be conducted to make a direct comparison of the two sources considering the paucity of the literature identified in this study and also to validate the findings arrived in the study.

FOOTNOTES

Author contributions: Muthu S, Patil SC, Jeyaraman N, and Jeyaraman M involved in the conception and design of the manuscript; Gangadaran P, Rajendran RL, Oh EJ, Khanna M, Chung HY, and Ahn BC contributed to the administrative support; Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, and Khanna M participated in the provision of study materials or patients; Muthu S, Patil SC and Jeyaraman N involved in the collection and assembly of data; Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, Gangadaran P, Chung HY, and Ahn BC analysied and interpreted data; Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, Gangadaran P, Rajendran RL, Oh EJ, Khanna M, Chung HY, and Ahn BC wrote the manuscript writing; Muthu S, Chung HY and Ahn BC are co-corresponding authors of this manuscript; Gangadaran P, Rajendran RL and Chung HY contributed to the funding acquisition; and all authors have read and agreed to the published version of the manuscript.

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MINIREVIEWS

Diagnosis and treatment of chronic osteomyelitis based on nanomaterials

Ming Zeng, Zheng Xu, Zhen-Qi Song, Jie-Xiao Li, Zhong-Wen Tang, Sheng Xiao, Jie Wen

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Abstract

Chronic osteomyelitis is a painful and serious disease caused by infected surgical prostheses or infected fractures. Traditional treatment includes surgical debridement followed by prolonged systemic antibiotics. However, excessive antibiotic use has been inducing rapid emergence of antibiotic-resistant bacteria worldwide. Additionally, it is difficult for antibiotics to penetrate internal sites of infection such as bone, thus limiting their efficacy. New approaches to treat chronic osteomyelitis remain a major challenge for orthopedic surgeons. Luckily, the development of nanotechnology has brought new antimicrobial options with high specificity to infection sites, offering a possible way to address these challenges. Substantial progress has been made in constructing antibacterial nanomaterials for treatment of chronic osteomyelitis. Here, we review some current strategies for treatment of chronic osteomyelitis and their underlying mechanisms.

Key Words: Osteomyelitis; Nanomaterials; Infectious disease; Drug delivery

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Core Tip: Chronic osteomyelitis is a painful and serious disease caused by infected surgical prostheses or infected fractures. Traditional treatment includes surgical debridement followed by prolonged systemic antibiotics treatment. But as antibiotics is difficult to penetrate into the internal infection areas of bone, thus limiting the efficacy of systemic antibiotic therapy, new therapeutic approach to treat this disease remains a major challenge for orthopedic surgeons. Substantial progress has been made in constructing antibacterial nanomaterials for treatment of chronic osteomyelitis. We review some current strategies for treatment of chronic osteomyelitis and their underlying mechanisms.

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INTRODUCTION

Pyogenic osteomyelitis is the inflammation of bone tissue caused by pyogenic bacterial infection, including bone marrow, bone cortex, periosteum, and surrounding soft tissue infections, confined to one site or distributed throughout the body. The infection types are as follows: (1) Blood-borne infection: Pathogenic bacteria are transferred from distant infection foci to the bone tissue through the blood circulation, which is termed as bloodborne osteomyelitis; (2) Post-traumatic infection, also known as post-traumatic osteomyelitis, includes direct contamination of open fractures or bone infection after fracture surgery, especially after internal fixation or prosthesis implantation; and (3) Adjacent infection: Foreign body infection, pressure ulcers, and other adjacent soft tissue infections spread to the bone tissue, ulcers caused by diabetes and arteriosclerosis, and osteomyelitis caused by tissue necrosis. The most common site in children is the metaphysis of the long bones (distal femur and proximal tibia), or penetrating bone injury due to trauma[1-4]. Pyogenic osteomyelitis can be divided into acute and chronic types according to disease progression. It is speculated that the formation of dead bone is asign of chronic osteomyelitis as it appears 6 wk after disease onset[5,6].

OSTEOMYELITIS

Epidemiology of osteomyelitis

The incidence of osteomyelitis has increased with the upgrade of diagnostic technology, increase in prosthetic implants in orthopedic surgery, and increase in diabetes. For example, German researchers conducted statistical analysis of patients with osteomyelitis and found that, compared with 10 years ago, the overall incidence of osteomyelitis rose from 15.5/100000 people/year to 16.7/100000 people/year, an increase of 10.44%; however, this number was higher in developing countries and lower in undeveloped countries[1,7,8]. Kremers *et al*[9] assessed osteomyelitis from January 1969 to December 2009 and found that the total annual incidence of osteomyelitis was 21.8/100000 people/year. Nonetheless, the annual incidence of osteomyelitis was lower in women than in men and the infection rate increased with age. The incidence increased significantly from 11.4/100000 person-years in 1969-1979 to 24.4/100000 person-years in 2000-2009. The rates were stable in children and young adults but almost three times higher in those aged > 60 years, which could be attributed to a large increase in cases of diabetes-related osteomyelitis[10], of which, 44% had *Staphylococcus aureus* (*S. aureus*) infection. Lindbloom *et al*[11] investigated diabetic-foot-related osteomyelitis and found that diabetic foot infection was 36.5 per 1000 people/year, and the incidence of diabetic foot ulcers was 25%. About 20%-68% of diabetic foot ulcers are potentially associated with osteomyelitis. The amputation rate after osteomyelitis in diabetic foot infection is 66%. In one study, diabetes was associated with a 1.6% in-hospital mortality rate for osteomyelitis[12].

Common pathogenic bacteria of osteomyelitis

Among many pathogenic bacteria, *S. aureus* is the most common cause of chronic osteomyelitis[13,14]. However, specific bacterial distribution and drug resistance may vary across some regions due to patterns of use of antibacterial drugs in different areas. Data from southwest China were as follows: 467 cases (92.8%) had antibiotic treatment before admission, 324 cases (64.4%) were positive for culture, and 377 strains of microorganisms were cultivated. *S. aureus* (159 strains) accounted for 42.2%, and 38 strains were methicillin-resistant *S. aureus* (MRSA). There were 49 strains of *Pseudomonas aeruginosa* (*P. aeruginosa*) (13.0%), 35 of *Enterobacter cloacae* (*E. cloacae*) (9.2%), 33 of *Escherichia coli* (*E. coli*) (8.8%), seven of fungi (1.9%), 17 of *Acinetobacter baumannii* (4.5%), and 77 other microorganisms (20.4%)[15]. Jiang *et al*

[16] retrospectively analyzed 394 patients with chronic osteomyelitis of limbs treated in the Nan Fang Hospital from January 2010 to April 2015. The study cohort comprised 307 men and 87 women at a sex ratio of 3.53. The mean age at initial visit of all patients was 42 years. The positive rate of intraoperative culture was 70.63% (214/303), of which a single-strain infection accounted for 78.97% (169/214). Most of the single-strain infections were *S. aureus* (59 cases), while a few were *P. aeruginosa* (29 cases) or *E. coli* (11 cases). From January 1, 2012 to December 31, 2015, 5268 patients with limb fractures were admitted to this hospital, and 108 cases were diagnosed as post-traumatic osteomyelitis[16]. The bacterial cultures were positive in 77.8% (84/108) of patients. Among them, 104 microbial strains were detected, including 56 Gram-positive bacteria (53.9%), 39 *S. aureus* (37.5%), and six *Staphylococcus epidermidis* (*S. epidermidis*) (5.8%). There were 48 Gram-negative strains (46.1%), including 16 (15.4%) *E.coli* and 11 (10.6%) *E. cloacae* [17]. Another study showed that most bacteria, such as *S. aureus*, *P. aeruginosa*, *S. epidermidis*, and *Streptococcus pneumoniae*, adhere to the contact surface after invading the host[18]. There are even rarer cases of osteomyelitis being caused by *Salmonella*[19,20]. Surface anchoring proteins play a critical role in host cell adhesion and invasion, biofilm formation, and secretion of polysaccharide matrix, fibrin, and lipoprotein[21], which form an organized microbial aggregate biofilm[22]. This makes the bacteria resistant to the immune system[23]. Also, it is difficult to remove the biofilm completely with antibiotics, but the antibiotics kill the free bacteria in the blood that cause outbreaks of infection. When the body's resistance is reduced, the bacteria living in the biofilm are released, causing repeat infection. Biofilms are like shelters for microorganisms, leading to repeated outbreaks of chronic infection, which are prolonged and unhealed[24,25].

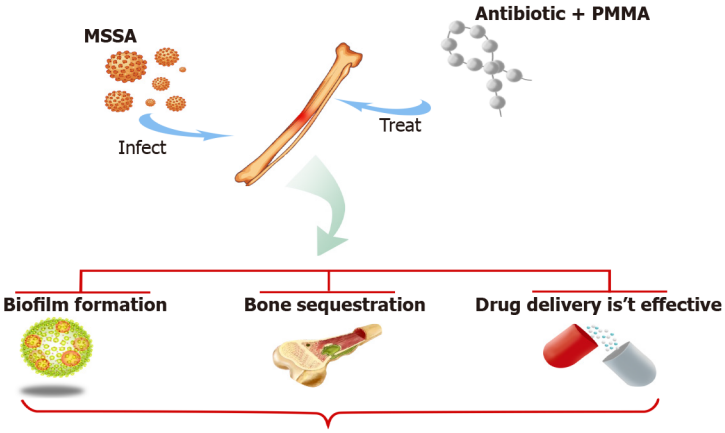
The interaction between osteoblasts and osteoclasts tightly regulates bone remodeling. The osteoblasts and osteoclasts communicate through direct contact between the cells or by secreting proteins that regulate their behavior, survival and differentiation[26]. *In vitro* studies have shown that bone tissue in an inflammatory and infective environment increases osteoclast activity and decreases osteoblast activity[27]. Biofilm-derived factors can decrease osteoblast activity by activating apoptosis under biofilm formation[28]. SPA mainly upregulates the expression of NFATc1 and C-FOS by activating the mitogen-activated protein kinase pathway, thus promoting the formation of osteoclasts [29]. It also binds to tumor necrosis factor receptor 1, which is highly expressed in osteoblasts[30], and then activates the downstream nuclear factor-kB pathway, leading to interleukin (IL)-6 release[31].

Therefore, we must focus on the research and development of new technologies and materials for the bacteria that cannot be controlled by antibiotics to achieve precise delivery of the drugs into the capsule. A specific drug can directly destroy the capsule of the bacteria to overcome the current disadvantages (Figure 1).

Pathophysiological mechanism of osteomyelitis

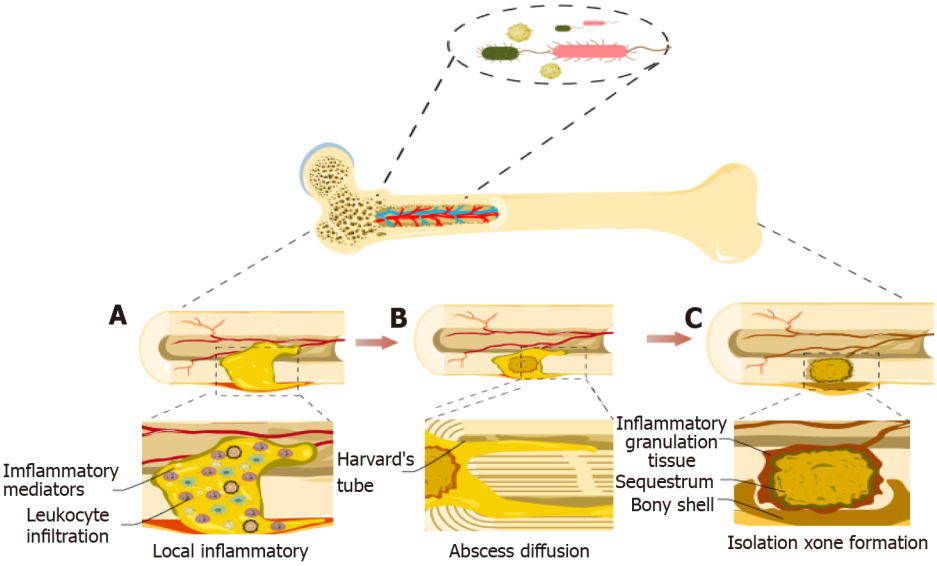
Before the onset of acute bloodborne disease, acute osteomyelitis often appears before the onset of disease in parts of the body with different degrees of infection foci[32], such as the upper respiratory tract and open fractures. With improper handling or immunodeficiency, the infection can spread throughout the body *via* the blood circulation and bacteria with the oven, and the bloodstream of children's long bone epiphysis nourishing artery is slow. The blood vessels are dense, retaining the bacteria and allowing their multiplication[33]. Bacteria multiply in cancellous bone and cause a local acute inflammatory reaction, such as hyperemia, edema, and leukocyte infiltration. Subsequently, local intraosseous pressure increases, causing severe pain, and then leukocyte necrosis releases lysozyme to destroy trabecular bone matrix abscess as it expands in the direction of low pressure. The local foci of infection can spread to the surrounding articular structures through the Havelian and Volkmann canals, and vascular occlusion exacerbates osteonecrosis. The necrotic bone is surrounded by granulation and fibrous tissues and is retained for a long time, resulting in the formation of dead bone, where a dead cavity is formed, termed a bone defect[34]. Often the course of osteomyelitis changes from acute to chronic. If the periosteum is not destroyed by infection, inflammation stimulates the formation of new bone beneath the periosteum, which can wrap around the dead bone and its upper and lower living segments. The dead bone and pericarp can cause the infected lesions to persist. Chronic osteomyelitis is likely to result from acute childhood osteomyelitis, followed by post-traumatic osteomyelitis, which causes bacterial colonization of bone tissue during open injury (Figure 2). In patients with reduced immunity, diabetes, atherosclerosis, and other conditions, the incidence of the disease is significantly increased.

In case of poor control of the lesion, the infection is surrounded by dead bone with no vascular supply, thickened periosteum, and fibrous tissue, eventually forming a zone of isolation. This isolation band can prevent the antibiotics from reaching this avascular region to kill the bacteria. Since the body's immune system cannot work correctly, it can easily lead to failure of drug treatment of osteomyelitis [35]. The lesions can exist for a long time and have intermittent episodes. If these persist for an extended period, they may become resistant to antibiotics[36]. In the face of intelligent bacteria, we must immediately find new materials that can fill bone defects, accurately deliver antibiotics to lesions, and assess auxiliary bactericidal and antibacterial effects.



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Figure 1 A schematic of major challenges in the treatment of osteomyelitis. MSSA: Methicillin-susceptible *Staphylococcus aureus*; PMMA: Polymethyl methacrylate.



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Figure 2 Pathophysiological mechanism of osteomyelitis. A: Leukocyte necrosis releases inflammatory mediators to destroy bone matrix and bone trabeculae, forming abscesses; B: The infected lesions spread to the adjacent bone structures through Harvard's tube, and the intraosseous pressure is increased; C: Bone destruction and vascular obstruction resulted in different degrees of osteonecrosis and encapsulation.

NANOMATERIALS FOR DIAGNOSIS AND TREATMENT OF OSTEOMYELITIS

Nanotechnology is defined as the ability to translate the theory of nanoscience into practical applications by observing, measuring, manipulating, assembling, controlling, and manufacturing matter at the nanoscale (1-100 nm)[37]. After decades of rapid development, nanotechnology has achieved excellent results in other industries, and human life has become more convenient[38]. During this period, scientists have shown significant interest in the medical application of nanomaterials. Since nanomaterials are of similar size as biological molecules, all kinds of materials can be designed as carriers with a variety of functions that allow nanomaterials to pass through the capillaries in the human body or through the cells to regulate cell behavior and genes[39]. Therefore, nanotechnology has potential medical applications[40]. In recent years, many researchers have proposed nanomaterials for treating osteomyelitis to overcome a series of previously encountered problems (Table 1). It has been found that nanomaterials have many advantages in the treatment of osteomyelitis[41].

Nanomaterials for the diagnosis of osteomyelitis

Osteomyelitis has an insidious onset. Current imaging techniques make it challenging to make an accurate and specific diagnosis of osteomyelitis, which needs to be differentiated from other diseases, such as bone metastases, nonspecific inflammation, and Charcot arthropathy. Early osteomyelitis

Table 1 Application of novel nanomaterials in the treatment of osteomyelitis

Ref.	Material	Conclusion	Application
Bruna *et al* [46], 2021	Silver nanoparticles	With antibacterial agents as organic compounds or antibiotics it has shown synergistic effect against pathogens bacteria such as *Escherichia coli* and *Staphylococcus aureus*	Treat infections or prevent them efficiently
Zheng *et al* [57], 2018	Gold nanoclusters	Exhibit excellent treatment effects in both macrophages and animal infection models induced by MRSA as representative	Inhibition of MRSA biofilm formation. The induction of intracellular ROS production in bacterial cells
Gowri *et al* [68], 2021	Ca-Alg nanoparticle	Clindamycin loaded Ca-Alg/PPAA system showed sustained Clindamycin release from the carrier. Exhibited better cell viability of synthesized materials against MG63 cells	Sustained drug release. Promotes bone regeneration
Krishnan *et al*[69], 2020	Silica coated nanohydroxyapatite-gelatin reinforced with poly-l-lactic acid yarns	The nanocomposite fibrous scaffold containing vancomycin can be proposed as a bifunctional graft that can reduce bacterial infection, while subsequently engineer new bone in osteomyelitis	Reduce bacterial growth engineer. New bone in osteomyelitis
Hassani Besheli *et al* [71], 2017	Silk fibroin nanoparticles	The VANCO-loaded silk fibroin nanoparticles entrapped in scaffolds reduced bone infections at the defected site with better outcomes than the other treatment groups	With good biocompatibility and sustained release properties
Mahon *et al* [75], 2020	BMnP	In-house generated BMnP preferentially polarize human macrophages towards an M2 phenotype, activate the transcription factor cMaf and specifically enhance production of the anti-inflammatory cytokine, IL-10	Driving pro-angiogenic responses in human macrophages and HUVECs. Promoted M2 macrophage polarization, tissue vascularization and increased bone volume
Chen *et al* [58], 2021	Aptamer-functionalized platinum nanozymes	The activity switching and enhanced antibacterial effect of the nanocapsule were verified *in vitro* and in diabetic wounds	Catalyzing H_2O_2 into OH. Chemodynamic sterilization

Ca-Alg: Calcium-Alginate; BMnP: Bone mimetic nano hydroxyapatite particles; IL: Interleukin; HUVECs: Human umbilical vein endothelial cells; ROS: Reactive oxygen species; PPAA: Phosphorylating polyallylamine; MRSA: Methicillin-resistant *Staphylococcus aureus*.

patients are not identified by X-ray lesions as symptoms usually appear 10-14 d after infection. Without timely treatment for osteomyelitis, most cases progress to chronic osteomyelitis, making diagnosis and treatment complex and painful. Therefore, improving the accuracy of early imaging of osteomyelitis has become essential to managing this disease.

Superparamagnetic iron oxide nanoparticles (SPIONs)-ferumoxytol have been approved by the United States Food and Drug Administration for clinical application, and they can be absorbed in lymphatic tissue and bone marrow with < 20-nm lesions. In preliminary animal studies, Tsuda *et al*[42] and Fukuda *et al*[43] found that ferucarbotran was able to identify and diagnose bone metastases. Hence, they performed controlled clinical trials, in which patients with injection of SPIONs had significantly lowered signaling in bone metastases (-12.2%), osteomyelitis (-35%) or normal bone marrow (-46.6%). This indicates that SPIONs have the potential to differentiate bone metastases from osteomyelitis. Xiao *et al*[44] prepared uniform and bio-efficient IL-13-TAMRA-Gd3N@C80(OH)30-(CH2CH2-COOH)20 nanoparticles, which are a novel gadolinium cluster-coated metal-fullerenes (Gd3N@C80) obtained by coupling with IL-13 fragments. In a mouse model of chronic post-traumatic osteomyelitis, this novel nano-targeted probe specifically bound lipopolysaccharide to stimulate macrophages, which showed a high signal on the T1-weighted sequence of infection foci. This suggested that this novel targeted magnetic resonance imaging probe detected and distinguished CPO from sterile inflammation. Quantum dots (QDs) comprise a type of low-dimensional semiconductor material with photostability. They are a new fluorescent probe that can be used for biomolecular and cell imaging. Yousefi *et al*[45] used intermittent fluorescence emission (optical scintillation), electron density, and biocompatibility of QD nanoparticles. The combination of two different color QDs (red and green) can be used to distinguish osteomyelitis from Charcot neuroarthropathy.

Nanomaterials for sterilization

We have found that nanomaterials have many antibacterial properties and specific characteristics, and silver and silver nanoparticles (Ag-NPs) have been used as antibacterial agents. These nanoparticles exhibited antibacterial properties against various microorganisms (*P. aeruginosa*, *S. aureus* and *Vibrio cholerae*)[46]. The prevailing view is that, based on the microscopic properties of Ag-NPs, Ag^+ infiltrates the bacteria through the cell wall, causing the cell wall to rupture and increase cell permeability[47].

The respiratory chain in the intima is modified to produce reactive oxygen species (ROS) and free radicals that cause protein denaturation. The positively charged Ag^+ can bind to the negatively charged cell membrane[48]. Aurore *et al*[49] found that Ag-NPs enhanced the cytotoxicity of osteoclasts to MRSA, *P. aeruginosa*, and other microorganisms, and increased the reaction of free radicals to pathogenic microorganisms. Nandi *et al*[50] demonstrated that high-dose Ag-NPs had a good effect on the treatment of infection in an animal model of osteomyelitis but caused no toxicity to other significant organs. Wang *et al*[51] found that Ag-NPs inhibited biofilm formation of pathogenic microorganisms and reduced bacterial adhesion by regulating expression of bacterial genes (*ICAR* and *ICAA* of *S. epidermidis* and *fnbA* and *fnbB* of *S. aureus*). Secinti *et al*[52] confirmed that nanosilver ion coating inhibits biofilm formation on implants. Afzal *et al*[53] showed that addition of hydroxyapatite (HA) and carbon nanotubes (CNTs) to 5% Ag-NPs enhanced the bactericidal performance of these composites.

However, in mammalian cell models, the antimicrobial efficacy of Ag-NPs is largely due to the production of Ag ions, which are potentially cytotoxic to both target bacterial cells and normal host cells [54], posing a serious safety threat to practical clinical applications. We are also looking for other unique materials that do not attack indiscriminately. Unlike silver, gold is inert and does not readily decompose into ions to produce cytotoxicity, but it has been observed in mammalian models with high biocompatibility and low biotoxicity. The biological activity of Au-NPs has been studied for a long time. Due to the characteristics of stability and high biocompatibility, Au-NPs have become the optimal choice for nanocarriers[55]. When Au-NPs attach to the surface of the microbial cell wall, due to their inherent antibacterial properties, both bacteria and nanoparticles combine to produce physical and chemical surface modifications and produce ROS, which cause bacterial protein degeneration, DNA damage, mitochondrial dysfunction, and ultimately cell death[56]. Zheng *et al*[57] evaluated the effects of gold-4-amino-6-hydroxy-2-mercaptopyrimidine (Au-DAMP) on biofilm formation and maturation in mice infected with MRSA. The results showed that Au-NPs had high anti-biofilm activity, and the formation of MRSA biofilm was inhibited significantly even at a low concentration of Au-NPs. Unlike other precious metal nanomaterials, Au-DAMP can eliminate MRSA mature biofilms at low concentrations; a property not possessed by the most common antibacterial agents. Chen *et al*[58] prepared an activated nanocase with chemodynamic therapy. This new platinum nanocase and glucose oxidase were encapsulated in an HA shell and termed APGH nanocapsules (Figure 3). *In vitro* experiments demonstrated that the novel nanocapsule reduced the pH and H_2O_2 constraints. The nanocapsule retained peroxidase-like activity, making it suitable for antibacterial treatment and accelerating healing in diabetic wound models.

In addition to chemodynamic therapy, photodynamic therapy (PDT) nanomaterials have been widely used in diagnosing and treating tumors, but relevant studies have assessed the antibacterial effect of PDT. Kuo *et al*[59] performed water-soluble C60 (OH) 30 on Gram-positive MRSA to prove that nanomaterial photochemokinetics also effectuate sterilization. In this study, ROS were produced using water-soluble fullerenol, and PDT killed most Gram-positive bacteria within a short period. Faced with the challenge of the increase in drug-resistant bacteria worldwide, scientists are looking for ways to replace or enhance the sterilization effect of antibiotics. Some scientists have started innovative research on the mechanism of action of magnetic nanomaterials on bacteria. The hyperthermic effect induced by low-intensity magnetic fields destroyed the bacterial biofilm and promoted absorption of antibiotics [60]. Hyperthermia has been evaluated in clinical trials for prostate cancer and glioma with remarkable results and no severe side effects[61,62]. By embedding the heating source into the tissue, magnetic particle hyperthermia uses an external alternating magnetic field to increase the accuracy and reduce the occurrence of damage to the surrounding normal cells. Magnetic particle hyperthermia improves the accuracy of heating. Fang *et al*[60] used magnetic nanoprecision-induced hyperthermia to destroy the bacterial biofilm of infected lesions, thus improving the sterilization effect of antibiotics. Fe_3O_4 nanoparticles implanted into a rat model of osteomyelitis were heated to 75 °C by magnetic heating, which did not cause tissue loss but could destroy the biofilm polysaccharide matrix to enhance the permeability of the antibiotics.

A previous study discovered carbon-based nanomaterials, such as graphene and CNTs[63]. Because of its unique structural characteristics and physical and chemical properties, carbon-based nanomaterials have high antibacterial activity. Embedded in the phospholipid bilayer, the phospholipid membrane structure and phospholipid molecular configuration are disturbed, which directly or indirectly achieve a bactericidal effect or oxidize bacterial molecules, such as lipids and proteins, through the generation of oxidative stress *via* ROS[64].

Nanomaterials for drug delivery

The main goal of our nanotechnology application is to load the treatment unit into the nanocarrier and transport the therapeutic drugs to a lesion without leakage, which increases the local concentration of the drug. Eventually, the disease-causing organism is destroyed because the carrier acts like a precision-guided missile to deliver a precise strike to the target. The standard treatment for osteomyelitis consists of thorough debridement of the infected bone-removal of dead bone and elimination of dead cavities-followed by long-term systemic antibiotic therapy based on bacterial culture results[65]. The major challenge to this method is how to keep the normal bone tissue while maintaining complete debridement to avoid nonunion, limb dysfunction, and pathological fracture. Furthermore, long-term

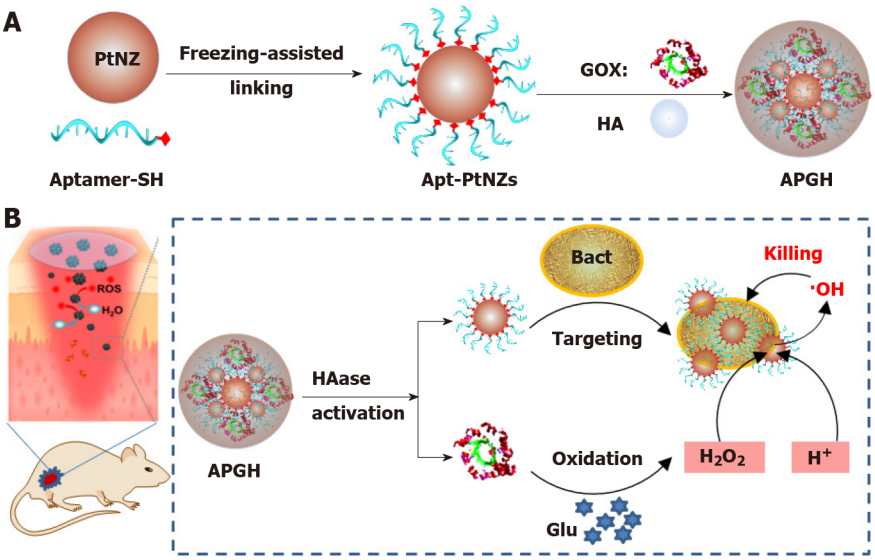


Figure 3 The illustration of APGH released the Aptamer-functionalized platinum nanozymes and glucose oxidase and its application for chemodynamic sterilization. A: The preparation route for the nanozyme capsule (APGH) with aptamer-functionalized platinum nanozymes, glucose oxidase and hyaluronic acid; B: Schematic illustration of APGH activation, activity switching in the infected wound, and its application for chemodynamic sterilization through *in situ* generation of COH on bacteria surface. Apt-PtNZ: Aptamer-functionalized platinum nanozymes; HA: Hyaluronic acid; GOX: Glucose oxidase. Citation: Chen L, Xing S, Lei Y, Chen Q, Zou Z, Quan K, Qing Z, Liu J, Yang R. A Glucose-Powered Activatable Nanozyme Breaking pH and H_2O_2 Limitations for Treating Diabetic Infections. *Angew Chem Int Ed Engl* 2021; 60: 23534-23539. Copyright ©The Author(s) 2021. Published by John Wiley and Sons. The authors have obtained the permission for figure using from the John Wiley and Sons and Copyright Clearance Center (Supplementary material).

systemic use of large doses of antibiotics can easily lead to antibiotic resistance and side effects, such as rashes, abdominal pain, and other gastrointestinal reactions. However, it is difficult for antibiotics to reach the osteomyelitic focus, resulting in insufficient local drug concentration and delayed healing.

Hence, we altered the treatment approach by filling the locally infected site with polymethyl methacrylate (PMMA) bone cement and microbeads loaded with antibiotics. The advantage of this approach is that it facilitates the delivery of a high concentration of the drug to the local infection site while reducing systemic toxicity. However, the PMMA bone cement delivery system also has some deficiencies in the treatment of osteomyelitis: (1) Heat generated during the preparation of PMMA implants affects the activity of loaded drugs; (2) PMMA is expensive; (3) PMMA bone cement cannot be absorbed in the body, requiring a second operation forits removal; (4) PMMA stents cannot achieve sustained drug release, and the drug release kinetics are poor; and (5) After the release of the loaded antibiotics, the remaining PMMA scaffold may become a site for bacterial determination[66]. Recent animal experiments and clinical applications show that nanoparticles have potential compared with existing drugs because of the size of nanoparticles that can enter pathogenic microorganisms or bone cells. Currently, we are exploring ways to target the drugs into specific bone sites, reducing costs, and improving compliance by maximizing controlled drug release such that the required drug concentration can be maintained over an extended period without exceeding toxicity levels or dropping below the minimum effective dose. Nanoparticles can deliver drugs through two mechanisms: (1) Nanoparticles bind to the microbial cell wall/membrane or osteoblast cell wall/membrane to release drugs into the cytoplasm; and (2) Nanoparticles can attach to the cell walls and act as drug repositories to continuously release the drug, which can then spread into the cell[67].

Currently, a variety of nanomaterials suitable for drug delivery for the precise treatment of osteomyelitis are being developed. Gowri *et al*[68] prepared calcium alginate (Ca-Alg) nanoparticles by salting out and loading clindamycin after crosslinking and phosphorylating polyallylamine (PPAA). The *in vitro* drug release experiments showed that the Ca-Alg/PPAA system had a sustained-release effect. The results of trypan blue colorimetry and MTT cytotoxic colorimetry showed that the system had good biocompatibility with osteoblasts (MG63). The Ca-Alg/PPAA/clindamycin system can control the synthesis of microbial flagella, affect the growth rate of cells, and reduce the viability of cell colonies by inhibiting viability. Krishnan *et al*[69] produced vancomycin-supported nanocomposite fiber Scaffidi (silica-coated nano-HA gelatin matrix). The porous structure (average pore size 150-350 μm) provides a large surface area and absorbs a large volume of antibiotics. In male Wistar rats (250-350 g), vancomycin release of all composite scaffolds was 10-20-fold higher than the minimum inhibitory concentration within 30 d. Anagar diffusion test, turbidity test, and bacterial adhesion test showed an excellent antibacterial effect, which could remove bacteria and promote the formation of new bone in 3 mo after implantation in a bone marrow disease model. Zhou *et al*[70] showed that mesoporous silica nanoparticle gelatin matrix composite fiber scaffold loaded with vancomycin promoted bone healing and significantly reduced bacterial contamination. Hassani Besheli *et al*[71] demonstrated that a silk

fibroin nanoparticle delivery system had strong antibacterial effect, targeted delivery, and continuous release of drug activity in a model of severe osteomyelitis induced by MRSA injection into the tibia of male Wistar rats (260-330 g). Wan *et al*[72] prepared polyvinyl alcohol/polycaprolactone (PCL) nanocomposite film and combined it with cefuroxime sodium. They measured the drug release from the nanocomposite material by spectrophotometry and concluded that the system was simple to prepare and had good biocompatibility. The stable and slow release of the drug may cause reversible absorption of the drug in PCL and forma hydrophobic layer.

Nanomaterials for treatment of chronic osteomyelitis

According to the clinicopathological mechanism of osteomyelitis, we considered the selection of nanomaterials for treatment after the formation of dead bone. The severe infection environment reduces the self-repair ability of bone tissue and delays bone regeneration[73]. A large area of the bone defect is often formed in the bone marrow cavity. There may be nonunion, pathological fracture, and other severe complications in the absence of intervention. Presently, autologous bone transplantation or artificial bone is used for clinical intervention; however, this scheme cannot inhibit bacterial growth and has a prolonged prognosis. Therefore, it is crucial to find materials that can promote proliferation of osteoblasts, inhibit osteoclast activity, and serve as vectors for antibiotics. This approach ensures antimicrobial efficacy, thereby minimizing the risk of antimicrobial resistance and infection recurrence, and stimulates osteoblast differentiation and proliferation, thereby promoting the formation of healthy bone tissue.

Jiang *et al*[74] divided 45 rabbits with chronic osteomyelitis into experimental, control, and blank groups, and evaluated them by X-ray, biopsy, and microbial culture. Vancomycin-loaded nano-HA pellets controlled the infection and repaired bone defects caused by MRSA-associated osteomyelitis. No significant or isolated nano-HA was observed in the experimental group 3 wk after implantation. The particles were involved in the formation of bone trabeculae or were replaced by medullary luminal tissue, and new bone was formed around the implanted particles. After 6 wk, the bone in the experimental group returned to normal and the periosteal reaction was weakened. Mahon *et al*[75] studied how nano-hydroxyphospholime promoted bone regeneration. They demonstrated that bone mimetic nano hydroxyapatite particles (BMnPs) preferentially polarized the M2 phenotype of human macrophages and specifically enhanced the production of the anti-inflammatory cytokine IL-10. The secretion of BMnP-treated macrophages promoted mesenchymal stem cell osteogenesis in an IL-10-dependent manner, suggesting that BMnPs directly promoted the osteogenic effect. In addition, BMnP-treated rats had significantly increased bone volume and stimulated expression of osteogenic genes, bone morphogenetic protein 2 (BMP2) and alkaline phosphatase (ALP), suggesting that BMnPs promote bone regeneration. IL-10 promotes chondrocyte differentiation and proliferation through the BMP pathway, and recombinant IL-10 promotes the expression of BMP-2, alkaline phosphatase, and osteopontin. Westhauser *et al*[76] observed that zinc-loaded mesoporous bioactive glass nanoparticles (5Zn-MBGNs) promoted osteogenic differentiation and expression of genes related to the extracellular matrix (ECM), and significantly promoted the formation and calcification of ECM, suggesting an excellent osteogenic effect. These genes also increased ALP activity, promoted DNA synthesis, and significantly increased calcium deposition. 5Zn-MBGNs IDPS upregulated expression of *OCN* and *COL1A1* genes, which significantly promoted ECM formation and calcification. The novel chitosan nanohybrid hydrogel and scaffold materials prepared by Mahanta *et al*[77] were highly porous, open, and three-dimensionally interconnected. In a rat femoral defect model, the bone healing rate of the nanohybrid scaffold was faster compared with that of the pure chitosan scaffold, while the cell growth rate of the nanohybrid scaffold was faster, and the cell proliferation was rapid.

BMP-2 is the most widely studied BMP, with the strongest activity in inducing endogenous bone formation, and it exists as a 30-kDa molecule in the form of a dimer[78]. Recombinant human (rh)BMP-2 has been expressed by gene recombination technology; however, the osteogenic activity of rhBMP-2 is lower than that of natural BMP-2, and the ideal vector has not been identified. Therefore, the search for a new nanomaterial containing BMP-2 has become a new direction for treatment of bone defect caused by osteomyelitis. Qiu *et al*[79] preloaded BMP-2 onto mesoporous HANPs and synthesized it into silk fibroin/chitosan composite. The results showed that scaffolds loaded with BMP-2 had better cell adhesion, provided an ideal microenvironment for cell proliferation, and significantly increased bone formation. SCH scaffolds containing BMP-2 had more material absorption and bone trabecular deposition than non-BMP-2 scaffolds had. The mesoporous HANPs maintained continuous release of BMP-2. This mode of delivery preserves the bioactivity of BMP-2. Therefore, the osteogenic effect of the scaffold can be improved. Qiao *et al*[80] reported a microwave-excited antibacterial nanocapturer system for treating deep tissue infections that consisted of microwave-responsive Fe_3O_4/CNT and gentamicin (Figure 4). They suggested that Fe_3O_4/CNT/gentamicin efficiently targeted and eradicated MRSA-infected rabbit tibia osteomyelitis.

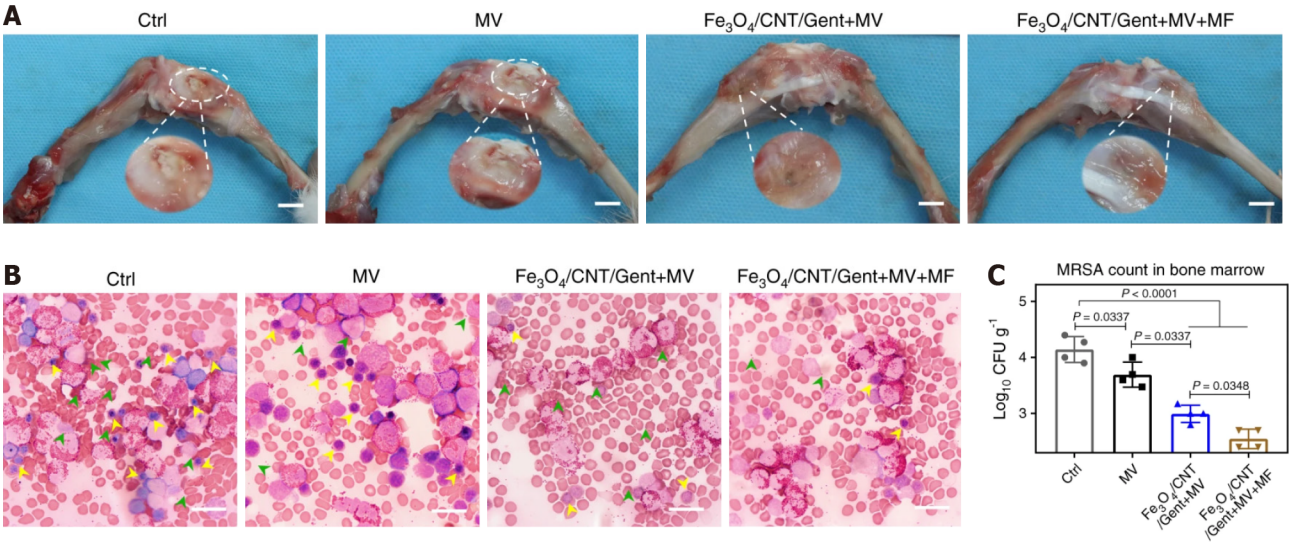


Figure 4 Antibacterial effects of Fe_3O_4/carbon nanotube/Gent on methicillin-resistant *Staphylococcus aureus*-infected osteomyelitis *in vivo*. A: Macro images of femur and tibia in each group of animal models 14 d after treatment. Scale bars = 1 cm; B: Wet-stained images, scale bars = 20 μm, 14 d after treatment; C: Methicillin-resistant *Staphylococcus aureus* count in bone marrow of each group after 2 d of antibacterial treatment. CNT: Carbon nanotubes. Citation: Qiao Y, Liu X, Li B, Han Y, Zheng Y, Yeung KWK, Li C, Cui Z, Liang Y, Li Z, Zhu S, Wang X, Wu S. Treatment of MRSA-infected osteomyelitis using bacterial capturing, magnetically targeted composites with microwave-assisted bacterial killing. *Nat Commun* 2020; 11: 4446. MRSA: Methicillin-resistant *Staphylococcus aureus*. Copyright ©The Author(s) 2021. Published by Springer Nature. The authors have obtained the permission for figure using from the Springer Nature group (Supplementary material).

CONCLUSION

Continuous research and development of nanomaterial preparations have enhanced the therapeutic effect of nanomaterials on infection, including improved treatment of osteomyelitis. Our goal is to perfect the treatment of chronic osteomyelitis by using a variety of new nanomaterials, which cannot be reached by either common antibiotics or sustained-releasing antibiotics. Because of the material properties, nanomaterials have antibacterial activity with as low-releasing and bone regeneration promoting ability. Recent research has been limited to animal experiments and has not been applied to clinical treatment. Thus, we need to understand the toxic effects and metabolism of nanoparticles, their properties, and the cost of preparing these materials to consider whether nanomaterials are suitable for treating chronic osteomyelitis. These tasks require a multidisciplinary collaboration.

FOOTNOTES

Author contributions: Zeng M and Xu Z contribute equally to this study, they share co-first author; Xu Z wrote the paper; Zeng M and Li J did the literature review; Tang ZW and Song ZQ did the data analysis; Xiao S conceived and coordinated the study; Wen J revised the paper; and all authors reviewed the results and approved the final version of the manuscript.

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MINIREVIEWS

Fungal arthritis: A challenging clinical entity

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Abstract

There has been an increasing incidence of fungal infections in recent years. Rarely joints are also affected by fungal infections. Mainly, these infections develop in prosthetic joints, but sometimes native joints are also involved. *Candida* infections are mostly reported, but patients may also develop infections secondary to non-*Candida* fungi, especially *Aspergillus*. Diagnosis and management of these infections is challenging and may involve multiple surgical interventions and prolonged antifungal therapy. Despite this, these infections are associated with high morbidity and mortality. This review described the clinical features, risk factors, and therapeutic interventions required to manage fungal arthritis.

Key Words: *Aspergillus*; *Candida*; Fungal arthritis; Invasive fungal infections; Osteomyelitis

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Core Tip: Fungal arthritis and osteomyelitis are rare diseases, but their incidence is increasing with the rising prevalence of predisposing factors. Most infections are secondary to *Candida spp.*, especially *Candida albicans*, but patients rarely develop infections secondary to other fungi, including *Aspergillus*, *Histoplasma*, *Cryptococcus* and *Coccidioides*. Fungal biomarkers may aid in rapid diagnosis in high-risk patients, but definitive diagnosis requires bone or synovial culture or biopsy. Surgical intervention and prolonged antifungal therapy form the mainstay of therapy, with azoles and echinocandins providing a safe and effective therapeutic option.

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INTRODUCTION

Fungal septic arthritis is a rare but severe and sometimes even life-threatening infection. It requires long-term medical and, in most cases, surgical management. During the past few years, there has been a dramatic surge in invasive fungal infections (IFIs). This is majorly attributable to the rise in the number of immunocompromised patients, including those on immunosuppression or broad-spectrum antibiotics, neutropenia, indwelling prosthesis, Human immunodeficiency virus (HIV), diabetes mellitus, burns, and long-term parenteral alimentation. A marked improvement in diagnostic techniques, including molecular methods, has also contributed to the early and rapid detection of these infections[1-3]. The course of bone and joint fungal infection can vary from indolent to highly aggressive. Spread is usually hematogenous (due to the high vascularity of synovial tissue), direct extension from a nearby infective focus or direct inoculation[4]. An indolent infection may be challenging to diagnose due to a lack of systemic inflammatory response and the absence of typical imaging features. However, the absence of a periosteal reaction and new bone formation at the site of osteomyelitis may indicate fungal etiology[5]. Therefore, diagnosing such cases may be highly dependent on a thorough history and physical examination. The clinical course and outcomes vary depending on the specific fungal species and the host factors.

PATHOPHYSIOLOGY

Hematogenous dissemination is the most frequent route of spread for IFIs. The other common route is direct inoculation from an exogenous source, such as surgery, prosthetic implantation, intra-articular corticosteroid injection, arthrocentesis, trauma, and open fractures[4,6]. The most common presenting complaint is localized pain followed by signs of local inflammation (swelling, erythema, and effusion), fever, and decreased range of motion. The large weight-bearing joints such as knees are most frequently affected[7]. However, there are no distinct clinical clues that may help differentiate fungal from bacterial arthritis. Hence, a detailed histopathological diagnosis is needed to elucidate a definitive pathogen in cases of high suspicion. In some cases, lytic lesions, cortical erosions, or adjacent osteoporosis and osteomyelitis may be seen on imaging scans. Findings of necrotizing granulomas on pathological examination make tubercular arthritis a close differential diagnosis (Table 1)[5,7].

DIAGNOSIS

Diagnosis of fungal arthritis can be quite challenging because of insidious disease onset with slow progression and lack of characteristic findings. The typical stains and smears used for fungal identification, such as potassium hydroxide or gram stain, may fail to identify the organism, and routine cultures are often non-diagnostic. The routine biochemistry and synovial fluid leukocyte count resemble a picture suggestive of non-infectious arthritis[7]. The demonstration of fungi on synovial, bone, or tissue culture and biopsy can be more indicative of an actual infection. However, the biggest limitation is the time taken to grow, especially in filamentous fungi cases, which potentially delays the treatment [3,8]. The fungal cultures are plated on Sabouraud dextrose agar at 24 °C-25 °C and should not be reported negative for growth until 4 wk after incubation[8].

As a consequence of difficult diagnosis and rising uncertainty of the classical phenotypic methods of fungal identification, there is now an increased focus on the use of molecular methods and antigen detection methods as surrogates for histopathology and cultures. The non-culture-based serological testing techniques that detect antibodies include enzyme immunoassay, immunodiffusion, and complement fixation. Among the molecular diagnostic tests, only a few tests, such as Film Array Blood Culture Identification (BioFire Diagnostics, Inc.), which is a PCR-based test, has been approved by the Food and Drug Administration. The matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) assay is a new test rapidly gaining popularity. It is a non-nucleic acid sequence-based molecular diagnostic assay for fungi, especially filamentous fungi such as *Aspergillus spp.*, and its strength lies in speed and accuracy[9].

There is an increasing interest in the use of biomarkers for diagnosing IFIs. β-D-glucan (BDG) is a non-specific fungal marker that may be positive in many fungal infections like *Candida*, *Aspergillus*, *Pneumocystis jirovecii*, and *Fusarium*. However, BDG may be negative in patients with *Cryptococcus*, *Blastomyces* (yeast form), or Zygomycetes (*Absidia*, *Mucor*, or *Rhizopus*) infection. Galactomannan is more

Table 1 Differential diagnosis for fungal arthritis

No.	Diagnosis
1	Bacterial arthritis
2	Tubercular arthritis
3	Sarcoidosis
4	Ewing's sarcoma
5	Osteogenic sarcoma
6	Langerhans cell histiocytosis
7	Malignant metastasis

specific to *Aspergillus* infections. These biomarkers have the advantage of rapid turn-around time and hence, if applied in high-risk patients with a moderate to high chance of IFI, may enable an early diagnosis. However, these biomarkers may also be falsely elevated in many patients, especially those on intravenous beta-lactam antibiotics (amoxicillin-clavulanate and piperacillin-tazobactam) and those on hemodialysis.

MANAGEMENT

Surgical

In cases of fungal native joint arthritis, a combined approach using medical and surgical therapy is typically desired for optimal results. Most cases of fungal osteomyelitis and septic arthritis need irrigation and surgical debridement. At the same time, tissue or fluid specimens can be collected for histopathological examination. Drainage and debridement are often unnecessary in the established diagnosis of cryptococcal infections.

The surgical process involves debridement of bony and soft tissues, removal of sinus tracts, and insertion of antifungal beads, if required[4]. Many cases of fungal vertebral osteomyelitis are associated with spinal instability and nerve root compression; hence spinal stabilization and arthrodesis are typically required. Early surgical interventions have been shown to prevent neurological injury in such patients[10].

Pharmacological management

Antifungal therapy, along with surgical intervention, forms the mainstay of therapy for fungal arthritis. Historically, the primary clinical experience treating invasive fungal arthritis has been with amphotericin B (Amp B), with or without flucytosine. However, recently azoles (fluconazole and extended-spectrum triazoles such as voriconazole, posaconazole, and isavuconazole) and echinocandins (caspofungin, micafungin, and anidulafungin) have been added to the list of available therapeutic options[11]. The recent clinical practice guideline for the management of osteoarticular candidiasis updated by the Infectious Diseases Society of America (IDSA) in 2016 recommends fluconazole and echinocandins as the first drugs of choice for *Candida* infections, given good efficacy and a better safety profile. Liposomal Amp B has been recommended as an alternative[12].

Azoles

The azole group blocks ergosterol synthesis in the cell membrane by inhibiting the enzyme lanosterol 14A demethylase and alters the functions of the membrane enzymes resulting in its dysfunction[13]. Fluconazole has good bone and tissue penetration, as indicated by the synovial fluid levels. Except for *Candida (C.) krusei*, *C. glabrata*, and some strains of *C. auris*, the majority of the *Candida* species are susceptible to fluconazole[14]. However, it has poor activity against *Aspergillus*. Voriconazole is the drug of choice for *Aspergillus* infections and has good bone penetration.

Polyenes

Amp B belongs to the polyene class of antifungal drugs that binds to ergosterol and results in the formation of pores, leakage of ions, and cell death. Additionally, Amp B also causes lipid peroxidation and oxidation reaction. The drug's newer lipid formulations are less nephrotoxic than conventional Amp B deoxycholate and have a better tolerability and toxicity profile. However, because of the better safety profile of azoles and echinocandins, it is typically reserved for invasive and resistant fungal infections. The toxicity profile of Amp B is directly related to its affinity and interaction with cholesterol. The most common adverse effects include infusion-related reactions (fever, chills, malaise, and hypotension), hypokalemia, hypomagnesemia, thrombocytopenia, leucopenia, normochromic, and

normocytic anemia with long-term use. Renal toxicity is dose-related, and renal failure is generally reversible after discontinuation of the drug. Adequate hydration and avoiding concomitant use of other nephrotoxic drugs may decrease the incidence of nephrotoxicity. The infusion-related toxicity can be reduced by administering a slow infusion over an extended period[4,15].

Echinocandins

Echinocandins inhibit the synthesis of 1,3 β-glucan, a major polysaccharide component of the cell wall and cause osmotic instability. This class of antifungals has a better tolerance profile with fewer adverse effects and ease of dosing in renal and liver dysfunctions. Echinocandins are active against most triazole-resistant pathogens and demonstrate fungicidal activity towards *Candida* species and fungistatic against mold (*Aspergillus* species)[16]. They are relatively less active against *C. guilliermondii* and *C. parapsilosis* and lack any activity against *Cryptococcus neoformans*, Zygomycetes and *Trichosporon* species due to the absence of β-glucan in the cell walls of these organisms[17]. Echinocandins are most effective against the biofilm formed by certain fungal species like *C. albicans* on retention hardware and medical devices. Studies have demonstrated the effectiveness of caspofungin and micafungin in killing preformed *Candida*-related biofilms at concentrations achievable *in vivo*[18].

Pyrimidine analogue

Flucytosine is an antimetabolite agent, approved by the Food and Drug Administration in 1971, for treating invasive cryptococcal and *Candida* infections. The drug carries a high risk of resistance to its use and is almost always used in combination with other antifungals, such as Amp B, for systemic and IFIs. It can cause acute hepatitis and severe hematological adverse effects, including pancytopenia, agranulocytosis, aplastic anemia, and bone marrow suppression[19].

COMMON PATHOGENS

Several different fungi may cause arthritis with varying clinical presentations. It is pertinent to make a pathological diagnosis as therapeutic options, the duration of therapy, and patient prognosis vary. Many risk factors have been identified for infection with different fungi, which may aid in raising suspicion and enabling early diagnosis (Table 2)[20,21].

Candida species

Candida species are the most common cause of fungal arthritis and osteomyelitis, especially in immunocompromised patients. An episode of candidemia, despite adequate antifungal treatment, may cause invasive joint and bone disease even after a long latent period of several months and sometimes even years[22]. *C. albicans* is the most commonly isolated species. *Candida* osteomyelitis often involves vertebrae, sternum, femur, humerus, and tibia. It usually starts as synovitis, eventually involving the adjacent bone causing osteomyelitis[4,5,23]. *Candida* arthritis, however, targets large-weight joints such as the knee, hip, shoulder, and ankle[20]. Joints affected by rheumatoid arthritis are predisposed to *Candida* infection. Infection can occur during aspiration, intra-articular steroid injection, or arthrotomy [11].

Surgical findings are cartilage erosion, thickening and hyperemia of the synovium with fibrosis, scarring, and purulence. Radiographically, *Candida* osteomyelitis of the spine shares certain findings with bacterial infections such as disc space narrowing, end plate destruction of adjacent vertebral bodies, and demineralization and mottled trabecular pattern in cases of long bone infections[5,24].

Treatment of *Candida* joint disease includes antifungal therapy and surgical debridement. Fluconazole remains the mainstay of medical management as most *C. albicans* are still susceptible. For septic arthritis, it is a 6-wk course of treatment with fluconazole or an echinocandin for 2 wk, followed by oral fluconazole for at least 4 wk. Lipid formulation of Amp B is another alternative, with therapy for 2 wk before transitioning to fluconazole. For osteomyelitis, a longer course of 6 mo of fluconazole is generally required. Alternatively, an echinocandin or liposomal Amp B may be used for 2 wk, followed by 6-12 mo of fluconazole, depending upon the clinical and radiographical improvement (Table 3). Surgical drainage is indicated in all cases of septic arthritis. Removal is recommended in cases of infected prosthetic joints[12].

Aspergillus species

Aspergillus spp. are ubiquitous saprophytes, and the pathogenic species are *Aspergillus (A.) fumigatus*, *A. niger*, *A. flavus*, and *A. terreus*. Infection most commonly occurs through inhalation of spores or hematogenous spread from a primary pulmonary focus. Extension of infection may involve maxillofacial structures, mastoids, sphenoid bones, or basilar skull, but most cases of *Aspergillus* osteomyelitis involve the vertebrae[25]. The lumbar spine is the most frequently involved site in cases of hematogenous spread[5].

The most common presentation is fever, pain, tenderness, and swelling of the joint. Cases of head and neck infections may present with headache, conjunctivitis, periorbital cellulitis, proptosis, and epistaxis. Radiologically, vertebral aspergillosis may be challenging to distinguish from tuberculosis. Cultures of

Table 2 Risk factors for specific fungal infections

Fungal infections	Risk factors
Candida spp.	Immunosuppression
	Chemotherapy
	Recent surgery
	Uncontrolled diabetes
	Corticosteroids
	Broad spectrum antibiotics
	Intravenous drug abuse
	Indwelling central venous catheters
	Hemodialysis
	Multiple site colonization
Aspergillus spp.	Neutropenia
	Chronic granulomatous disease
	Post-organ transplant
Coccidioides immitis	Uncontrolled diabetes
	Immunosuppression
	Advanced age
	HIV
Histoplasma capsulatum	HIV
	Advanced age
	Post-organ transplant
	Corticosteroids
	Immunosuppression

HIV: Human immunodeficiency virus.

biopsy specimens or synovial fluid growing the characteristic acutely branching hyphae are usually diagnostic of *Aspergillus*[26]. Identification tests for *Aspergillus* also include serum beta-d-glucan, galactomannan antigen test, and PCR testing. Serum assays for BDG are not specific to *Aspergillus*. Galactomannan antigen test has prognostic value with a serial decline in the serum levels indicating an effective antifungal treatment[27].

Triazoles and Amp B have long been used to treat invasive aspergillosis. Voriconazole is recommended as the drug of choice in managing invasive aspergillosis as it has a broad antifungal spectrum of activity and lesser nephrotoxicity than amphotericin[28]. Antifungal treatment is recommended for 6 wk to 8 wk, along with surgical debridement. Surgical debridement of the infected material helps with reducing the infective burden and allowing better drug penetration[13].

Coccidioides species

Coccidioides species are dimorphic fungi found predominantly in regions of Mexico and central, southern, and southwestern regions of the United States. Extrapulmonary dissemination of the disease is rare, but polyarticular arthritis may occur during primary infection with rash, fever, eosinophilia, and bilateral hilar lymphadenopathy as hypersensitivity syndrome[29]. Although rare, hematogenous dissemination may result in septic arthritis, and weight-bearing joints, like the knee, are at greater risk of involvement. On standard laboratory tests, raised erythrocyte sedimentation rate, C-reactive protein, peripheral eosinophilia, and raised *Coccidioides* complement fixation titer may be seen[4].

Radiological findings include joint space narrowing with effusion, osteopenia, and lytic lesions with bone destruction. Histopathology may show villonodular synovitis, pannus and sinus tract formation, non-necrotizing granulomas, and spherules containing endospores. It is a septic arthritis demonstrating synovial proliferation rather than synovial fluid accumulation[30]. The main antifungal drugs are oral azoles (fluconazole and itraconazole), which have largely replaced the role of Amp B, except in immunocompromised patients and disseminated coccidioidomycosis[31].

Table 3 Therapeutic options for fungal arthritis

Antifungal drugs	Indication/pathogen	Dosage
Fluconazole	Candidiasis	400 mg (6 mg/kg) daily (IV/PO)
	Histoplasmosis	
	Blastomycosis	
	Coccidioides	
	Cryptococcus	
Voriconazole	*Aspergillus*	4-6 mg/kg BD; 200 mg BD (IV/PO)
	Candidiasis	
	Coccidioides	
	Blastomycosis	
	Cryptococcus	
	Histoplasmosis	
Itraconazole	*Aspergillus*	100-400 mg/d (PO)
	Sporothrix	
	Candidiasis	
	Coccidioides	
	Histoplasmosis	
	Cryptococcus	
	Blastomycosis	
Ketoconazole	Blastomycosis (mild to moderate cases)	200-400 mg OD (PO)
	Coccidioides	
	Cryptococcus	
	Histoplasmosis	
Liposomal amphotericin B	*Candida species* (except *C. lusitaniae*)	3-5 mg/kg/d (IV)
	Cryptococcus	
	Aspergillus	
	Coccidioides	
	Histoplasmosis	
	Sporothrix	
Echinocandins: Caspofungin, anidulafungin, micafungin	Candidiasis (fungicidal)	Caspofungin: 70 mg on day 1 followed by 50 mg OD (IV); anidulafungin: 200 mg on day 1 followed by 100 mg OD (IV); micafungin: 100 mg OD (IV)
	Aspergillus (fungistatic)	
5-Flucytosine	*Cryptococcus*	100 mg/kg/d divided q 6 h (PO)
	Candida	

IV: Intravenous; PO: Per os (oral administration).

Cryptococcus species

Cryptococcus is a basidiomycete that primarily involves the lungs and central nervous system. The route of infection could be inhalational, hematogenous from infected lungs in cases of disseminated disease, or rarely a direct trauma causing arthritis. Septic arthritis usually results from the contiguous spread of infection from adjacent osteomyelitis[32]. *Cryptococcus neoformans* has a unique polysaccharide capsule that protects it against phagocytosis and opsonization in the host[4].

The stains that aid in diagnosing cryptococcosis include periodic acid Schiff stains and methenamine silver nitrate. The diagnostic and prognostic value of serum cryptococcal antigen in osteoarticular cases needs to be better defined[33]. Histopathologic examination of tissue or bone specimens may demonstrate granulomatous changes with extensive fibrosis and giant cells. Radiological findings elicit

discrete, well-defined lytic lesions, usually without sclerotic or periosteal change. In cases of vertebral osteomyelitis, the intervertebral space is spared despite contiguous vertebral body involvement[26]. In non-complicated single-site infections and the absence of any immunosuppressive risk factors, fluconazole 400 mg (6 mg/kg) OD for 6-12 mo is the antifungal treatment of choice. In case of disseminated disease (at least 2 non-contiguous sites involved or high levels of serum cryptococcal antigen titer ≥ 1:512), a combination of liposomal Amp B and flucytosine for 2 wk followed by fluconazole as maintenance therapy for 6-12 mo is recommended by IDSA 2010 guidelines[34].

Histoplasma species

Histoplasma (*H.*) *capsulatum* usually causes a self-limited respiratory flu-like illness. The spores of this fungus have a predilection for the reticuloendothelial system and can spread to regional lymph nodes. Patients with impaired cellular immunity, such as HIV AIDS infection, are predisposed to *Histoplasma* primary infection or reactivation disease. It usually causes aseptic arthritis as a spectrum of immunologically mediated diseases. Synovial fluid analysis is inflammatory and demonstrates mononuclear cell predominance. The joint involvement is symmetric but may be migratory, and the most common sites of involvement include the knee, ankle, and small joints of the hands and wrist. Other than osteoarticular disease, *H. capsulatum* may also cause tenosynovitis and carpal tunnel syndrome[4,26,35]. *H. capsulatum*, along with *Coccidioides immitis*, are the two fungi most implicated in immune complex arthritis. This leads to joint swelling secondary to synovial proliferation rather than fluid accumulation, often manifested by symmetrical joint involvement[7]. The treatment recommendation is liposomal Amp B for 12 wk before transitioning to oral itraconazole. For mild cases, oral itraconazole is recommended[35].

PROSTHETIC JOINT INFECTION

Prosthetic joint infection (PJI) is a known complication of joint arthroplasty procedures and occurs in 1%-2% of cases of prosthetic joint implantations[36]. Overall, *Staphylococcus* is the most common organism isolated in 50% of cases, and *C. albicans* is the most common cause of fungal PJI. Most cases are encountered after revision arthroplasty. The risk factors include diabetes, immunosuppressive therapy, malignancy, obesity, prior antibiotic use, multiple revision surgeries, and preceding bacterial PJI. The clinical presentation is usually similar to septic arthritis as pain, effusion, erythema, joint tenderness with raised levels of erythrocyte sedimentation rate, C-reactive protein, and possibly a positive aspirate culture in cases of deep PJI[4,36,37].

The management consists of two-stage revision arthroplasty, separated by 3-6 mo with a prolonged systemic antifungal treatment[37]. Even after two-stage revision arthroplasty there may be a significant recurrence rate of 20%[38]. Fungal infections are relatively more difficult to treat and require longer time intervals for reimplantation in order to reduce the risk of infection recurrence. The reimplantation is based on the patient's stability and surgical wound status. Some surgical centers also practice joint re-aspiration before proceeding with reimplantation[3,8]. As updated by IDSA in 2016, drug therapy for *Candida* PJI includes fluconazole, liposomal Amp B and echinocandins, and prosthetic device removal [12]. Echinocandins are a lucrative alternative as they have the potential to penetrate the biofilm with the advantage of better tolerance and safety profile and fewer drug interactions than most antifungals [39].

CURRENT CHALLENGES AND FUTURE DIRECTION

In the present era of evolving anti-fungal resistance, treating invasive fungal diseases poses an immense challenge. Due to limited bone penetration for most of the anti-fungal drugs and high relapse and recurrence rates, there is a need for prolonged duration of therapy resulting in increased financial burden and high drop-out rates. Experiments are now being conducted to search for newer potential targets and generate new antifungal combinations to overcome drug resistance. An example of such a new target is heat shock protein 90, which modulates fungal virulence and drug resistance through certain downstream effectors and proteins such as calcineurin. The calcineurin inhibitor analogues have been studied to possess antifungal properties and may hold a promising role in abrogating drug resistance. Similarly, pharmacological inhibition of heat shock protein 90 expression with geldanamycin has been shown to reduce resistance to azoles and echinocandins, including resistance that has already evolved in humans treated with these antifungal drugs[40]. Development of newer drugs like ibrexafungerp, a triterpenoid anti-fungal agent, which has advantages of having oral formulation, broad-spectrum activity, and efficacy against newer strains of *Candida* like *C. auris*, may help in managing difficult and resistant infections[41].

CONCLUSION

Fungal arthritis and osteomyelitis are rare but difficult to treat conditions. The incidence of fungal disease is increasing as predisposing factors are more prevalent in the general population. The treatment for fungal arthritis requires surgical intervention and a prolonged course of antifungal agents. The treatment targets preservation of joints, eradication of the infection, and protection from future recurrence.

FOOTNOTES

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ORIGINAL ARTICLE

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Mechanism of spinal cord injury regeneration and the effect of human neural stem cells-secretome treatment in rat model

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Abstract

BACKGROUND

Globally, complete neurological recovery of spinal cord injury (SCI) is still less than 1%, and 90% experience permanent disability. The key issue is that a pharmacological neuroprotective-neuroregenerative agent and SCI regeneration mechanism have not been found. The secretomes of stem cell are an emerging neurotrophic agent, but the effect of human neural stem cells (HNSCs) secretome on SCI is still unclear.

AIM

To investigate the regeneration mechanism of SCI and neuroprotective-neuroregenerative effects of HNSCs-secretome on subacute SCI post-laminectomy in rats.

METHODS

An experimental study was conducted with 45 Rattus norvegicus, divided into 15 normal, 15 control (10 mL physiologic saline), and 15 treatment (30 µL HNSCs-secretome, intrathecal T10, three days post-traumatic). Locomotor function was evaluated weekly by blinded evaluators. Fifty-six days post-injury, specimens were collected, and spinal cord lesion, free radical oxidative stress (F2-Isoprostanes), nuclear factor-kappa B (NF-κB), matrix metallopeptidase 9 (MMP9), tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), B cell lymphoma-2 (Bcl-2), nestin, brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF) were analyzed. The SCI regeneration mechanism was analyzed using partial least squares structural equation modeling (PLS SEM).

RESULTS

HNSCs-secretome significantly improved locomotor recovery according to Basso, Beattie, Bresnahan (BBB) scores and increased neurogenesis (nestin, BDNF, and GDNF), neuroangiogenesis (VEGF), anti-apoptotic (Bcl-2), anti-inflammatory (IL-10 and TGF-β), but decreased pro-inflammatory (NF-κB, MMP9, TNF-α), F2-Isoprostanes, and spinal cord lesion size. The SCI regeneration mechanism is valid by analyzed outer model, inner model, and hypothesis testing in PLS SEM, started with pro-inflammation followed by anti-inflammation, anti-apoptotic, neuroangiogenesis, neurogenesis, and locomotor function.

CONCLUSION

HNSCs-secretome as a potential neuroprotective-neuroregenerative agent for the treatment of SCI and uncover the SCI regeneration mechanism.

Key Words: Secretome; Regeneration mechanism; Spinal cord injury; Locomotor; Biomarkers

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Core Tip: The human neural stem cell secretomes is effective in spinal cord injury (SCI) treatment, based on locomotor function improvement, decreased size of spinal cord lesions, and biomarkers expression. Based on partial least squares structural equation modeling analysis, the regeneration mechanism of SCI started with pro-inflammation, anti-inflammation, anti-apoptotic, neuroangiogenesis, neurogenesis, finally, locomotor improvement.

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INTRODUCTION

Spinal cord injury (SCI) can result in permanent neurologic deficits; complete SCI neurological recovery is still less than 1%, and 90% experience permanent disability[1]. Secondary damage is caused by oxidative stress, inflammation, ischemia, apoptosis, and glial scar formation[2]. It can result in axon regeneration failure, leading to neurological deterioration[2]. The SCI regeneration mechanism is still uncertain[3]. Pajer *et al*[4] stipulate that SCI pathophysiology can be divided into three overlapping stages: Acute, subacute, and chronic. The injury begins with trauma that results in microvascular damage in the form of bleeding, thrombosis, and vasospasm[5]. This microvascular damage causes the spinal cord to undergo hypoperfusion, hypoxia, and ischemia[6]. Ischemia in the spinal cord affects cellular and molecular inflammation processes, neuron and neuroglia cell apoptosis, and glial scar formation, which mechanically and chemically inhibit SCI regeneration[5,6].

SCI management is still controversial, as there is no global consensus guideline and no effective pharmacological neuroprotective-neuroregenerative agent[7,8]. Current SCI management is focused on treating the secondary injury[2]. The secretomes of stem cell help mitigate the risk of immune rejection, reduce the risk of tumorigenesis, and cryopreserve treatments while avoiding the issues of maintaining cell viability[9]. The secretomes of stem cell are more economical and readily available in emergency cases as they can be mass-produced[10].

The effect of human neural stem cells (HNSCs) secretome on SCI is still unclear. Consequently, this study aimed to investigate the SCI regeneration mechanism and HNSCs-secretome treatment effects on subacute SCI post-laminectomy by analyzing free radical oxidative stress (F2-Isoprostanes), nuclear factor-kappa B (NF-κB), matrix metalloproteinase (MMP)-9, tumor necrosis factor (TNF)-α, interleukin-10 (IL-10), transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), B cell lymphoma (Bcl)-2, nestin, brain-derived neurotrophic factor (BDNF), gleal cell line neurotrophic factor (GDNF), spinal cord lesion, and locomotor function. For this purpose, we used a well-established Rattus norvegicus model of SCI contusion-compression.

MATERIALS AND METHODS

Ethics statement

The study protocol was reviewed and approved by the Faculty Dentistry, University of Jember (REC.1112/UN25.8/KEPK/DL/2021). All rats were approved by the animal health office (No.503/A.1/0005. B/35.09.325/2020).

Study design

The research was a proper experimental study. The Lemeshow formula counted the sample size (n = 15 rats), with correction factors of 20%. The rats were randomly grouped into the following three groups: Normal (15 experimental rats did not have SCI and did not get HNSCs-secretome), control (15 experimental rats did have SCI with physiologic saline), and treatment (15 experimental rats did have SCI with HNSCs-secretome) (Figure 1). The treatment group received a 30 μL HNSCs-secretome intrathecal injection in T10 three days after the SCI and laminectomy. Treatment and control groups were replicated 15 times, and we observed the study over 56 d. The study's independent variable was HNSCs-secretome treatment, whereas the dependent variables were GDNF, BDNF, nestin, Bcl-2, VEGF, TGF-β, IL-10, MMP9, F2-Isoprostanes, TNF-α, NF-κB, locomotor function, and spinal cord lesion size.

Preparation of the HNSCs-secretome

HNSCs-secretome is characterized by the presence of nerve cells as well as the nestin, BDNF, and growth associated protein-43. NSCs were derived from 2 × 5 × 10^6 adipose-mesenchymal stem cells (MSC) with fresh frozen nerve scaffolds under 5% hypoxic conditions. Secretom does not provide an immune compatibility effect, therefore in this study secretoms were used from humans, not from rats[3, 11]. HNSCs-secretome 50 cc produced on June 21, 2021 at the Stem Cell Installation and Network Bank of RS Dr. Soetomo No. 301/VAL/FORM/BJRS/10/2021, with ethical clearance No. 0059/KEPK/IX/2020.

Rats and SCI models

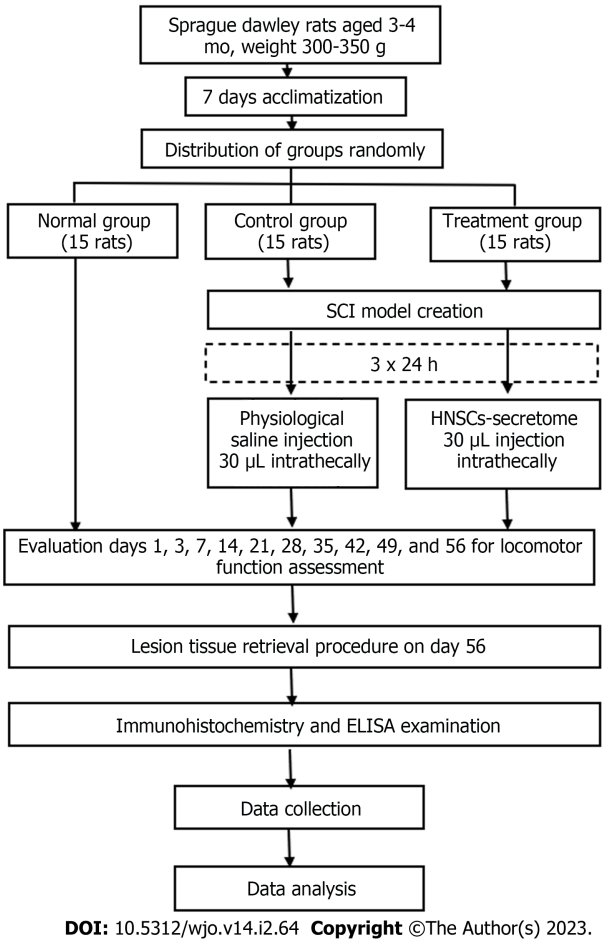
The adult male Rattus norvegicus pure strain Sprague Dawley rats were three to four months old and weighed 300-350 g. Inclusion criteria were male, age 3-4 mo, weight 300-350 g, pure line, and healthy with a healthy statement from a veterinary polyclinic. The exclusion criteria were experimental rats that had received immunomodulatory therapy and were fatally ill. Acclimatization was carried out for seven days by one laboratory assistant and two veterinarians. The rats were kept in separate cages, consisting of a plastic box with woven wire as a cover, with each cage (45 cm × 30 cm × 15 cm) containing one rat. The floor mat was covered with wood shavings and a pad underneath to absorb urine and retain moisture. Air conditioning provided comfort and maintained a room temperature of 20-24 ˚C and humidity of 50%-70%. An exhaust fan was used to remove the ammonia smell, and the environment was a quiet room with 12-h light and dark cycles. The light sources were 300 Lux electric lamps positioned 1 m from the floor. The cage was cleaned every three days with soap and running water. Feed comprised 30-35 g of pellets (10% of bodyweight) and 30-35 mL of mineral water (10% of bodyweight).

Contusion-compression of the spinal cord was performed with the commercially available spinal cord impactor aneurysm Yasargil clip, with a length of 7 mm and a 65 g load (equivalent to 150 k Dyne). The rats were anesthetized using ketamine (75 mg/kg) and acepromazine 3 mg/kg intraperitoneal. The rats were placed on a fixation board in a prone position, and the back fur was shaved to approximately 2 mm. The operating area was disinfected with 10% betadine and 75% alcohol. The surgical level was marked by tracing the level of the T12 rib to the T12 spinous process using a 2 cm skin incision. A T10-T11 partial laminectomy was conducted to expose the spinal cord. The tip of the titanium aneurysm Yasargil clip was placed at a 1-mm distance from the anterior and posterior of the spinal cord, and the spinal cord was impacted suddenly for 60 s by retracting the tip using an applicator. This retraction induced an SCI contusion-compression model with the dura appearing flat and cloudy white. The operating field was cleaned using saline, and the muscle and skin were sutured together in layers.

Three days post-injury, the treatment and control group rats were completely paraplegic. The control group was administered an intrathecal injection of 10 mL physiologic saline. The treatment group was administered an intrathecal injection of 30 μL HNSCs-secretome under general anesthesia, which was centered at the injury site and 1.5-2 mm deep from the dura to the subarachnoid space, with a tilt angle of 30°–40° using a 50 μL Hamilton Syringe. The rats received normal saline, tolfenamic acid 4 mg/kg, and enrofloxacin 10 mg/kg subcutane, were placed under a 5 W heating lamp. Manual bladder drainage was conducted twice daily until micturition was normal.

Locomotor assessment

The Basso, Beattie, Bresnahan (BBB) open-field test was performed on days one, three, seven, 14, 21, 28, 35, 42, 49, and 56 after injury to assess locomotor expression. The BBB measures the tail, body, legs, trunk stability, limb movement, and toe clearance, all of which are examined to measure locomotor abilities. The score shows a range of numbers between 0 and 21. A score of 0 indicates no movement,



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Figure 1 Diagram of the animal model and grouping. SCI: Spinal cord injury; HNSCs: Human neural stem cells; ELISA: Enzyme-linked immunosorbent assay.

whereas a score of 21 represents normal movement without a locomotor disorder. The data collector and outcome adjudicator/data analyst were blinded.

Preparation of the tissue for the immunohistochemical and enzyme-linked immunosorbent assay assessment

The rats' termination was carried out on day 56 through the induction of inhalation anesthetics. The 5-cm SCI was separated from the vertebral column and marked at the cranial end. The SCI materials were put in a pot and fixed in a 10% formalin buffer. All SCI specimens were sent to the Anatomy and Pathophysiology Laboratory for enzyme-linked immunosorbent assay (ELISA), and immunohistochemistry examination, tabulation of results, and analysis were conducted according to the blinding principle. The data collector and outcome adjudicator/data analyst were blinded.

Spinal cord lesion assessment

With hematoxylin and eosin staining, measurements of the spinal cord lesions were carried out in both the control and treatment groups, then analyzed with Statistical Package for Social Science (SPSS) software (Version 25, IBM) was used to analyze the differences between groups by non-parametric test, followed by Mann Whitney test. A *P*-value of more than 0.05 was considered statistically significant.

Immunohistochemical assessment

GDNF, BDNF, nestin, Bcl-2, VEGF, TGF-β, IL-10, MMP9, and NF-κB were evaluated using indirect immunohistochemical quantitative measurements. The data collector and outcome adjudicator/data analyst were blinded. Fifteen specimens of spinal cord tissue taken from animals in each group. In each group, we observed an average value of 10 fields of view, and every field of view had 625 μ^2 with 400 × magnification.

Immunohistochemical operational procedures were as follows: The specimens were immersed in the xylol solution for 3-5 min, then in absolute ethanol for 1-3 min, and finally in 70% ethanol for 1-3 min. They were then washed 3 times with Aquabidest, and the edge of the slide was cleaned with a tissue. They were then dropped with H_2O_2 3%, incubated at room temperature for 10 min, washed 3 times in

phosphate-buffered saline (PBS), and the edge of the slide was again cleaned with a tissue. They were then dropped with Trypsin 0.025%, and incubated at 37 °C for 6 min, washed 3 times in PBS, and the edge of the slide again cleaned with a tissue. Specimens were then dropped with Ultra V Block and incubated at room temperature for 5 min, with the edge of the slide cleaned again (no need to wash). They were then dropped with monoclonal antibody which has been diluted (1:100) and incubated at room temperature for 25-30 min, washed with PBS 3 times, and the edge of the slide cleaned with a tissue. Drops of biotin, incubation at room temperature for 10 min, washed with PBS 3 times, and the edge of the slide cleaned with a tissue. Specimens were then dropped with horseradish peroxidase polymer (streptavidin peroxidase conjugate), incubated at room temperature for 10 min, washed with PBS 3 times, and the edge of the slide cleaned with a tissue. They were then dropped with diaminobenzidine chromogen (20 mL/1 mL substrate), incubated at room temperature for 5-15 min in a dark room, washed Aquabidest 3 times, cleaned, painted with Meyer Hematoxylin at room temperature, then incubated for 6-15 min, washed in running water 3 times, and finally soaked in water for 10 min, drained, mounting, and microscopic readings were taken.

ELISA

The specimen for ELISA was collected from cardiac blood. The TNF-α analysis used serum, and F2-Isoprostanes used plasma for the analysis. The ELISA kit for the TNF-α analysis used the Sandwich-ELISA principle, while the ELISA kit for the F2-Isoprostanes analysis used the Competitive-ELISA principle. TNF-α and F2-Isoprostanes were evaluated using quantitative measurements.

Statistical methods

The data in this research is reported as the mean ± standard deviation of the mean. SPSS software (Version 25, IBM) was used to analyze the differences between groups by ANOVA, followed by Tukey's post-hoc test. A *P*-value of more than 0.05 was considered statistically significant.

Partial least squares structural equation modeling (PLS SEM) was used to analyze the pathway mechanism of SCI regeneration through analysis of the outer model, inner model, and hypothesis testing. The outer model measurement of PLS SEM is based on convergent validity, discriminant validity, and composite reliability. Convergent validity can be determined from the value of the loading factor and average variance extracted (AVE). If the loading factor value is more than 0.7, the correlation between indicator and variable is valid. If the AVE value more than 0.5, the ability of the variable value to represent the original data score is valid. Discriminant validity testing the construct indicator has a higher cross-loading value than other construct indicators, whereas composite reliability is used to measure the consistency of variables. If the composite reliability value is more than 0.7, it is declared valid.

Path bootstrapping analysis is a description of the inner model and the results of the path analysis hypothesis test, based on the original sample value and the statistical T value. If the statistical T value is greater than 1.9 (T table value) or the *P* value is less than 0.05, the direct effect of the latent variable/construct is stated to be significantly different. The relationship between latent variables in the inner model can be tested with R square (coefficient of determination on endogenous variables), path coefficients, F square (effect size), and Q square (prediction relevance).

RESULTS

The mechanism of SCI regeneration

The SCI regeneration mechanism was analyzed using PLS SEM. The test results of the measurement model (outer model) are valid, based on the PLS algorithm (Figure 2), the analysis of convergent validity is more than 0.7 (Table 1), the AVE value is more than 0.5 (Table 2), the Cronbach's Alpha value is more than 0.5 (Table 2), composite reliability is more than 0.7 (Table 2), and discriminant validity is good (Table 3).

The results of the analysis of the inner model (structural model) using bootstrapping and blindfolding PLS SEM procedures are valid and show the path coefficients that are in accordance with the hypothesized theory, significant with T-statistics greater than 1.9 (T-table) and *P* value less than 0.05 (Figure 3, Table 4). The relationship between latent variables in the inner model was analyzed, with F square (effect size) more than 0.05 (Table 5), Q square (prediction relevance) more than 0 (Table 6), and path coefficients positive. For R square (coefficient of determination on endogenous variables), the anti-inflammatory value of 0.860 indicates an effect of 86%, the anti-apoptotic value of 0.680 indicates an effect of 68%, neuroangiogenesis of 0.776 indicates an effect of 77%, neurogenesis of 0.444 indicates an influence of 44%, and locomotory of 0.536 indicates an influence of 53% (Table 7).

Locomotor by BBB score

The rats were examined for eight weeks to assess the recovery of their motor function. Locomotor recovery recorded on day seven and continued until day 56. The treatment group's mean BBB score was

Table 1 Loading factor value

	Anti apoptotic	Anti inflammatory	Lokomotorius	Neuroangiogenesis	Neurogenesis	Pro inflammatory
Anti apoptotic	1.000					
Anti inflammatory 1		0.978				
Anti inflammatory 2		0.978				
Lokomotorius			1.000			
Neurogenesis 1					0.932	
Neurogenesis 2					0.928	
Neurogenesis 3					0.892	
Neuroangiogenesi				1.000		
Pro inflammatory 1						0.940
Pro inflammatory 2						0.901
Pro inflammatory 3						0.936
Pro inflammatory 4						0.770

Table 2 Average variance extracted value

	Cronbach's alpha	rho_A	Composite reliability	Average variance extracted
Anti apoptotic	1.000	1.000	1.000	1.000
Anti inflammatory	0.954	0.954	0.978	0.956
Lokomotorius	1.000	1.000	1.000	1.000
Neuroangiogenesis	1.000	1.000	1.000	1.000
Neurogenesis	0.907	0.915	0.941	0.842
Pro inflammatory	0.917	0.979	0.938	0.792

Table 3 Discriminant validity values

	Anti apoptotic	Anti inflammatory	Lokomotorius	Neuroangiogenesis	Neurogenesis	Pro inflammatory
Anti apoptotic	1.000	0.697	0.271	0.850	0.815	0.085
Anti inflammatory 1	0.663	0.978	-0.293	0.714	0.704	0.642
Anti inflammatory 2	0.699	0.978	-0.140	0.796	0.739	0.532
Lokomotorius	0.271	-0.220	1.000	0.064	0.072	-0.869
Neurogenesis 1	0.725	0.691	-0.037	0.961	0.932	0.369
Neurogenesis 2	0.776	0.612	0.313	0.862	0.928	-0.006
Neurogenesis 3	0.748	0.736	-0.084	0.804	0.892	0.338
Neuroangiogenesi	0.850	0.772	0.064	1.000	0.958	0.319
Pro inflammatory 1	0.078	0.580	-0.865	0.268	0.201	0.940
Pro inflammatory 2	-0.073	0.496	-0.760	0.192	0.118	0.901
Pro inflammatory 3	0.257	0.654	-0.740	0.455	0.392	0.936
Pro inflammatory 4	-0.206	0.153	-0.881	0.012	0.046	0.770

19.93, whereas the control group's score was 10.33. The mean difference in the BBB scores was 9.6 (BBB score 0-21). Based on the Tukey HSD test, control and treatment groups were different, with a significance value of $P = 0.001$ ($P < 0.05$). The treatment group demonstrated a higher effect on improving the value of locomotor recovery in the rat SCI subacute contusion-compression model (Figure 4).

Table 4 Results of bootstrapping and blindfolding partial least squares structural equation modeling

	O	M	STDEV	T statistics (|O/STDEV|)	*P* values
Anti apoptotic - > lokomotorius	0.109	0.129	0.210	4.519	0.000
Anti inflammatory - > anti apoptotic	0.697	0.692	0.145	4.818	0.000
Anti inflammatory- > neuroangiogenesis	0.772	0.768	0.125	6.196	0.000
Neuroangiogenesis - > neurogenesis	0.176	0.183	0.258	4.682	0.000
Neurogenesis - > lokomotorius	0.754	0.782	0.130	5.789	0.000
Pro inflammatory - > anti inflammatory	0.600	0.622	0.193	3.102	0.002

O: Original sample; M: Sample mean; STDEV: Standard deviation.

Table 5 F square value

	Anti apoptotic	Antiinflammatory	Lokomotorius	Neuroangiogenesis	Neurogenesis	Pro inflammatory
Anti apoptotic			0.197			
Anti inflammatory	2.126			3.458		
Lokomotorius						
Neuroangiogenesis					0.797	
Neurogenesis			0.563			
Pro inflammatory		6.163				

Table 6 Q square value

	SSO	SSE	Q^2 (= 1-SSE/SSO)
Anti apoptotic	15.000	8.131	0.458
Anti inflammatory	30.000	24.178	0.194
Lokomotorius	15.000	6.222	0.585
Neuroangiogenesis	15.000	13.410	0.106
Neurogenesis	45.000	44.724	0.006
Pro inflammatory	60.000	60.000	

Table 7 R square value

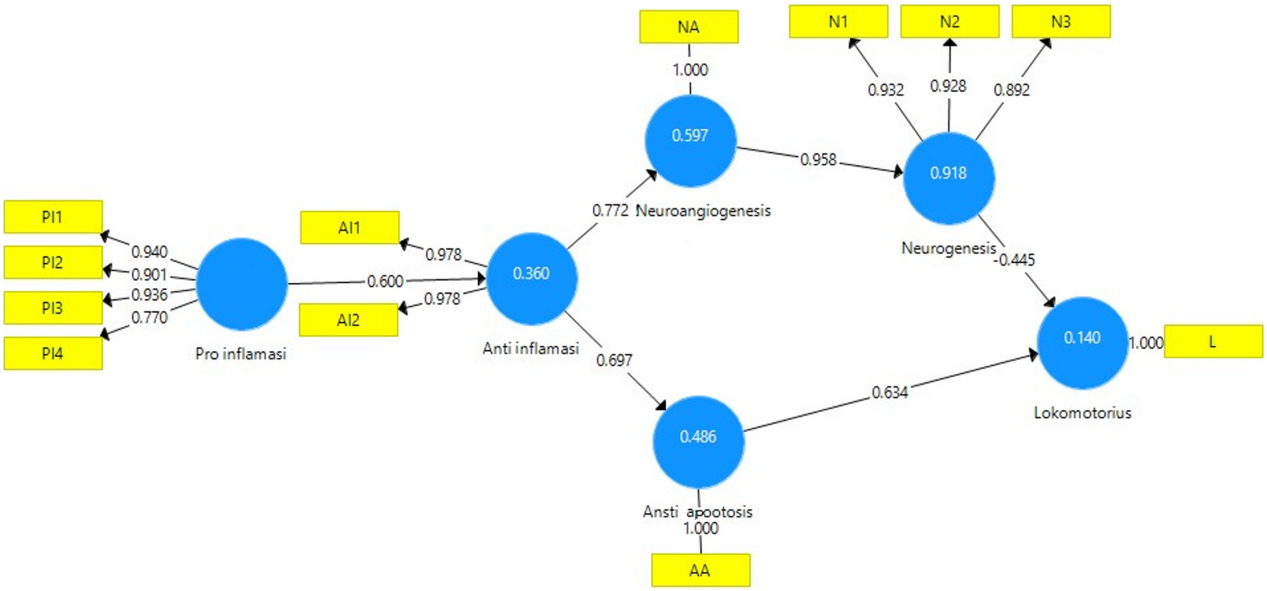
	R square	R square adjusted
Anti apoptotic	0.680	0.655
Anti inflammatory	0.860	0.850
Lokomotorius	0.536	0.459
Neuroangiogenesis	0.776	0.758
Neurogenesis	0.444	0.401

Spinal cord lession

The results of measurements size of spinal cord lesions in the control and treatment groups, successive mean values of 304.019 and 51.676, with the non-parametric test (Mann Whitney) found a significant difference in the size of the spinal cord lesion with a $P = 0.000$ (Figure 5).

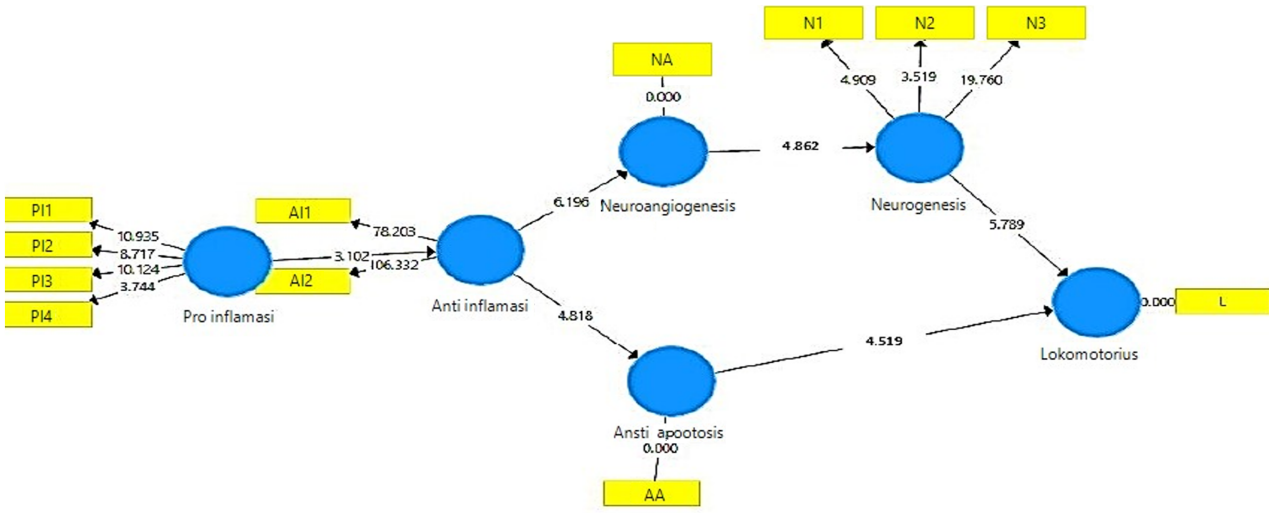
Oxidative stress cytokine (F2-Isoprostanes)

The examination results of oxidative stress (F2-Isoprostanes) showed a significant decrease in the



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Figure 2 Diagram outer model based on partial least squares algorithm.



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Figure 3 Diagram inner model using bootstrapping and blindfolding partial least squares structural equation modeling.

treatment group compared to the control group, with significance values of $P = 0.001$. The level of F2-Isoprostanes in the treatment group 258.40, were smaller than the control groups 338.82 (Figure 6A, Table 8).

Pro-inflammatory cytokine (NF-κB, TNF-α, MMP9)

The examination results of neuro pro-inflammation biomarkers (NF-κB, TNF-α, and MMP9) showed a significant decrease in the treatment group compared to the control group, with successive significance values of $P = 0.000$, $P = 0.032$, and $P = 0.001$. The number of cells expressing NF-κB, TNF-α, and MMP9 in the treatment group, with successive mean values of 1.400, 171.85, and 1.19, were smaller than the control groups, with values of 2820, 215.1, and 3.09 (Figures 6A, 6B and Figure 7, Table 8).

Anti-inflammatory cytokine (IL-10, TGF-β)

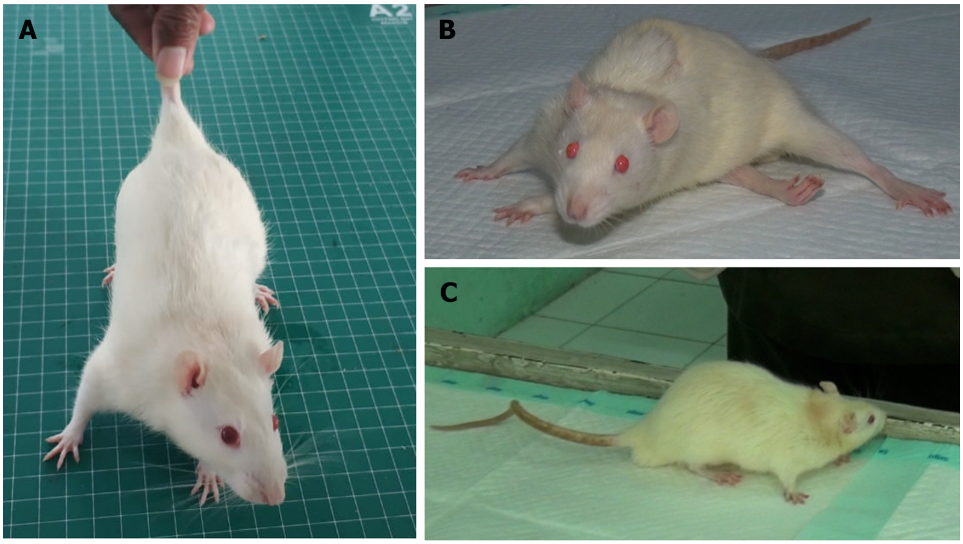
The immunohistochemical examination of neuro anti-inflammation biomarkers (IL-10 and TGF-β) showed a significant increase in the treatment group compared to the control group, with successive significance values of $P = 0.022$ and $P = 0.047$. The number of cells expressing IL-10 and TGF-β in the treatment group, with successive mean values of 3.160 and 2.740, were greater than the control groups, with values of 1.900 and 1.840 (Figures 6B and Figure 8, Table 8).

Table 8 Tukey HSD test results of all biomarkers

	Biomarker	Group	Group	*P* value
Oxidative stress	F2-Isoprostanes	Treatment (mean = 258.40; SD = 12.45)	Normal (mean = 252.59; SD = 25.54)	0.938
			Control (mean = 338.82; SD = 36.87)	0.001
Pro-inflammatory	NF-kB	Treatment (mean = 1.400; SD = 0.254)	Normal (mean = 0.475; SD = 0.206)	0.003
			Control (mean = 2.820; SD = 0.531)	0.000
	MMP-9	Treatment (mean = 1.19; SD = 0.931)	Normal (mean = 0.160; SD = 0.213)	0.217
			Control (mean = 3.09; SD = 1.056)	0.001
	TNF-α	Treatment (mean = 171.85; SD = 35.84)	Normal (mean = 105.07; SD = 11.34)	0.002
			Control (mean = 215.14; SD = 15.38)	0.032
Anti-inflammatory	IL-10	Treatment (mean = 3.160; SD = 0.801)	Normal (mean = 0.240; SD = 0.167)	0.000
			Control (mean = 1.900; SD = 0.734)	0.022
	TGF-β	Treatment (mean = 2.740; SD = 0.684)	Normal (mean = 0.260; SD = 0.181)	0.000
			Control (mean = 1.840; SD = 0.572)	0.047
Neuroangiogenesis	VEGF	Treatment (mean = 5.12; SD = 0.878)	Normal (mean = 0.220; SD = 0.130)	0.000
			Control (mean = 2.120; SD = 0.889)	0.000
Anti-apoptotic	Bcl-2	Treatment (mean = 2.02; SD = 0.712)	Normal (mean = 0.160; SD = 0.151)	0.000
			Control (mean = 0.500; SD = 0.380)	0.001
Neurogenesis	Nestin	Treatment (mean = 1.96; SD = 0.610)	Normal (mean = 0.160; SD = 0.114)	0.000
			Control (mean = 1.000; SD = 0.524)	0.018
	BDNF	Treatment (mean = 2.01; SD = 0.576)	Normal (mean = 0.40; SD = 0.482)	0.000
			Control (mean = 0.57; SD = 0.468)	0.001
	GDNF	Treatment (mean = 3.420; SD = 2.480)	Normal (mean = 1.420; SD = 0.356)	0.000
			Control (mean = 2.480; SD = 0.788)	0.043

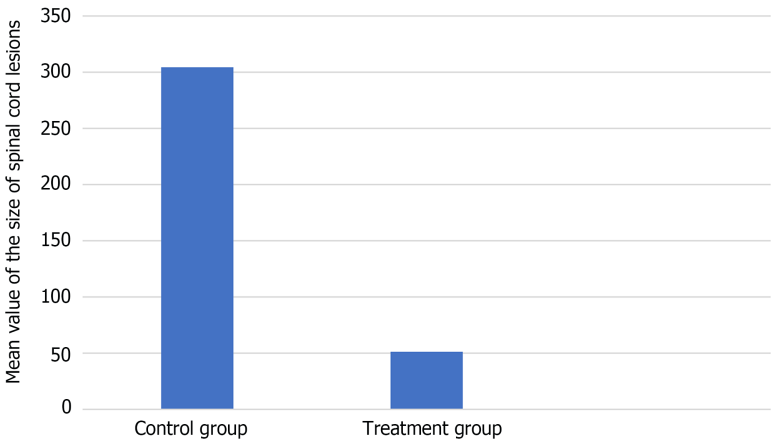
SD: standard deviation; NF-kB: Nuclear factor-kappa B; MMP9: Metalloproteinase matrix-9; TNF-α: Tumor necrosis factor-α; IL-10: Interleukin-10; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor; Bcl-2: B-cell lymphoma 2; BDNF: Brain-derived neurotrophic factor; GDNF: Glial cell line-derived neurotrophic factor; F2-Isoprostanes: Free radical oxidative stress.

Neuroangiogenesis cytokine (VEGF): The number expressing VEGF in the treatment group significantly differed from the control group (P = 0.000). Moreover, the number of cells expressing VEGF in the treatment group (5.12) was greater than the control group (2.120) (Figures 6B and Figure 9, Table 8).



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Figure 4 Evaluation Basso, Beattie, Bresnahan scores in different rat groups. A: Normal group; B: Control group; C: Treatment group.



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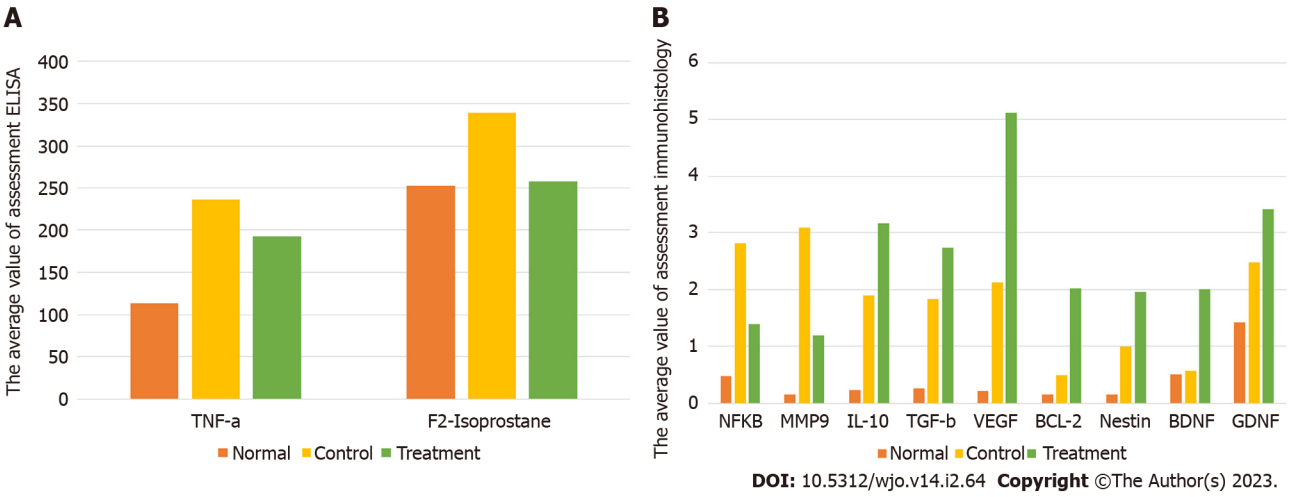
Figure 5 The mean value of the size of spinal cord lesions in the control and treatment groups.

Anti-apoptotic cytokine (Bcl-2): The number expressing Bcl-2 in the treatment group significantly differed from the control group (P = 0.001). Moreover, the number of cells expressing Bcl-2 in the treatment group (2.02) was greater than the control group (0.500) (Figures 6B and 10, Table 8).

Neurogenesis cytokine (nestin, BDNF, GDNF): The results of the immunohistochemical examination of neurogenesis biomarkers (nestin, BDNF, and GDNF) showed a significant increase in the treatment group compared to the control group, with successive significance values of P = 0.018, P = 0.001, and P = 0.043. The number of cells expressing nestin, BDNF, and GDNF in the treatment group with successive mean values of 1.96, 2.01, and 3.420 were greater than the control groups, which had mean values of 1.00, 0.57, and 2.480 (Figures 6B and 11, Table 8).

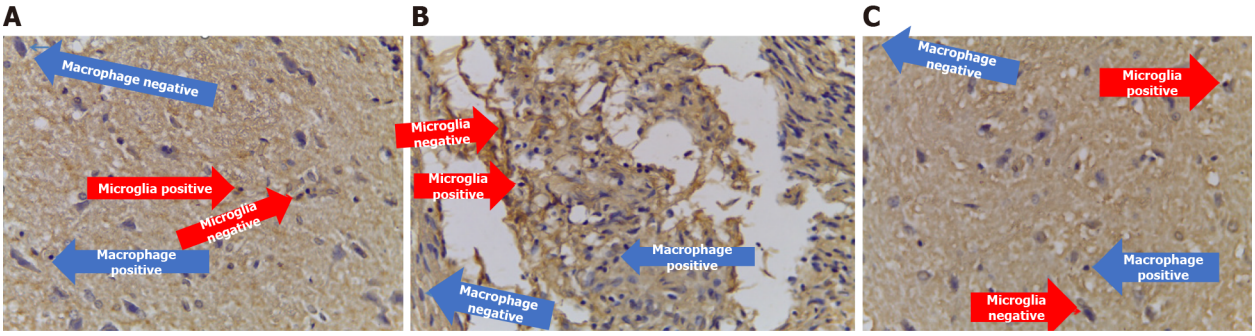
DISCUSSION

After HNSCs-secretome intrathecal injections in model SCI post-laminectomy rats, the results showed that HNSCs-secretome increased locomotor function, decreased size of spinal cord lesion, increased GDNF, BDNF, nestin, VEGF, Bcl-2, TGF-β, IL-10, and decreased TNF-α, F2-Isoprostanes, MMP-9, NF-κB. The mechanism of SCI was valid, based on the analyzed outer model, inner model, and hypothesis testing. It began with pro-inflammation, anti-inflammation, anti-apoptotic, neuroangiogenesis, neurogenesis, and locomotor function.



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Figure 6 The mean value of biomarker by enzyme-linked immunosorbent assay and immuhistochemichal assessment. A: Diagram showing the average value of enzyme-linked immunosorbent assay assessment; B: Diagram showing the average value of immuhistochemichal assessment. NF-kB: Nuclear factor-kappa B; MMP9: Metalloproteinase matrix-9; TNF-α: Tumor necrosis factor-α; IL-10: Interleukin-10; TGF-β: Transforming growth factor-β; VEGF: Vascular endothelial growth factor; Bcl-2: B-cell lymphoma 2; BDNF: Brain-derived neurotrophic factor; GDNF: Glial cell line-derived neurotrophic factor; F2-Isoprostanes: Free radical oxidative stress; ELISA: Enzyme-linked immunosorbent assay.



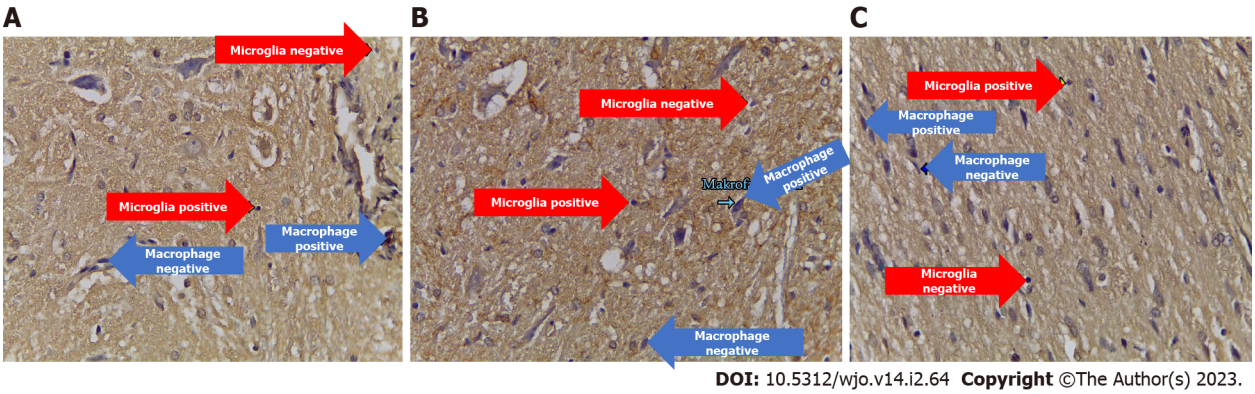
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Figure 7 We observed immunohistochemical matrix metalloproteinase 9 average value of 10 field of views, every field of view have 625 μ² with 400 × magnification. A: Treatment group; B: Control group; C: Normal group. Microglia (red arrow) are small round cells, solid nuclei and give a positive reaction with anti matrix metalloproteinase 9 (MMP9) indicated by brown color. While macrophage (blue arrow) cells are large, vesicular nucleus, and sometimes elongated resembling fibroblasts (macrophages like fibroblast) and give a positive reaction with anti MMP9 indicated by brown.

The results of this study are in accordance with findings from Cunningham *et al*[3] who stated that MSC-secretome in brain ischemia could modulate neurogenesis with an increase in BDNF, GDNF, and NT3. Kim *et al*[12] stated that adipose derived stem cell-secretome can provide anti-free-radical effects and reduce oxidative stress with the expression of F2-Isoprostane. Honmou *et al*[13] also stated that mononuclear stem cell secretome in SCI inhibited microvascular obstruction and thrombosis, promoted vasodilation, immunomodulation, and neuroprotection, while Santos *et al*[14] and Yang *et al*[15] stated that NSC-secretome in SCI stimulated the transformation of phenotype M1 to phenotype M2 of macrophages, microglia, and astrocytes through PgE2, IL-10, TGF-β, proliferator-activated receptor gamma[14,15]. Macrophage M2 secreted anti-inflammatory cytokines IL-4, IL-10, TGF-β, and hepatocyte growth factor, whereas macrophage M1 secreted pro-inflammatory cytokines IL-1, IL-6, IL-8, TNF-α, MMP9, and F2-Isophostane[14,15]. Miranpuri *et al*[5] stated that after trauma, there was an increase in inflammatory cells, such as macrophages, neutrophils, dendrites, and T-cells, as a result of ruptured blood vessels and increased vascular permeability.

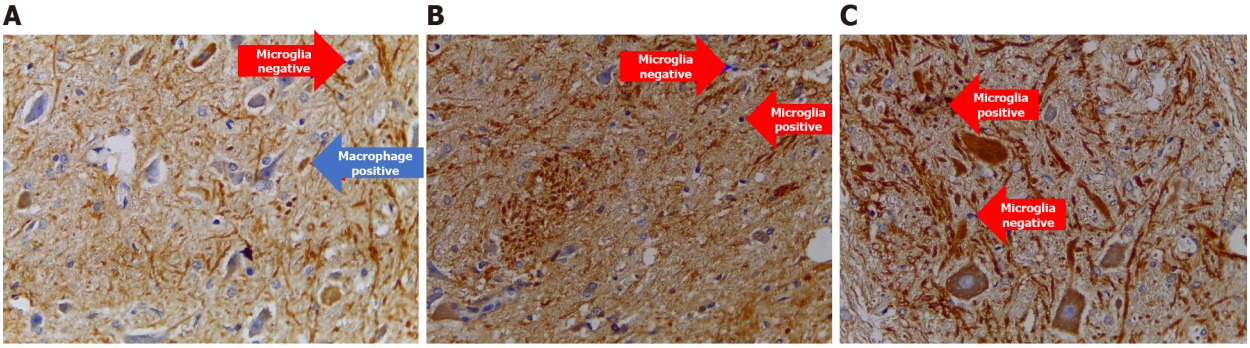
Oxidative stress cytokine (F2-Isoprostane)

The results of the HNSCs-secretome in SCI study, there was a decrease in the oxidative stress cytokine F2-Isoprostane, accordance with previous research by Kim *et al*[12] who stated that NSC-secretome acts as an anti-free radical and anti-oxidative stress agent in mouse-model SCI. Santos *et al*[14] stated that NSC-secretome has an antioxidant role that reduces F2-Isoprostane by inhibiting endoperoxidase, arachidonic acid, and reactive oxygen species (ROS). Oxidative stress plays an important role in the secondary phase of SCI[16]. The high oxidative stress of F2-Isoprostan affects the production of pro-



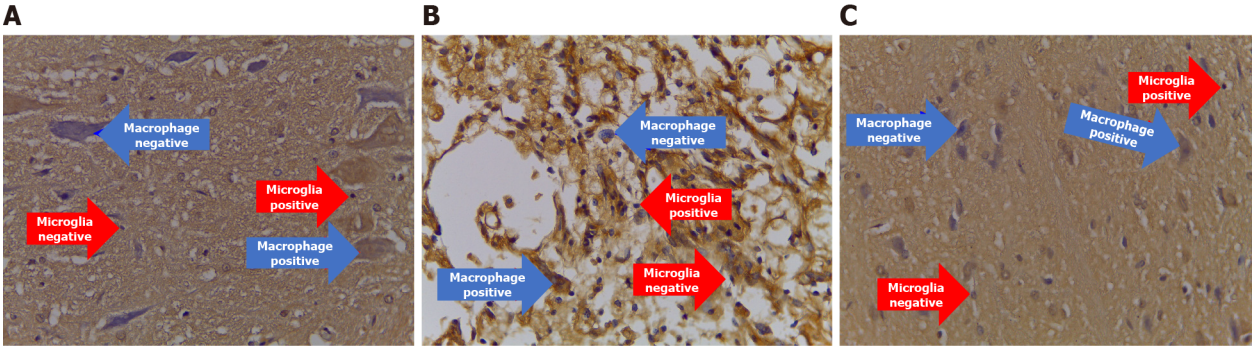
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Figure 8 We observed immunohistochemical transforming growth factor-β average value of 10 field of views, every field of view have 625 μ² with 400× magnification. A: Treatment group; B: Control group; C: Normal group. Microglia are small round cells, solid nuclei and give a positive reaction with anti-transforming growth factor-beta (TGF-β) indicated by brown color. While macrophage cells are large, vesicular nucleus,and sometimes elongated resembling fibroblasts (macrophages like fibroblast) and give a positive reaction with anti TGF-β indicated by brown.



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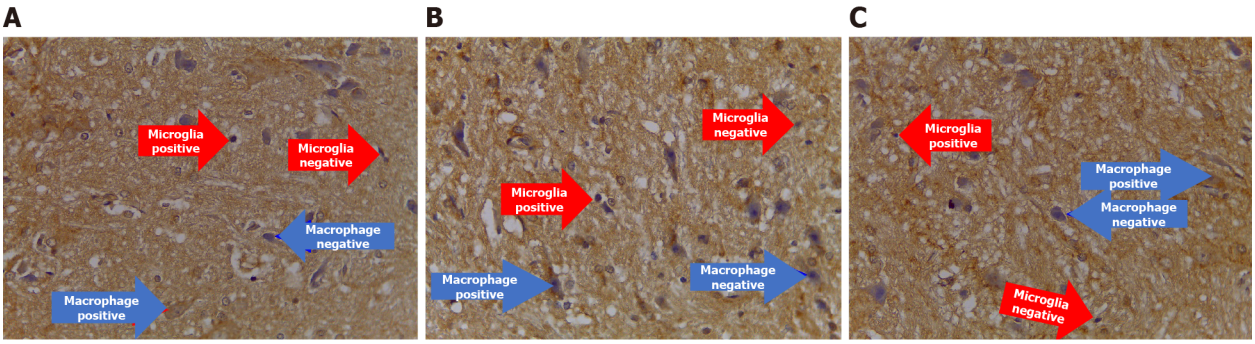
Figure 9 We observed immunohistochemical vascular endothelial growth factor average value of 10 field of views, every field of view have 625 μ² with 400 × magnification. A: Treatment group; B: Control group; C: Normal group. Microglia are small round cells, solid nuclei and give a positive reaction with anti-vascular endothelial growth factor (VEGF) indicated by brown color. While macrophage cells are large, vesicular nucleus, and sometimes elongated resembling fibroblasts (macrophages like fibroblast) and give a positive reaction with anti-VEGF indicated by brown.



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Figure 10 We observed immunohistochemical B cell lymphoma-2 average value of 10 field of views, every field of view have 625 μ² with 400 × magnification. A: Treatment group; B: Control group; C: Normal group. Microglia are small round cells, solid nuclei and give a positive reaction with anti B-cell lymphoma 2 (Bcl-2) indicated by brown color. While macrophage cells are large, vesicular nucleus, and sometimes elongated resembling fibroblasts (macrophages like fibroblast) and give a positive reaction with anti Bcl-2 indicated by brown.

apoptotic proteins, inhibits the anti-apoptotic protein Bcl-2, damage to the function of the mitochondria, and affects DNA fragmentation, resulting in apoptotic[17]. The decrease in antioxidants also through neurotrophic NSC factors such as BDNF by increasing the activity of antioxidant enzymes super oxide dismutase, glutathione peroxidase, glutathione reductase, sulfiredoxin, and sestrin2[18]. Antioxidant activity reduces ROS, increases mitochondrial uncoupling protein 2, and restores the mitochondrial



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Figure 11 We observed immunohistochemical brain derived neurotrophic factor average value of 10 field of views, every field of view have 625 μ² with 400 × magnification. A: Treatment group; B: Control group; C: Normal group. Normal group. Microglia are small round cells, solid nuclei and give a positive reaction with anti-brain derived neurotrophic factor (BDNF) indicated by brown color. While macrophage cells are large, vesicular nucleus, and sometimes elongated resembling fibroblasts (macrophages like fibroblast) and give a positive reaction with anti BDNF indicated by brown.

electron-coupling capacity to its original state by inducing the accumulation of phosphorylated cAMP response element binding protein in the mitochondrial matrix and membrane, assisting the synthesis of complex V mitochondria to protect apoptotic[13].

Pro-inflammatory cytokines (NF-κB, TNF-α, and MMP9)

After administering HNSCs-secretome to SCI-affected rats, there was a decrease in the pro-inflammatory cytokines NF-κB, MMP9, and TNF-α. Cheng *et al*[19] stated that NSC-secretome in SCI can suppress the inflammatory process by reducing the number of macrophages and microglia, decreasing inducible nitric oxide synthase by promoting SCI regeneration. Rong *et al*[20] stated that a decrease in proinflammatory cytokines occurred due to the autophagy activity of macrophages after administration of NSC-secretome. TNF-α, MMP9, and F2-Isoprostan decreased due to the transformation of macrophages phenotypes M1 to M2[14,15].

The decrease in NF-κB levels in this study is in accordance with research conducted by Wang *et al*[21] and Chen *et al*[22], which stated that there was a decrease in NF-κB levels after MSC-secretome intervention in mouse-model SCI. Chen *et al*[22] stated that a decrease in NF-κB will encourage axon regeneration through the phosphatase and tensin homolog/AKT/mammalian target of rapamycin pathway, where NF-κB serves to provide intracellular signals for macrophages to release pro-inflammatory cytokines such as MMP9 and TNF-α.

In this study, after administering HNSCs-secretome to SCI-affected rats, there was a decrease in the pro-inflammatory cytokine TNF-α, accordance with five previous studies by Huang *et al*[23], Cizkova *et al*[24], Huang *et al*[25], and Borhani-Haghighi *et al*[26], who stated that there was a decrease in TNF-α after MSC-secretome intervention in mouse-model SCI. The cytokine TNF-α is the most influential proinflammatory mediator in SCI, followed by other proinflammatory mediators such as interferon gamma, IL-6, and IL-8[27]. M1 phenotype macrophages secrete TNF-α through several mechanisms, namely NF-κB signaling, mitogen activated protein kinase, c-Jun N-terminal kinase, extrinsic apoptotic pathway, and extracellular signal-regulated kinase 1/2[28]. TNF-α influences the development of secondary injury by increasing inflammation, oxidative stress (F2-Isoprostane), and modulating apoptotic mechanisms[20]. TNF-α plays a role in increasing the endogenous migration of NSCs to the site of SCI by upregulating the chemokine receptors (CCR)2, CCR3, and CCR4 and motif C-C receptors [29].

This study showed that HNSCs-secretome in SCI could reduce MMP9 biomarkers, accordance with the research of Xin *et al*[30], who stated that there was a decrease in MMP9 and an increase in tissue inhibitor of metalloproteinases (TIMP) after administration of human bone marrow MSC (hBMSC) secretome in mouse-model SCI. MMP9 is inhibited by TIMP, while TIMP is inhibited by TGF-β[5]. This system modulates macrophage invasion and myelin destruction, which has an important role in neuropathic pain and contributes to glail scar formation[5].

Anti-inflammatory cytokines (IL-10 and TGF-β)

In this study, after administering HNSCs-secretome to SCI-affected rats, in addition to decreasing pro-inflammatory cytokines, there was also an increase in anti-inflammatory cytokines IL-10 and TGF-β. The increase in IL-10 cytokines accordance with a study conducted by Chudickova *et al*[31], who stated that there was an increase in IL-10 as an anti-inflammatory factor in the systemic immunological response after BMSC secretome intervention on SCI. IL-10 can decrease MMP9 synthesis, induce macrophage polarization from M1 to M2 phenotypes, reduce inflammatory response, and suppress inflammatory cells[32,33]. IL-10 can inhibit the initial effect of MMP9 in terms of the degradation of the basal lamina blood medulla spinal barrier matrix[5,32]. Previous studies have shown that systemic IL-10 injection

results in significant neuroprotection and greater functional improvement after SCI trauma[33]. IL-10 also provides anti-apoptotic support to neurons, reduction of lesion size, and improvement of locomotor function[33,34].

In this study, TGF-β increased in the treatment group compared to the control and normal groups, accordance with research by Cunningham *et al*[3], who state that there was an increase in TGF-β after MSC-secretome intervention in the ischemic brain. In addition to TGF-β, other anti-inflammatory agents, including BDNF, CXCL12, GDNF, hypoxia-inducible factor -1alpha (HIF-1α), IL-10, and VEGF, were also found. TGF-β also plays a role in overcoming matrix degradation, which is caused by the effect of MMP9[5]. TGF-β is involved in neuronal repair and regeneration and has been observed to inhibit neuronal damage and stimulate cell survival, growth, proliferation, differentiation, and invasion of neurons and glial cells[33].

Neuroangiogenesis cytokine (VEGF): The results of the HNSCs-secretome study in SCI showed an increase in the neuroangiogenesis cytokine VEGF, accordance with three previous studies by Cizkova *et al*[24], Liu *et al*[35], and Zhong *et al*[36], who stated that there was an increase in VEGF after MSC-secretome administration in mouse-model SCI. Cunningham *et al*[3] stated that in addition to VEGF, there was also an increase in other angiogenesis factors such as PDGF, BDNF, GDNF, basic fibroblast growth factor, CXCL12, Ang-1, Ang-2, and HIF-1α. Zhong *et al*[36] stated that administration of NSC-secretome in acute SCI can increase the expression of VEGF-A, which promotes axon proliferation and the migration of spinal cord microvascular endothelial cells from the third day post-injection, reduces lesion size, glial scars, and improves locomotor function in a mouse-model of SCI. VEGF is the highest protein found in the angiogenesis process, while VEGF-A is more commonly found in NSC-secretomes than in NSCs themselves[36]. VEGF plays a role in neuroprotection, with blood vessel formation starting on day 3 to 10 and optimally on day 14, where perfusion, oxygenation, and carbohydrate metabolism occur[24,35-37].

Anti-apoptotic cytokine (Bcl-2): In this study, there was an increase in Bcl-2 as an anti-apoptotic factor of HNSCs-secretome in a mouse model of SCI, consistent with three previous studies by Huang *et al*[23], Liu *et al*[35], and Zhou *et al*[27], who stated that there was an increase in Bcl-2 levels after MSC-secretome intervention in mouse-model SCI. Rong *et al*[20] stated that there was an increase in Bcl-2 and a decrease in caspase 3 due to the role of secretome anti-apoptotic factors in SCI regeneration. Bcl-2 functions as an anti-apoptotic factor by blocking the release of cytochrome-c from the mitochondria into the cytosol, thereby preventing the activation of caspase-3 and caspase-9[27,38,39].

Neurogenesis growth Factor (nestin, BDNF, and GDNF): The results of the HNSCs-secretome study in SCI, an increase in the neurogenesis growth factors nestin, BDNF, and GDNF. Cunningham *et al*[3] state that neurogenesis in brain ischemia is influenced by an increase in BDNF and GDNF after MSC-secretome administration.

Červenka *et al*[40] state that HNSCs-secretome increases nestin levels in brain and spinal cord trauma, and nestin is a more significant biomarker than SRY-box 2, doublecortin, tubulin-3 chain, and microtubule-associated protein 2 in identifying the differentiation of NSCs from pre-progenitor NSCs. Accordance with the research of Zhong *et al*[36], who found that the presence of nestin growth factor is a marker of the presence of neuron cells. Pajer *et al*[8] and Gilbert *et al*[41] also state that nestin is a neurotrophic factor that expresses the presence of NSC progenitors.

In this study, BDNF increased in the treatment group compared to the control and normal groups. Chudickova *et al*[31] and Gu *et al*[42] state that NSC-secretome in animal models with SCI, there was an increase in BDNF at week 1 and a maximum increase at week 6 that could reduce lesion size, minimize glial scar formation, and promote axon regeneration. BDNF is produced mostly by neuronal cells and is a neurotropin that is important in the regulation of neurogenetic processes such as increased axon collateral growth, nerve branching, dendrite formation, and synaptic plasticity[43]. BDNF works through cannabinoid receptor type 1 (CB1R) and CB2R receptors to promote neuronal differentiation and prevent nuclear degeneration[44]. In addition, BDNF also works through the tropomyosin kinase B receptor and low-affinity nerve growth factor receptor (GFR) commonly called p75[45]. Shahsavari *et al*[46] state that BDNF has neurophysiological functions such as nociception, cognition, and memory.

In this study, GDNF increased sharply in the treatment and control groups compared to the normal group, and the treatment group was slightly higher than the control group. Cheng *et al*[19] and Zhong *et al*[36] found that NSC-secretome increase the occurrence of axon regeneration, collateral formation, and the occurrence of new circuits in axon pathways by activating neurons and glial cells. Rosich *et al*[47] state that GDNF plays a role in the spinal cord in reducing lesion size, cystic cavity, increasing locomotor function improvement, nerve differentiation, chemoattractant, migration, neuroprotectant, neuroplasticity, and axon regeneration. GDNF also exerts a substantial neuroprotective effect by increasing the number of neurons in the SCI and the supraspinal central canal area[48]. GDNF acts through GFRα 1-4 receptors and is rearranged during transfection tyrosine kinase[49]. GDNF is a neurotropin involved in increasing the number of motor neurons, regenerating distal nerve axons, forming synapses, and myelination[48].

Locomotor function BBB score: Locomotor function is one of the most significant therapeutic intervention goals demonstrating the efficacy of administering HNSCs-secretome treatment in subacute SCI. Administration of HNSCs-secretome significantly improved locomotor function starting on day 7 and continuing until day 56, with mean value is 19.93 and standard deviation is 6.28. This is in accordance with previous studies that showed an increase in locomotor function improvement after NSC-secretome intervention in three studies[19,20,36].

Spinal cord lession: The treatment group showed significant differences where the treatment group showed smaller lesion sizes compared to the control group, successive mean values of 304.019 and 51.676. This is in accordance with previous studies that showed an descreased size of spinal cord lesion after MSC-secretome intervention in three studies[24,31,37].

Mechanism of SCI regeneration: The mechanism of SCI regeneration is still uncertain[3,8]. In this study, we found that analysis of the outer model, inner model, and hypothesis testing were valid. SCI regeneration begins with pro-inflammation and continues with anti-inflammatory, anti-apoptotic, neuroangiogenesis, neurogenesis, and locomotor function. Inner model by path bootstrapping analysis found that all pathways had positive original sample values, with T-statistics more than 1.96 and *P*-values more than 0.05, determined to be significantly different. The relationships between latent variables in the inner model were valid based on an F square (effect size) more than 0.05, Q square (prediction relevance) more than 0, and positive path coefficients. The R square (coefficient of determination on endogenous variables) anti-inflammatory value of 0.860 indicated an effect of 86%, the anti-apoptotic value of 0.680 indicated an effect of 68%, the neuroangiogenesis value of 0.776 indicated an effect of 77%, the neurogenesis value of 0.444 indicated an influence of 44%, and the locomotory value of 0.536 indicated an influence of 53%. The outer model was valid based on the PLS SEM algorithm, the convergent validity value was more than 0.7, the AVE value was more than 0.5, and the Cronbach's alpha value was more than 0.5. The discriminant validity based on cross-loading indicator was higher than the other construct variable indicators, while composite reliability was more than 0.7.

Assinck *et al*[50] state that spinal cord regeneration has five mechanisms: neuroprotection, immunomodulation, axon growth/regeneration, human neural relay formation, and myelin regeneration. Anjum *et al*[6] also state that tissue regeneration is divided into three overlapping phases, namely, cell death and inflammation, cell proliferation and tissue replacement, and tissue remodeling. Vizoso *et al*[11], and Cunningham *et al*[9], stated that advantages of secretome (cell free therapy) compared to stem cell, are the secretome solves problems that have so far arisen in stem cell applications, namely from the aspect of live cell transplantation to donors (immune compatibility, tumorigenicity, embolism formation, and infection transmission); storage is easier by not giving it a toxic cryopreservative agent for a long time; it is more practical and economical because it does not use invasive cell retrieval procedures compared to stem cell based therapy; mass production is more possible; time and maintenance costs for stem cell culture can be reduced, it is said that it takes hundreds of millions of MSCs each time for therapy, and cell expansion *in vitro* is needed for 10 wk before implantation, implantation time is also said to take quite a long time to be effective; in one study it was said that < 1 percent of MSCs survived after systemic administration; and it is also said that the main factor in stem cell therapy is through the paracrine effect, which is owned by the secretome[3,11]. The key limitations of study do not cover the chronic SCI model. HNSCs-secretome is expected to be the basis for use in SCI cases in the primary research stage, translational research, and neurological research for the benefit of managing SCI disease problems.

CONCLUSION

These findings may identify HNSCs-secretome as a neuroprotective-neuroregenerative agent for treating SCI. The SCI regeneration mechanism started with pro-inflammation and continued with anti-inflammation, anti-apoptotic, neuroangiogenesis, neurogenesis, and locomotor function.

ARTICLE HIGHLIGHTS

Research background

Globally, complete neurological recovery of spinal cord injury (SCI) is still less than 1%, and 90% experience permanent disability. The key issue is that a pharmacological neuroprotective-neuroregenerative agent and SCI regeneration mechanism have not been found. The secretomes of stem cell are an emerging neurotrophic agent, but the effect of human neural stem cells (HNSCs) secretome on SCI is still unclear.

Research motivation

HNSCs-secretome is expected to be the basis for use in SCI cases in the primary research stage, translational research, and neurological research for the benefit of managing SCI disease problems.

Research objectives

To investigate the effects of HNSCs-secretome and the regeneration mechanism on subacute SCI in rats.

Research methods

An experimental study was conducted with 45 Rattus norvegicus, divided into 15 normal, 15 control (10 mL physiologic saline), and 15 treatment (30 μL HNSCs-secretome, intrathecal T10, three days post-traumatic). The strategies to increase the HNSCs-secretome production capacity include hypoxic preconditioning, tissue engineering, and growth medium composition. Locomotor function was evaluated weekly by blinded evaluators. Fifty-six days post-injury, specimens were collected, immunohistochemical-enzyme-linked immunosorbent assay assessment, and hematoxylin-eosin staining. We analyzed free radical oxidative stress (F2-Isoprostanes), nuclear factor-kappa B (NF-κB), matrix metallopeptidase 9 (MMP9), tumor necrosis factor-alpha (TNF-α), interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), B cell lymphoma-2 (Bcl-2), nestin, brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and spinal cord lesion. The regeneration mechanism of SCI was analyzed using partial least squares structural equation modeling (PLS SEM).

Research results

The regeneration mechanism of SCI is valid by analyzed outer model, inner model, and hypothesis testing in PLS SEM, started with pro-inflammation followed by anti-inflammation, anti-apoptotic, neuroangiogenesis, neurogenesis, and locomotor function. HNSCs-secretome significantly improved locomotor recovery, reduced spinal cord lesion size, increased neurogenesis (nestin, BDNF, and GDNF), neuroangiogenesis (VEGF), anti-apoptotic (Bcl-2), anti-inflammatory (IL-10 and TGF-β), but decreased pro-inflammatory (NF-κB, MMP9, TNF-α), F2-Isoprostanes.

Research conclusions

HNSCs-secretome as a potential agent for the treatment of SCI and uncover the SCI regeneration mechanism.

Research perspectives

Future research investigating the chronic phase of SCI models may provide further evidence regarding the mechanism of SCI regeneration given HNSCs-secretome injection.

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FOOTNOTES

Author contributions: Semita IN, Utomo DN, and Suroto H designed and coordinated the study; Semita IN performed the experiments, acquired and analyzed data; Semita IN interpreted the data; Semita IN wrote the manuscript; and all authors approved the final version of the article.

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LETTER TO THE EDITOR

Effect of SARS-CoV-2 infection on trauma throughput to alternative elective care approaches

Beuy Joob, Viroj Wiwanitkit

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Abstract

In response to the paper on coronavirus disease 2019's effects on trauma throughput, elective care models should be modified. Concerns about the relevant factors and their potential therapeutic applications are brought up and looked into.

Key Words: Trauma; Model; Adaptive care; COVID-19

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Core Tip: This letter to the editor is in reaction to the article: The influence of coronavirus disease 2019 (COVID-19) on trauma throughput and the adaptation of elective care paradigms. Concerns are raised and examined concerning the factors involved and their therapeutic application. The model's influence may be limited to the COVID-19 pandemic phase and may not be applicable to the post-COVID-19 period.

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TO THE EDITOR

We read with interest a case report on "Utilising the impact of COVID-19 on trauma throughput to adapt elective care models for more efficient trauma care" by Kulkarni *et al*[1]. Kulkarni *et al*[1] investigated the effect of severe acute respiratory syndrome

coronavirus 2 infection on service delivery. A comparison between throughput and productivity parameters during the pandemic with those observed in the previous years was performed in order to search for successful, cost-effective, and long-term differences in practice[1]. Coronavirus disease 2019 (COVID-19) has resulted in a practical change in the delivery and access to care, according to Kulkarni *et al*[1], with many changes and adaptations anticipated to affect healthcare services in the future.

We all believe that coronavirus disease 2019 (COVID-19) necessitates medical care adjustments. During an emergency, adjustments may be made, but it should be recognized that the standards of care must still be met. Kulkarni *et al*'s recent report may reflect their experience during the pandemic[1]. However, if the models are to be employed in the post-crisis period, they must be carefully considered. In the absence of an emergency, resuming full-scale normal treatment may be necessary. Some options, such as delayed case management and telemedicine management, may be avoided. While some studies have demonstrated that different orthopaedic surgeries may be considered elective, medically required surgery must continue in areas with minimal medical care[2]. This could be the fundamental medical notion of first doing no harm to the patient. Furthermore, the COVID-19 period's epidemiological pattern of the medical problem may differ from the pre-COVID-19 period. The model's effect may differ depending on the disease pattern[3]. The model's influence may be limited to the COVID-19 pandemic phase and may not be applicable to the post-COVID-19 period. In order to assess the exact effect of adapting elective care models, there should be a long term follow-up, and the relationship with the changing background situation should also be assessed. Finally, in addition to the present clinical outcome measurement, it should place a greater emphasis on the patient's perspective on the change. This is a point that is frequently overlooked in many investigations.

FOOTNOTES

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LETTER TO THE EDITOR

New classification for septic arthritis of the hand

Konstantin V Lipatov, Arthur Asatryan, George Melkonyan, Aleksandr D Kazantcev, Ekaterina I Solov'eva, Irina V Gorbacheva, Alexander S Vorotyntsev, Andrey Y Emelyanov

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Abstract

The severity of septic arthritis of the hand and the prospects for restoration of joint function are determined by a complex of factors. Among them, the leading role belongs to local changes in tissue structures. This includes the destruction of articular cartilage and bone tissue with the development of osteomyelitis, the involvement of paraarticular soft tissues in the purulent process, and the destruction of the flexor/extensor tendons of the fingers. The currently missing specialized classification of septic arthritis could help in systematizing the diseases, determining treatment tactics, and predicting the results of treatment. The classification of septic arthritis of the hand proposed for discussion is based on the following principle: Joint–Wound–Tendon ($J_xW_xT_x$); J_x characterizes damage to the osteochondral structures of the joint, W_x is the presence of paraarticular purulent wounds or fistulas, and T_x is destruction of the flexor/extensor tendons of the finger. The classification of the diagnosis makes it possible to assess the nature and severity of damage to the structures of the joint and may also be useful when comparing the results of treatment of septic arthritis of the hand.

Key Words: Hand; Septic arthritis; Classification; Osteomyelitis; Paraarticular wounds

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Core Tip: The absence to date of a specialized classification of septic arthritis of the hand determines the relevance of its development. The proposed classification is based on the principle JOINT-WOUND-TENDON and reflects in aggregate the lesion of the osteo-cartilaginous structures of the joint, paraarticular soft tissues, and tendons of the flexor/extensor of the finger.

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TO THE EDITOR

Septic arthritis of the hand is a common infectious pathology of the joints and ranks second in frequency after inflammation of the knee joint[1]. Given the high functional significance of the small joints of the hand, their inflammation often leads to serious consequences, sometimes ending in limitation or even disability. The most common cause of septic arthritis of the hand is various penetrating wounds. The pathogenic microflora that has entered the joint cavity causes the development of an infectious process, which, if surgical care is not provided in time, leads to the destruction of the articular cartilage and the development of osteomyelitis. In septic arthritis of the hand, a purulent process often occurs in paraarticular tissues with the formation of wounds and fistulas, which has a significant impact on the extent of surgical intervention and the results of treatment in general. The inflammatory process in the small joints of the hand, proceeding with purulent-necrotic lesions of the surrounding soft tissues, may be accompanied by destructive changes in the area of the flexor/extensor tendons of the finger, which negatively affects the prospects for restoring movements in the joint. This fact distinguishes the course of septic arthritis of the hand from purulent arthritis of large joints, in which tendon damage is uncharacteristic[2].

Thus, the course of septic arthritis of the hand and the features of treatment and its results are determined by a complex of pathological changes in the osteochondral apparatus, paraarticular soft tissues, and flexor/extensor tendons of the finger. While analyzing the literature on septic arthritis of the hand (published in the *World Journal of Orthopedics* 2022; 13: 622-630)[3], we faced problems comparing the results of surgical treatment presented by different authors.

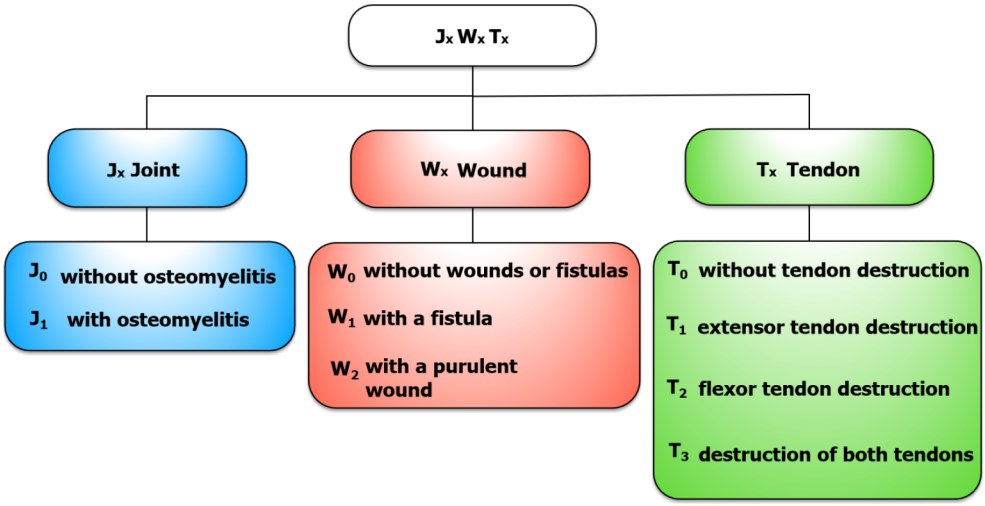
To obtain reliable results, it is necessary to understand the nature and extent of tissue damage in the observations that we compare.

Evaluating the response to treatment of isolated septic arthritis, septic arthritis with osteomyelitis, purulent process in the paraarticular soft tissues, and tendon destruction can hardly be justified. However, in most cases, the authors use the term "septic arthritis of the hand" when formulating the diagnosis, only occasionally highlighting cases with osteomyelitis[4].

As a consequence, comparison of the results of treatment presented by different experts may be incorrect since the severity of the disease was initially different. In this regard, the use in clinical practice and in the course of scientific analysis of the classification of the pathological process is of great importance. However, to date, there has been no specialized classification of septic arthritis of the hand. According to the most common classification of hand infection given by Brown[5], only two forms can be attributed to the characteristics of purulent arthritis: Osteomyelitis and septic arthritis. However, this is clearly not enough in view of the above arguments[5]. This can be partially compensated for by using the classification of Tan *et al*[6] for infection of the joints of the hand, which was developed to characterize the inflammatory process in large joints[6]. It presents information about the damage to the osteochondral structures of the joint and paraarticular soft tissues (*isolated septic arthritis; septic arthritis with soft-tissue extension, but no osteomyelitis; septic arthritis with contiguous osteomyelitis*). At the same time, this classification does not reflect the presence/absence of destruction of the tendon apparatus, which is rare in arthritis of large joints but is extremely important in septic arthritis of the hand. In addition, the classification of Tan *et al*[6] is quite voluminous, which makes it difficult to use it in wide clinical practice.

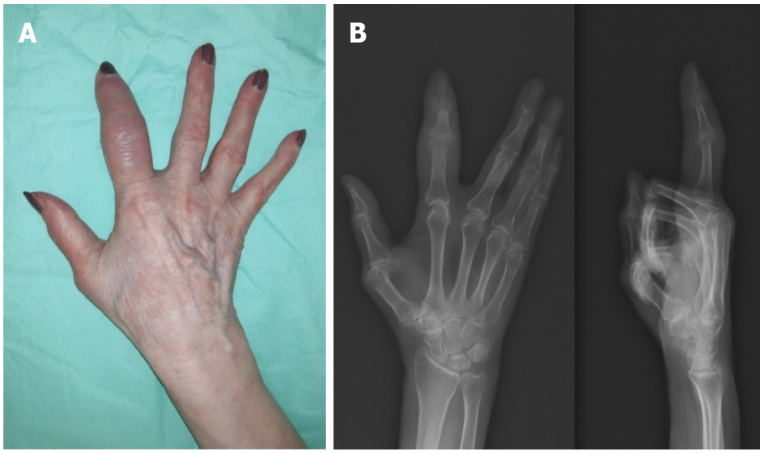
We have significant experience in the treatment of patients with septic arthritis of the hand and would like to propose our classification of septic arthritis of the hand.

The classification is based on the principle of Joint−Wound−Tendon ($J_xW_xT_x$) and takes into account the presence of damage to the osteochondral structures of the joint, paraarticular soft tissues, and tendon apparatus.



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Figure 1 New classification for septic arthritis of the hand. $J_xW_xT_x$: Joint−Wound−Tendon.



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Figure 2 Septic arthritis of the proximal interphalangeal joint of the index finger ($J_1W_0T_0$). A: Hand after repeated treatment; B: X-ray.

The symbol J_x characterizes the lesion of the osteochondral structures of the joint, where the index "x" determines the presence or absence of a sign: J_0–without osteomyelitis; J_1–with osteomyelitis.

The symbol W_x characterizes the presence of purulent wounds or fistulas in the paraarticular region: W_0–without wounds or fistulas; W_1–with a fistula; W_2–with a purulent wound.

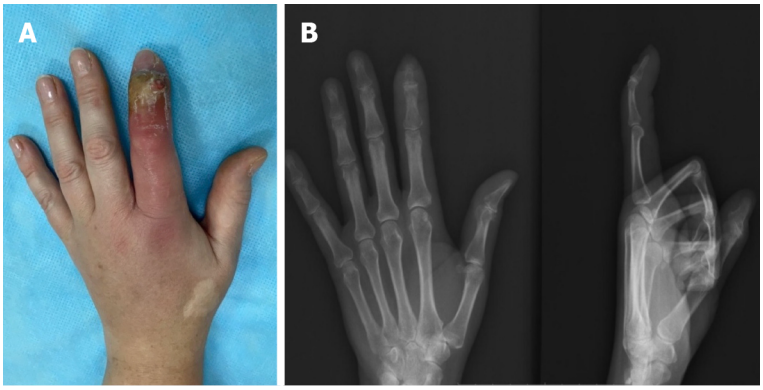
The symbol T_x characterizes the destruction of the flexor/extensor tendons: T_0–without tendon destruction; T_1–extensor tendon destruction; T_2–flexor tendon destruction; T_3–destruction of both tendons.

Schematically, this classification can be represented below (Figure 1).

Examples of the application of this classification in the formulation of a diagnosis are shown below (Figures 2-4).

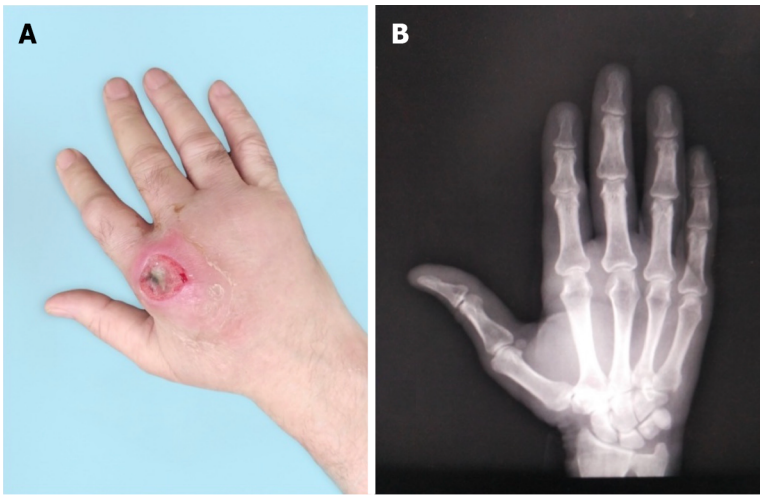
A 58-year-old woman pricked the index finger of her right hand with a needle while doing embroidery 3 wk ago. A day later, she noticed swelling of the finger and aching pain, aggravated by bending the finger. She was examined by a polyclinic surgeon and received a course of antibacterial drugs with some positive effect. Despite this, finger edema and pain on flexion persisted, which served as the basis for a second visit to the doctor. Upon further diagnostic testing, X-ray showed osteomyelitis in the proximal interphalangeal joint. On magnetic resonance imaging, there was purulent inflammation in the joint without destruction of the capsule and tendon apparatus (Figure 2).

A 54-year-old woman pricked the index finger of her left hand with a plant thorn while gardening a month ago. The next day, she noted swelling of the nail phalanx and reddening of the skin. She was self-treated using topical antiseptics and oral antibiotics (amoxicillin). The inflammation subsided, but a week ago, swelling and redness of the skin and pain reappeared in the same area. After using ointment dressings, a purulent fistula opened. X-ray showed signs of osteomyelitis in the area of the distal interphalangeal joint (DIP). On examination, there was a purulent fistula in the DIP projection. Intraop-



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Figure 3 Septic arthritis of the distal interphalangeal joint of the index finger ($J_1W_1T_1$). A: During hospitalization; B: X-ray.



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Figure 4 Septic arthritis of the 2nd metacarpophalangeal joint of the right hand ($J_0W_2T_1$). A: During hospitalization; B: X-ray.

erative finding included the destruction of the joint capsule and extensor tendon (Figure 3).

A 30-year-old man injured his right hand as a result of a blow with a fist in a fight 10 d ago. The patient did not consult a doctor. He treated himself independently with topical antiseptics. During the last few days, the pain increased, the swelling of the hand increased, and the discharge from the wound became purulent. Wound revision revealed damage to the extensor tendon of the finger and a violation of the integrity of the capsule of the metacarpophalangeal joint and purulent exudate in the joint cavity. Upon further diagnostic testing, X-ray showed no evidence of osteomyelitis (Figure 4).

Thus, a specialized classification of septic arthritis of the hand takes into account the main pathological changes that occur in this disease: Destruction of bone and cartilage structures, paraarticular soft tissues, and tendon apparatus. Its use can help in predicting the course of the inflammatory process, determining treatment tactics, and determining the nature and timing of the start of rehabilitation measures. The use of the classification will make it possible to objectify the comparison of the results of treatment of septic arthritis of the hand presented by various authors.

FOOTNOTES

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The primary aim of *World Journal of Orthopedics* (*WJO*, *World J Orthop*) is to provide scholars and readers from various fields of orthopedics with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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REVIEW

Utility of D-dimer in total joint arthroplasty

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Abstract

As the number of patients receiving total joint replacements continues to rise, considerable attention has been directed towards the early detection and prevention of postoperative complications. While D-dimer has long been studied as a diagnostic tool in venous thromboembolism (VTE), this assay has recently received considerable attention in the diagnosis of periprosthetic joint infection (PJI). D-dimer values are substantially elevated in the acute postoperative period after total joint arthroplasty, with levels often exceeding the standard institutional cutoff for VTE (500 μg/L). The utility of D-dimer in detecting VTE after total joint replacement is currently limited, and more research to assess its value in the setting of contemporary prophylaxis protocols is warranted. Recent literature supports D-dimer as a good to excellent biomarker for the diagnosis of chronic PJI, especially when using serum sample technique. Providers should exercise caution when interpreting D-dimer levels in patients with inflammatory and hypercoagulability disorders, as the diagnostic value is decreased. The updated 2018 Musculoskeletal Infection Society criteria, which includes D-dimer levels > 860 μg/L as a minor criterion, may be the most accurate for diagnosing chronic PJI to date. Larger prospective trials with transparent lab testing protocols are needed to establish best assay practices and optimal cutoff values for D-dimer in the diagnosis of PJI. This review summarizes the most current literature on the value of D-dimer in total joint arthroplasty and elucidates areas for future progress.

Key Words: D-dimer; Diagnosis; Periprosthetic joint infection; Venous thromboembolism; Deep vein thrombosis; Arthroplasty

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Core Tip: Venous thromboembolism (VTE) and periprosthetic joint infection (PJI) are potentially devastating complications after total joint arthroplasty. D-dimer has limited utility with current cutoff values in the detection of VTE in the acute postoperative period. The D-dimer assay is a valuable biomarker in the diagnosis of chronic periprosthetic joint infection, and its utility may be optimized by using serum sample technique. Larger prospective trials with transparent lab testing protocols are necessary to establish best assay practices and optimal cutoff values for D-dimer in the diagnosis of VTE and PJI in arthroplasty patients.

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INTRODUCTION

Venous thromboembolism (VTE) and periprosthetic joint infection (PJI) are serious complications of total joint arthroplasty (TJA). Deep vein thrombosis (DVT) is a leading cause of morbidity and mortality during the postoperative phase[1,2]. The early diagnosis and treatment of DVT is extremely important, as delay can result in post-thrombotic syndrome and pulmonary embolism (PE). Although D-dimer has proved to be a valuable biomarker in the detection of VTE, its interpretation after total joint arthroplasty has been controversial, as postoperative levels often exceed the common institutional cutoff of 500 μg/L. Recent literature has focused on establishing new thresholds during the immediate postoperative period, in addition to using the test in new predictive models. While D-dimer has long been studied as a diagnostic tool in thromboembolism, this assay has recently received considerable attention in the evaluation of infection.

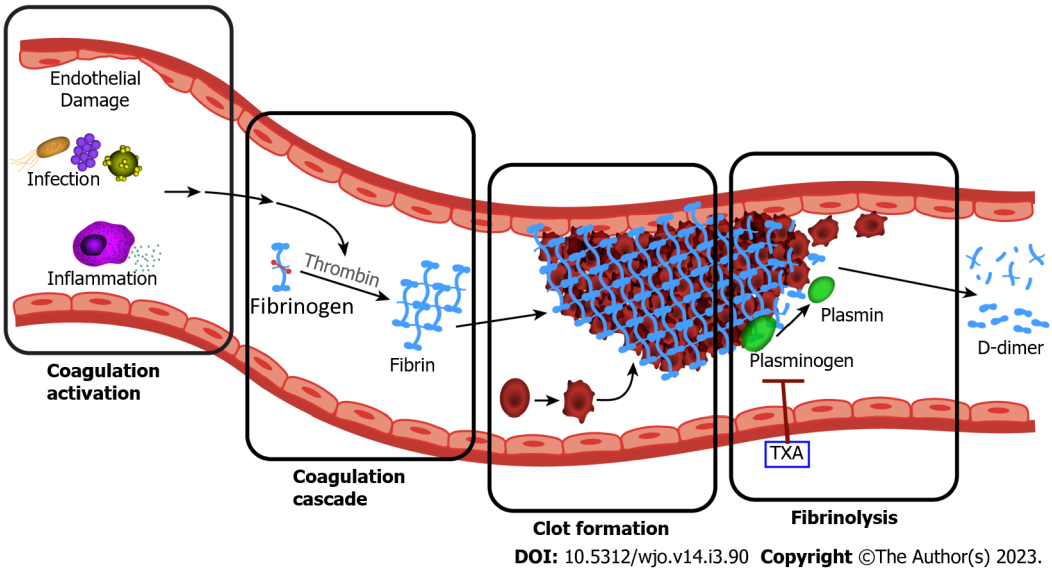
Periprosthetic joint infection continues to be a devastating complication in orthopaedic surgery, affecting roughly 2% of patients undergoing primary total joint arthroplasty[3,4]. The development of PJI dramatically decreases a patient's quality of life and accounts for a large financial burden to the patient and national health system[5-8]. Its timely detection is important, yet establishing the diagnosis can be challenging as there is no single "gold standard" test. In 2011, the Musculoskeletal Infection Society (MSIS) introduced a diagnostic criteria (later modified by the International Consensus Meeting (ICM) in 2013) based on a combination of clinical, serum, synovial, histologic, microbial, and operative findings[9,10]. Recently, emphasis has shifted to a large number of novel hematologic and synovial biomarkers. In a 2017 study, D-dimer demonstrated excellent performance in the diagnosis of chronic PJI, with sensitivity and specificity above both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)[11]. As an inexpensive, rapid, and convenient hematologic test, it was quickly adopted into the 2018 MSIS and ICM criteria for PJI diagnosis as a minor criterion[12,13]. Although initial studies found D-dimer to exhibit excellent performance in determining PJI, other authors have published conflicting results[14-20]. Since its inclusion in the updated MSIS and ICM criteria, the utility of D-dimer as a biomarker for PJI has been intensely debated. The goal of this review is to summarize the most current literature on the value of D-dimer in total joint arthroplasty and elucidate areas for future progress.

D-DIMER

Mechanism of formation

D-dimer is a small protein fragment produced by the breakdown of vascular thrombi through a process known as fibrinolysis (Figure 1). The creation of D-dimer begins with thrombus formation: thrombin is generated through the coagulation cascade, which in turn converts plasma fibrinogen into fibrin. Through multiple interactions, fibrin molecules are cross-linked to form a meshwork for the resulting blood clot. The degradation of this thrombus occurs through fibrinolysis, where plasmin (a fibrinolytic enzyme) cleaves the fibrin scaffolding, resulting in the creation of the D-dimer molecules. D-dimer is therefore a unique marker of both thrombus formation as well as subsequent thrombolytic activity[21].

Deep venous thrombosis occurs due to the creation of an intravascular clot as the result of three main mechanisms: hypercoagulability, vascular wall injury, and venous stasis[22]; all of which can be present in patients with recent surgery. In patients with infection, the initiation of the coagulation cascade by microorganisms and inflammatory mediators is a common and early event[23]. Although this hypercoagulable state can alone increase D-dimer levels, another mechanism appears to be at play. Ribera *et al*[24] first demonstrated significantly increased levels of synovial D-dimer within the septic joints of foals.



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Figure 1 Pathophysiology of D-dimer formation. TXA: Tranexamic acid.

Other studies have supported that inflamed synovium secretes large amounts of fibrin, ultimately resulting in increased intra-articular concentrations of D-dimer which can efflux out of the joint and into circulation[25].

Applications in the field of medicine

D-dimer has been widely used as a hematogenous biomarker for the detection and exclusion of VTE, comprised of both DVT and PE, and is strongly recommended in the diagnostic algorithms of multiple medical organizations, including the American Society of Hematology[26,27]. Despite its low specificity, D-dimer has long been advocated as an effective method to screen patients for VTE, with a sensitivity up to 97%, therefore reducing expensive testing such as venography or ultrasonography. In recent years, it has also been recognized as a valuable marker for inflammation and infection. Contemporary research has found elevated D-dimer levels to be a prognostic indicator for septic shock, bacterial pneumonia, bacteremia, and COVID-19 infection[28-33]. In 2011, Saxena *et al*[34] first described an association between D-dimer and periprosthetic joint infection. Since that time, a considerable amount of research evaluating the relationship between D-dimer levels and total joint-related infection has been published.

Methods of measurement

Blood sample technique: There are two common and distinct methods to collect and prepare the blood sample for testing[35,36]: (1) Serum D-dimer: Serum is the liquid portion of the blood after coagulation has occurred. The sample tubes contain either coagulation enhancers or no additives and are exposed to room temperature for a defined time period (often 30-60 min). After mandatory coagulation, serum samples have significantly less fibrinogen and coagulation factors due to recent consumption; and (2) Plasma D-dimer: Plasma is the liquid portion of the blood when coagulation has been prevented. The blood collection tubes contain additives (commonly citrate), which prevent coagulation and can therefore be handled much easier than serum samples. The tubes can be immediately cooled or centrifuged in order to separate plasma from blood cells.

Assay methods: After the sample is collected and prepared, a variety of quantification methods can be utilized. D-dimer is most commonly detected and quantified using monoclonal antibodies that distinguish a specific epitope on the cross-linked D-dimer molecule, differentiating it from other coagulation related products such fibrinogen or fibrin monomers[21,37]. There are over thirty commercial D-dimer assays on the market, but these can be broadly divided into three categories: enzyme-linked immunosorbent assays (ELISA), immunofluorescent assays, and latex-agglutination assays. In general, ELISA-based assays are more sensitive (nearing 100%) than agglutination assays, however automated techniques such as immunoturbidimetric detection have narrowed the gap[37,38]. Each individual assay has its own calibration standards, cutoff values, sensitivity, and specificity for the detection of VTE[39].

D-dimer levels in total joint arthroplasty patients

Many patient conditions are known to elevate D-dimer levels, including advanced age, inflammatory disease, auto-immune disorders, cardiovascular disease, and/or a recent surgical procedure (Table 1)

Table 1 Conditions associated with elevated D-dimer levels

Venous thromboembolism
Surgery
Age
Trauma
Inflammation
Disseminated intravascular coagulation
Cancer
Infection/sepsis
Pregnancy
Cardiovascular disease
Liver disease
Renal disease

References: [21,23,26-31,40-43].

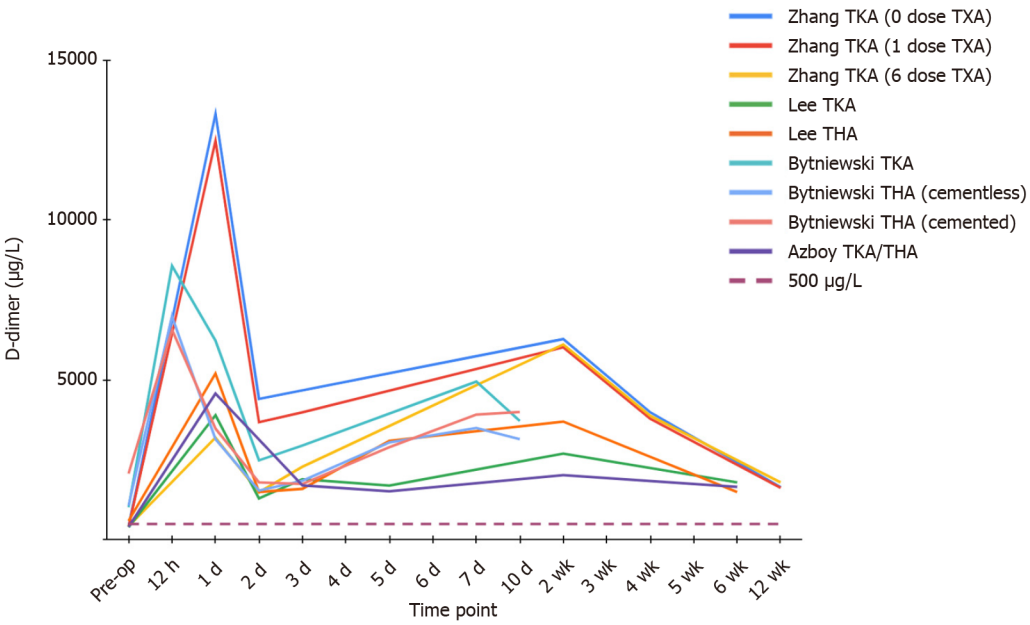
[39-43]. As total joint patients commonly share many of these features, surgeons have difficulty interpreting elevated D-dimer levels in this population. Age-adjusted D-dimer values have helped increase the accuracy of DVT detection in elderly patients before undergoing TJA, but spiking levels in the postoperative period pose additional challenges[43,44]. Inflammatory biomarkers such as ESR and CRP are often elevated after any recent surgical procedure, so it is not surprising that D-dimer follows this trend[45,46]. In addition, D-dimer is known to be the predominant product of extravascular fibrinolysis, a process which is emerging as an essential step in wound healing and tissue regeneration after orthopaedic surgery[47-49]. D-dimer values are substantially elevated after total joint arthroplasty, and recent investigations have discovered a consistent pattern of distribution in the postoperative phase.

D-dimer levels appear to display a biphasic distribution after total joint replacement, with two distinct peaks (Figure 2). Levels rise sharply after the operation, peaking within the first 24 h, then sharply decrease to a trough by postoperative day 2 to 3. This is followed by a gradual increase to a second peak around the 7 to 14-d mark, with a gradual decrease thereafter[46,50-52]. Azboy *et al*[46] found the first peak to be almost 9-fold higher than baseline, with the mean levels of the two troughs, on day 3 and 45, still representing elevation of at least 3 times preoperative values. D-dimer appears to maintain elevation well beyond the acute post-surgical period, with Zhang *et al*[52] reporting persistently raised values at 3 mo. To our knowledge, there is no literature reporting D-dimer levels beyond 90 d after an uneventful joint replacement, and the time it takes to return to baseline is currently unknown.

VENOUS THROMBOEMBOLISM

According to the National Quality Improvement Program database, venous thromboembolism still represents one of the most common complications in patients undergoing total joint arthroplasty, affecting approximately 0.6% of patients after total hip arthroplasty (THA) and 1.4% after total knee arthroplasty (TKA)[1]. The majority of DVTs and their related complications occur within two weeks of joint replacement surgery, but can present up to 6 wk postoperatively[2,53]. In a group of 283 symptomatic PEs, Parvizi *et al*[54] found that 89% occurred within the first postoperative week, and 94% occurred within two weeks. As D-dimer remains considerably elevated during this period, it is clear that standard institutional cutoffs for VTE exclusion, most commonly 500 μg/L, are inappropriate in this population. At 6 wk after operation, An *et al*[55] found that 92% of THA patients and 100% of TKA patients had D-dimer levels above their DVT threshold for a "positive" quantitative test. The potential value of D-dimer in the detection or exclusion of DVT after total joint arthroplasty remains controversial and unclear.

Recent research has focused on establishing new D-dimer thresholds during the postoperative period after TJA. Many studies have confirmed an association between elevated D-dimer levels and the presence of DVT in total joint patients, with some establishing useful cutoffs at specific postoperative days. Shiota *et al*[56] reported a threshold of 10000 μg/L on postoperative day (POD) 7 to have the highest sensitivity (THA- 95.5%, TKA- 94.4%) and specificity (THA- 96.9%, TKA- 90.0%) for DVT



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Figure 2 D-dimer levels after total joint arthroplasty. TXA: Tranexamic acid. References: Zhang *et al*[52], Lee *et al*[51], Bytniewski *et al*[50], Azboy *et al*[46].

detection. Other authors have determined cutoffs on POD1, POD3, and POD4 to be useful as well[57-60]. This data should be interpreted with caution, however, as none of these investigations used DVT chemoprophylaxis. Agents such as low molecular weight heparin, Fondaparinux, Warfarin, and factor Xa inhibitors have been shown to decrease D-dimer levels and reduce its diagnostic performance in detecting DVT[60-64]. Other authors, some of whom used chemoprophylaxis and others who did not, have determined that D-dimer has limited or no value in DVT diagnosis after a recent total joint operation[65-70].

With this conflicting evidence, the role of D-dimer in the detection of VTE after TJA is undetermined. There is a lack of research assessing the value of D-dimer when the primary prophylactic agent is aspirin, which has overwhelmingly become the most popular agent used in primary joint arthroplasty according to an American Association of Hip and Knee Surgeon survey in 2020[71]. In contrast to other contemporary anticoagulants, authors have shown that antiplatelet drugs such as aspirin and clopidogrel (Plavix) do not alter D-dimer levels, however these studies did not specifically evaluate arthroplasty patients[72,73]. Many previous investigations were also performed without the use of tranexamic acid, a known inhibitor of fibrinolysis, which has been shown to decrease D-dimer levels up to 3 days postoperatively (Figures 1 and 2)[52]. Larger trials focusing on symptomatic VTE events using contemporary prophylactic protocols are necessary. In addition, future investigations must determine when D-dimer levels finally normalize after the operation, establishing a time point for when institutional VTE cutoff values (commonly 500 μg/L) can be properly applied in this population.

Ultimately, D-dimer may be more useful as an adjunct within other diagnostic tools rather than a standalone test. In recent years, mathematical based predictive models have emerged as potentially groundbreaking tools in multiple medical fields[74]. These algorithms, which are widely used in data mining, machine learning, and artificial intelligence, can efficiently and accurately create models for the classification and prediction of adverse events based on historical case data. Chen *et al*[75] constructed an algorithm utilizing predictive indicators of VTE, including elevated D-dimer levels on POD 1, capable of accurately predicting the incidence of DVT after total knee arthroplasty. Although this algorithm needs validation in larger populations, the use of D-dimer in combination with other DVT indicators in computer based models will likely form the basis of future research.

PERIPROSTHETIC JOINT INFECTION

Chronic periprosthetic joint infection

D-dimer first emerged as a promising biomarker for PJI in 2017, when Shahi *et al*[11] demonstrated it outperformed both ESR and CRP in diagnosing chronic PJI in their cohort of 245 patients. With a cutoff of 850 μg/L, the authors found serum D-dimer to have a sensitivity of 89% and a specificity of 93% in distinguishing PJI from aseptic failure. In Parvizi *et al*'s 2018 evidence-based and validated criteria for the diagnosis of PJI, the authors found D-dimer, with an updated threshold of 860 μg/L, to be a valuable initial hematologic test, weighted similar to CRP and above ESR as a minor criterion in their

new model[12]. This updated MSIS criteria displayed a significant increase in sensitivity compared to the prior MSIS (97.7% *vs* 86.9%) and ICM (97.7% *vs* 86.9%) criteria with similar specificity (99.5%). Furthermore, it has been validated in both American, German, and Chinese populations[12,76-77]. Since acceptance into the MSIS and ICM criteria, a growing body of literature assessing D-dimer's value as a biomarker for PJI has emerged, with conflicting results and conclusions.

Investigations by Hu *et al*[78] and Qin *et al*[79] both supported the promising early findings, with D-dimer demonstrating better sensitivity, specificity, and diagnostic accuracy in detecting PJI when compared to ESR and CRP. Hu *et al*[78] found D-dimer to demonstrate a sensitivity of 87.50% and a specificity of 89.19%, superior to those of ESR (82.50% and 64.86%, respectively) and CRP (80.00% and 78.38%, respectively). Qin *et al*[79] determined D-dimer to have outstanding diagnostic accuracy with an area under the curve (AUC) of 0.915, far above that of ESR (0.719) and CRP (0.761). Other authors, however, have published less optimistic data. Xu *et al*[17] concluded that with sensitivity of 68.3% and specificity of 50.7%, D-dimer had limited value compared to traditional biomarkers. Using the previously established threshold of 850 μg/L, Pannu *et al*[14] demonstrated poor accuracy (61%) and low specificity (32.3%) to discriminate PJI from aseptic loosening in their population. Furthering the confusion, many studies have established different cutoffs from the recommended 860 μg/L of the new MSIS criteria, with published thresholds varying widely from 410 μg/L to 2750 μg/L[18,20].

A collection of systematic reviews and meta-analyses were recently published in an effort to eliminate confusion and draw clarity from the literature[80-87]. The overall pooled data displays that D-dimer has good diagnostic accuracy to detect PJI. Zhang *et al*[86] and Wang *et al*[84] reported D-dimer to have an overall sensitivity of 82%, a specificity of 73%, and an AUC of 0.85. However, these studies have revealed considerable heterogeneity in the current literature. Through meta-regression and subgroup analysis, this compilation of review papers published some interesting findings that illuminate possible ways to best optimize D-dimer as a biomarker for PJI. These conclusions are summarized as follows.

Serum versus plasma D-dimer: Serum D-dimer displayed better diagnostic accuracy *vs* plasma D-dimer: Blood sample technique was commonly found to be the number one determinant of heterogeneity among the current literature. After subgroup analysis, Li *et al*[81] found that serum D-dimer exhibited a superior pooled sensitivity and specificity (86% and 84%, respectively) *vs* plasma D-dimer (67% and 60%, respectively). Serum D-dimer demonstrated excellent diagnostic value with an AUC of 0.91, far above that of plasma D-dimer (AUC of 0.66). Other authors have further supported this finding [80,82-87]. Some studies have reported no difference in baseline D-dimer levels when using either of the two techniques, however, Boisclair *et al*[89] reported significant differences in sensitivity and specificity when examining serum *vs* plasma D-dimer in the diagnosis of disseminated intravascular coagulation, DVT, and myocardial infarction[88,89]. Large comparative trials are needed to elucidate the true value of blood sample technique in arthroplasty patients, but studies utilizing serum sampling have displayed much better accuracy in diagnosing PJI.

Inflammatory and hypercoagulability disorders: Exclusion of inflammatory and hypercoagulability disorders improved diagnostic accuracy: In their 2020 meta-analysis, Yan *et al*[85] found that studies which excluded patients with hypercoagulability disorders displayed higher sensitivity (85% *vs* 68%) and specificity (83% *vs* 62%) *vs* those that did not. Similarly, they reported D-dimer to demonstrate a higher sensitivity (81% *vs* 75%) when patients with inflammatory arthritis were excluded[84]. These results are not unexpected, as baseline D-dimer levels are substantially elevated in patients with inflammatory joint disease, thrombosis, malignancy, pregnancy, and heart disease *vs* healthy controls[41,90-93]. In addition to systemic hypercoagulation, the degradation of large quantities of fibrin deposited in the synovium of rheumatoid patients has been shown to increase D-dimer levels[94]. In patients with cardiovascular disease, autoimmune disease, and malignancy, Li *et al*[16] found that plasma D-dimer had no meaningful capacity to discriminate PJI from aseptic loosening (AUC of 0.50, 0.52, and 0.58, respectively). As patients with these comorbidities also display elevated inflammatory markers such as ESR and CRP, this population presents significant challenges in regard to properly establishing a diagnosis of chronic PJI.

Race and geography: White and black american populations displayed increased diagnostic accuracy *vs* east asian populations: In a meta-analysis of 8 studies, Lu *et al*[82] found geographic and racial differences to have a major impact on the diagnostic accuracy of D-dimer in PJI diagnosis. Caucasian and African American races demonstrated increased sensitivity (92%) and specificity (74%) *vs* those of East Asian populations (72% and 65%, respectively). Variances in study protocol and laboratory assay practices may confound these findings, however racial differences in D-dimer levels are well documented in the literature, even when controlling for social factors and comorbidities[92,95]. Providers should be mindful of demographic differences when interpreting D-dimer research, and investigators should be encouraged to disclose ethnicity to increase the external validity of future studies.

Optimal D-dimer cutoff: Current literature uses a wide range of cutoff values: There is wide variation in D-dimer threshold values used for the diagnosis of chronic PJI in the current literature. While some of the recent investigations used the previously established cutoff of 850 μg/L, others calculated their own

using receiver operating characteristic curve analysis to best optimize the diagnostic value of the biomarker[11]. Furthermore, there is a scarcity of studies utilizing the cutoff of 860 μg/L, the current threshold recommended by the MSIS and ICM[12,13]. The establishment of an appropriate threshold is essential, as any change in this value can have significant impacts on diagnostic accuracy.

This wide variation is likely due to many factors, including differences in laboratory protocols and population characteristics. In addition to blood sample technique, there is potential for substantial differences in D-dimer levels depending on each laboratory's diagnostic platform. The development of a universal reference standard for D-dimer has been infamously difficult, making standardization between assays impossible up to this point[35,38-39]. In a simulation utilizing data from 3903 Laboratories, Pearson *et al*[96] calculated that given identical blood samples, the mean D-dimer value varied from 540 to 880 μg/L depending on the platform utilized. In their model, a sample with a true value of 760 μg/L produced levels exceeding the 860 μg/L cutoff in 18% of their results. Likewise, a sample with a true value of 960 μg/L reported a level less than 860 μg/L in 24% of the samples. Provided the variability in D-dimer results, the authors concluded that each site should conduct their own research to determine an optimal threshold for their unique testing platform. While this may not be practical for most institutions, a surgeon's knowledge of their center's testing protocols combined with improved transparency in the literature will help improve the reproducibility of best cutoff values.

In summary, the inclusion of inflammatory patients, population differences, and a lack of standardization of lab protocols can all be responsible for the inconsistent results and thresholds. However, the largest reason for conflicting conclusions appears to be a difference in the type of sample technique used. With current literature in mind, we advise utilizing serum D-dimer, as opposed to plasma D-dimer, to best optimize its diagnostic value in determining chronic PJI. We conclude that serum D-dimer is an excellent serological biomarker for diagnosing chronic PJI, especially when used in combination with other infectious indicators as part of diagnostic tools such as the MSIS criteria.

Acute periprosthetic joint infection

Lee *et al*[51] displayed that D-dimer values fall more rapidly than ESR and CRP after total joint arthroplasty, leading to speculation it could be useful in the diagnosis of acute PJI. However, persistent elevation of D-dimer levels during the acute postoperative phase (up to 6 wk), poses issues with currently established cutoffs for chronic PJI. Azboy *et al*[46] reported that 88.7% of their uneventful TJA patients had D-dimer levels above the 860 μg/L threshold on postoperative day 15, with 77% exceeding the cutoff on day 45. As baseline D-dimer levels are already substantially inflated within the first four to six weeks due to postsurgical inflammation and fibrinolysis, D-dimer does not appear to be useful for the diagnosis of acute PJI with the currently recommended threshold. Further research is needed to determine an optimal cutoff for early PJI diagnosis, as well as establish a time point for when chronic PJI criteria can be appropriately applied.

Timing of reimplantation in two-stage revision

Two-stage revision continues to be one of the most common approaches for chronic PJI treatment. There is currently no gold standard for confirmation of infection eradication prior to reimplantation, and markers such as ESR, CRP, and even alpha defensin have demonstrated limited utility in this regard[97-99]. Shahi *et al*[11] first predicted the utility of D-dimer in this setting. In 5 patients with "elevated" D-dimer at the time of reimplantation, 2 went on to experience septic failure. Pannu *et al*[100] demonstrated that D-dimer had low specificity (47%) and accuracy (AUC of 0.62) to predict persistence of infection after the second stage. However, it displayed a sensitivity of 90% and a negative predictive value of 94%, indicating promise as a biomarker to rule out residual infection and indicate safe timing for reimplantation. Furthermore, they discovered that when combined with ESR and CRP, the specificity increased to 91%. Although this study is limited by a small sample size (n = 10), it certainly sets the stage for future multicenter investigations and creates optimism that D-dimer can have an important role in this setting.

Plasma fibrinogen: An alternative to D-dimer?

Plasma fibrinogen, the precursor to fibrin, is well known for its role in the coagulation cascade and has also been found to be a promising biomarker for the diagnosis of PJI[101]. Several recent publications have found plasma fibrinogen to exhibit significantly better diagnostic performance than plasma D-dimer in identifying chronic PJI[16,18,102]. However, all of these investigations utilized plasma sampling, and to our knowledge, there are no studies comparing serum D-dimer to plasma fibrinogen. In 2021, a meta-analysis by Xu *et al*[103] reported that plasma fibrinogen had better diagnostic accuracy than D-dimer when plasma and serum data was combined. However, after subgroup analysis, D-dimer actually displayed better accuracy than plasma fibrinogen when serum sample technique was utilized (AUC 0.91 *vs* 0.83, respectively). The authors concluded that serum D-dimer may have better diagnostic potential than plasma fibrinogen, and that plasma D-dimer has limited diagnostic value. Regardless, plasma fibrinogen appears to be a good alternative to D-dimer, especially at sites that are limited to a plasma testing protocol.

LIMITATIONS

In addition to the heterogeneity of the existing literature, it is important to note additional limitations. Most studies fail to adequately describe their laboratory protocol for D-dimer testing. As Pearson *et al* [96] demonstrated, assay practices can have a large effect on D-dimer values. In addition, the terms "serum" and "plasma" have incorrectly been used interchangeably in the literature, promoting fear that they may be mislabeled in other investigations[55,104]. Surgeons and researchers should appreciate which type of blood sample technique is being used at their institution, and transparency of both sample technique and assay utilized is imperative for reproducibility of future research. Lastly, although pooled data seems to confirm that serum D-dimer is superior to plasma D-dimer, no comparative studies have been performed between the two sampling methods in the setting of chronic PJI. A prospective, paired trial comparing the diagnostic values of plasma and serum D-dimer for the diagnosis of PJI is necessary to provide more clarity.

CONCLUSION

D-dimer values are substantially elevated in the acute postoperative period after total joint arthroplasty, and standard institutional cutoffs for VTE (most commonly 500 μg/L) are inappropriate in these patients. The utility of D-dimer in detecting VTE after total joint arthroplasty is currently limited, and more research assessing its value in the face of contemporary DVT prophylaxis protocols is warranted. D-dimer appears to be a promising biomarker for the diagnosis of chronic PJI, especially when using serum sample technique. Providers should exercise caution when interpreting D-dimer levels in those with inflammatory and hypercoagulability disorders, as the diagnostic value is decreased in these patients. Larger prospective studies with transparent lab testing protocols are needed to establish best assay practices and optimal cutoff values. Despite the demand for further research to optimize the diagnostic performance of D-dimer, the current identification of PJI does not rely on a single test. More research assessing the value of combined biomarkers may be more useful, and the updated MSIS and ICM criteria, which include D-dimer levels > 860 μg/L as a minor criterion, may be the most accurate for diagnosing chronic PJI to date.

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FOOTNOTES

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MINIREVIEWS

Advances in wrist arthroscopic surgery in Indonesia

Oryza Satria, Seti Aji Hadinoto, Irfan Fathurrahman

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Abstract

Since the 1990s, new insights in wrist arthroscopy have led to the introduction of numerous treatment methods. Consequently, therapeutic procedures are no longer limited to resection as more specialized repair and functional reconstruction methods, involving tissue replacement and essential structural augmentation, have been shown to be beneficial. This article discusses the most prevalent reasons and uses for wrist arthroscopy, with an emphasis on Indonesia's most recent and major advances in reconstructive arthroscopic surgery. Joint debridement, synovectomy, ganglionectomy, capsular release, and osteotomies are frequent resection operations. Ligament repair and arthroscopy-aided reduction and fixation for fractures and nonunion are all examples of reconstructive surgery.

Key Words: Arthroscopy; Synovectomy; Ganglionectomy; Arthrolysis; Arthroscopic-assisted reduction and internal fixation; Scaphoid fractures; Carpal nonunion; Triangular fibro cartilage complex injury

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Core Tip: Several novel procedures with specific surgical indications have been developed over the past 15 years. More difficult and precise procedures can now be performed with fewer complications as both techniques and instrumentation improve. Debridement and resection are no longer the only therapeutic treatment available. Functional reconstruction treatments involving the repair of tissue defects and augmentation of important structures with graft material as well as more particular anatomical structure fixing procedures have been performed with established clinical benefit. This article covers current arthroscopic techniques used in clinical practice in Indonesia, some of which represent cutting-edge breakthroughs in therapeutic arthroscopy.

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INTRODUCTION

The constant development of numerous treatment methods since the 1990s has triggered significant advancements in wrist arthroscopy. Due to the simultaneous development of tailored instruments adapted for small joints, most techniques used in large joint arthroscopy are either transferred or inspired from already established methods. The increase of popularity in therapeutic arthroscopy has increased the usage and role of arthroscopy in the treatment of wrist disorders including acute and elective settings. Wrist arthroscopy has become a new standard for evaluation and treatment in specific clinical disorders, such as chronic ulnar wrist pain. Similarly, in an increasing variety of clinical illnesses, such as scaphoid fractures, carpal nonunion, ganglion, and triangular fibro cartilage complex (TFCC) lesions, novel therapeutic strategies are challenging traditional surgical treatment methods, thinking, and long-term outcomes. Consequently, wrist arthroscopy could eventually reach the same level of popularity as other arthroscopy surgery.

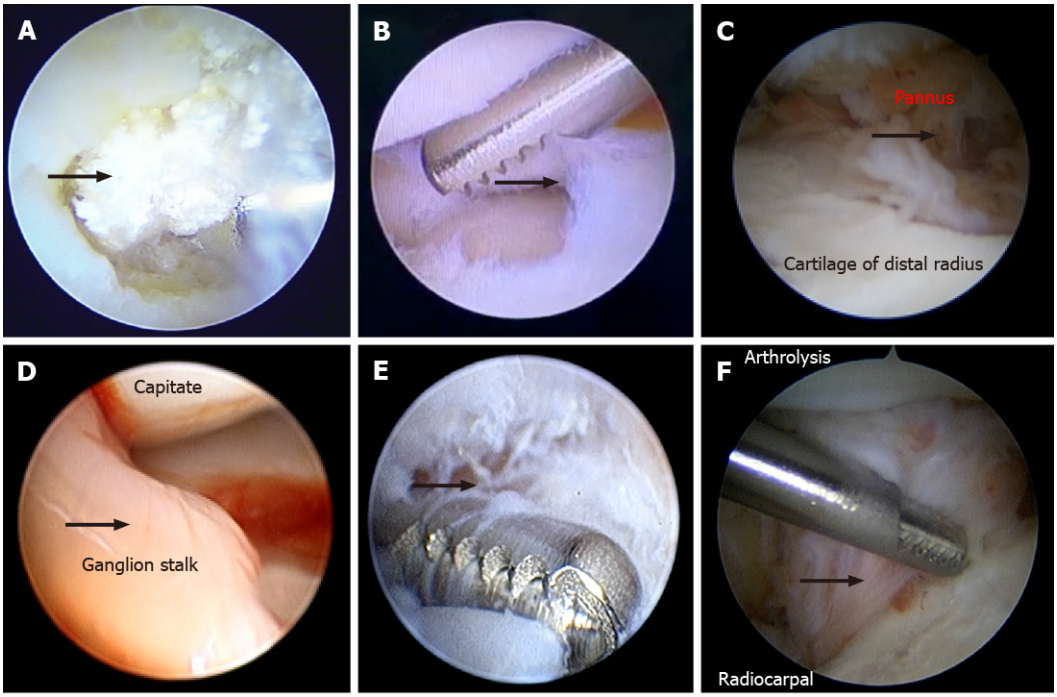
Several novel procedures with specific surgical indications have been developed over the past 15 years. More difficult and precise procedures can now be performed with fewer complications as both techniques and instrumentation improve. Debridement and resection are no longer the only therapeutic treatment available. Functional reconstruction treatments involving the repair of tissue defects and augmentation of important structures with graft material as well as more particular anatomical structure fixing procedures have been performed with established clinical benefit. This article covered current arthroscopic techniques used in clinical practice in Indonesia on a regular basis, some of which represent cutting-edge breakthroughs in therapeutic arthroscopy.

DEBRIDEMENT

This method is used when the accumulated debris in the joint contributes either directly or indirectly to the manifestation of symptoms. Degenerative arthritis, gout, central TFCC tear[1], Kinbock disease[2], and partial interosseous ligament tear[3] are all examples. In the partial excision of a central TFCC tear, several devices such as suction punches, motorized shavers, arthroscopic knives, and more recently radiofrequency devices can all be used. In the absence of carpal dissociation, debridement can provide clinical alleviation in partial intraosseous ligament rupture[4]. If the ulnar variance of the wrist is neutral or minus[5,6], clinical improvement should be expected after partial excision of a central TFCC rupture. Wafer procedure[7], or formal ulnar shortening[8] is frequently needed for definitive treatment in patients with ulnar positive (Figure 1A and B).

SYNOVECTOMY

Rheumatoid arthritis and other systemic diseases affecting the wrist joint are the best candidates for this operation. Arthroscopic synovectomy can reduce surgical trauma while allowing simple access to different wrist compartments. The first series of arthroscopic synovectomy on 18 wrists of 16 patients was reported by Adolfsson and Nylander[9] in 1997, and the results showed a significant improvement in pain intensity and range of motion in all patients. At a mean follow-up of 7.9 years, Lee *et al*[10] revealed the long-term results of arthroscopic synovectomy in 49 subjects with 56 wrists. The mean Mayo wrist score increased from 48 to 76; the mean of wrist pain calculated using visual analogue score reduced from 6.3 to 1.7. Synovitis was successfully managed in 42 wrists (75%) but recurred in the



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Figure 1 Image of the radiocarpal joint. A: The crystals seen are destructing the lunate; B: Debridement of a central triangular fibro cartilage complex tear; C: The pannus seen are destructing the cartilage of distal radius; D: Ganglion stalk seen protruding into the joint; E: Resection of the ganglion stalk; F: Arthrolysis was performed by shaving the fibrous tissue inside the radiocarpal joint.

remaining 14 wrists at the final follow-up[10] (Figure 1C).

GANGLIONECTOMY

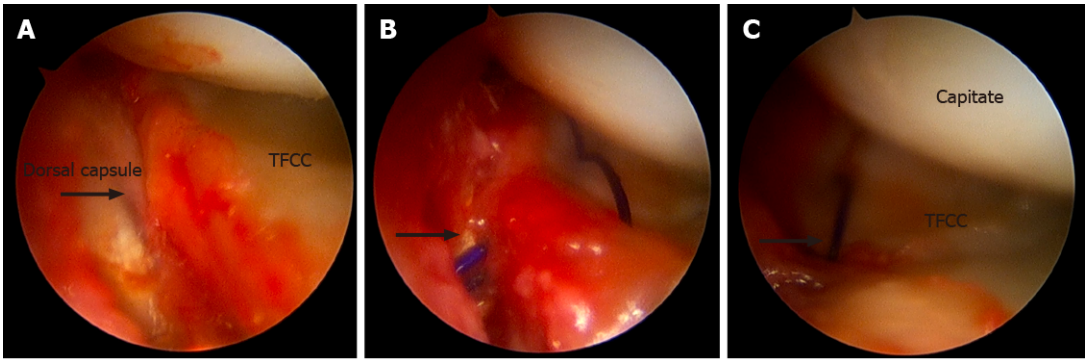
Ganglionectomy is better described as marsupialization of the ganglion because the ganglion cyst is not anatomically removed. This method is based on the idea of eliminating the "check valve" effect by producing a capsular defect at the stalk section of the ganglion cyst, where it communicates with the wrist joint, allowing the ganglion to drain, diminish, and resolve spontaneously. The approach for the usual dorsal wrist ganglion originating proximal to the scapholunate joint was first published by Osterman[11] in 1995; 6R was the viewing portal. To resect a 1-cm defect in the dorsal capsule, a full-radius resector can be introduced *via* the 3-4 portal. The goal of this process is to induce a flood of mucinous fluid drain into the joint, which allow the ganglion to entirely vanish outwardly. All 18 cases in the Osterman series had full resection and no recurrence (Figure 1D and E).

ARTHROLYSIS AND RELEASE

In 2 cases of significant post-traumatic capsular fibrosis and stiff wrist[12], Verhellen and Bain[12] used combined volar and dorsal portals to accomplish arthroscopic release. Except for the ulno-carpal ligament complex and the volar radio-ulnar ligament, all volar capsular ligaments were entirely separated with a shaver, RF probe, or arthroscopic knife and then gently manipulated under anesthesia (Figure 1F).

Ligament repair

The TFCC is prone to damage because it is subjected to significant axial loading and shear stresses[13, 14]. Palmer[15] demonstrated and classified tears concerning the TFCC in 1989. This laid the foundation for current ulnar-sided wrist pain diagnosis and treatment. Thiru *et al*[16] and Bednar *et al*[17] found that the outside 10%-40% of the articular disc was highly perfused, implying that these wounded areas could heal if they were repaired. Consequently, there has been a lot of effort directed to preserve and repair peripheral TFCC lesions. In 1991, Hermansdorfer and Kleinman[18] reported that open TFCC repair produced good results, with 8 of 11 patients able to go back to regular activities. Using open repairs, Cooney *et al*[19] reported 26 good to excellent results in 33 operated wrists. With the introduction of wrist arthroscopy, surgeons have been able to duplicate, if not exceed, the results of



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Figure 2 Repair of triangular fibro cartilage complex tear. A: Tear seen on the dorsal aspect of the triangular fibro cartilage complex (TFCC); B: Suture of TFCC; C: Suture tightened.

open repairs[20-24]. The majority of research focused on palmar 1B tear healing, with types 1C and 1D tears reported less frequently. The inside-out and outside-in approaches to arthroscopic repair have been advocated. Simple hypodermic needles[25], epidural Tuohy needles, meniscal needles, and zone-specific repair kits[26] were among the instruments used.

In terms of clinical outcomes, the open group had a higher rate of postoperative superficial ulnar nerve discomfort and reoperation. There has been no recent study comparing the outcomes of various arthroscopic repair procedures. To promote healing and induce fibrovascular in growth, it is critical to debride the rim of the torn ligament down to healthy vascular tissue in all TFCC mending procedures. To ensure healing, the torn peripheral rim of the TFCC is positioned against the fovea or the capsular tissue (Figure 2).

Ligament reconstruction with tendon graft

The optimum surgical reconstruction for painful distal radioulnar joint (DRUJ) instability induced by TFCC disruption has been a source of debate until recently. The dorsal and palmar of radio-ulnar marginal ligaments, which are linked during various stages of prono-supination, are now recognized as the most important stabilizers of the DRUJ. During forearm rotational movement, damage to one or both of these ligaments resulted in pain and instability. Adams *et al*[27] and Adams[28] conducted a thorough biomechanical analysis and advocated anatomical repair of the distal radio-ulnar ligaments as the optimal treatment option for this complex problem. The authors found good results from open reconstruction with graft from palmaris longus tendon in 12 patients with post-traumatic DRUJ instability with 1-4 years of follow-up evaluation[28].

ARTHROSCOPIC-ASSISTED REDUCTION AND INTERNAL FIXATION

For proper reduction and fixing, arthroscopic-assisted reduction and internal fixation is still necessary. Furthermore, arthroscopy can be used to treat related soft tissue injuries in the same setting, with success rates ranging from 40%-75% in distal radius fracture and up to 50% in scaphoid fracture. Intra-articular fracture with comminution and displacement is the best indication for arthroscopic intervention in distal radius fractures, and the target of articular reduction is within 2 mm of step or gap [29]. Percutaneous access to and assessment of depressed intra-articular fragments is notoriously difficult. In terms of measuring joint surface reduction, arthroscopy has been proven to be superior to intraoperative fluoroscopy and plain radiograph[30]. When compared to the conventional reduction method with fluoroscopy alone, patients that underwent arthroscopically-assisted reduction of intra-articular distal radius fractures had better clinical outcomes, improved radiologic variable regarding displacement and angulation, and greater range of motion[31,32].

Through arthroscopic portals, the misplaced fragments can be attacked, elevated, and reduced using a fine bone or a probe under direct visualization. When volar plating is being considered, both dorsal and volar ports can be utilized. While the articular reduction is monitored and regulated arthroscopically, the fragments can also be elevated with an osteotome or a bone spike injected through the metaphyseal region. Subchondral screws or pins are used to repair the decreased fracture. Dry arthroscopy has grown in favor in recent years, especially for fracture reduction and fixation because it allows for easier fracture manipulation and reduces the possibility of fluid extravasation, which can lead to compartment syndrome[33]. Arthroscopy can also detect and treat unnoticed soft tissue and cartilage injuries.

In the treatment of acute scaphoid fractures, percutaneous screw fixation is gaining popularity. The majority of series had a high rate of union and a positive functional outcome. Arthroscopy can become a useful adjuvant to a minimally invasive method for treating tricky cases, such as misplaced fractures, fracture comminution, and delayed presentation, and can often eliminate the need for open reduction. It causes minimum vascular and soft tissue disruption, promoting fracture union. In most cases, including proximal third fractures, we undertake reduction and percutaneous fixation using the volar route. In many series, the volar approach not only has a higher union rate and lower complication rate but also provides safer and easier screw entry, maintains and corrects fracture deformity in the extended wrist, does not disrupt the load bearing proximal scaphoid cartilage, has minimum hardware issues, and gives no harm to the tendons and dorsal wrist structures, which have been expressed in dorsal approach surgeries[34] (Figures 3 and 4).

NONUNION OF SCAPHOID

The complete intra-articular position of scaphoid nonunion favor an arthroscopic approach for diagnostic and therapeutic interventions while preserving as much blood supply and ligamentous architecture as possible, which favors union and functional restoration.

Between 2019 and 2021, we used arthroscopic bone grafting to treat osseous abnormalities in 6 cases of scaphoid nonunion. In all situations, we obtained union within 4 mo on average. Minimal disruption to complex ligamentous structures, maximum preservation of carpal bone vascularity, holistic assessment of wrist joint allowed prior to surgical intervention, minimum scar and pain, unnecessary tourniquet, stitch-less surgery, and faster healing process were all potential benefits of this approach (Figures 5-7).

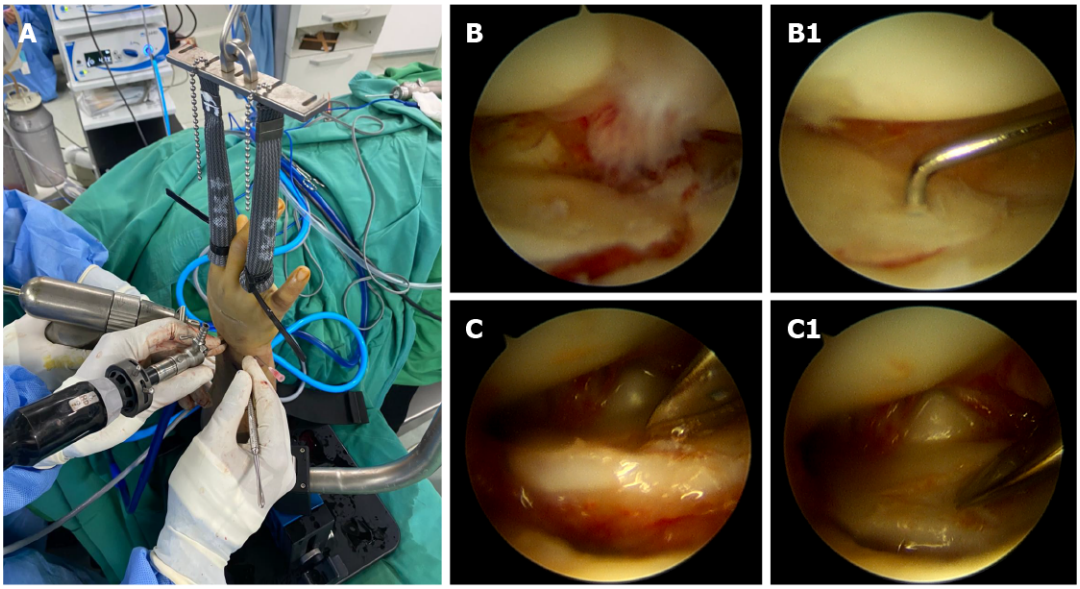
OSTEOTOMY

Radial styloidectomy for post-traumatic arthritis secondary to scaphoid nonunion and rheumatoid or carpal instability, as well as the Wafer operation for ulnar impaction syndrome, are two of the most common indications for osseous resection plasty. The advantage of arthroscopic radial styloidectomy is that it allows for improved vision and conserves the radio-scapho-capitate ligament that acts as a crucial stabilizing structure of the wrist.

Furthermore, the Wafer method is a well-established therapy for the ulnar impaction syndrome. A completely perforated TFCC is required for an arthroscopic operation, which is usually only possible for degenerative TFCC tears of Palmer stage 2C or higher. In cases of distal radius malunion, osteotomy may also be used for reconstruction. A challenging intra-articular distal radius malunion can be restored using osteotomy assisted by arthroscopy in conjunction with a three-dimensional-printed surgical guide (Figure 8).

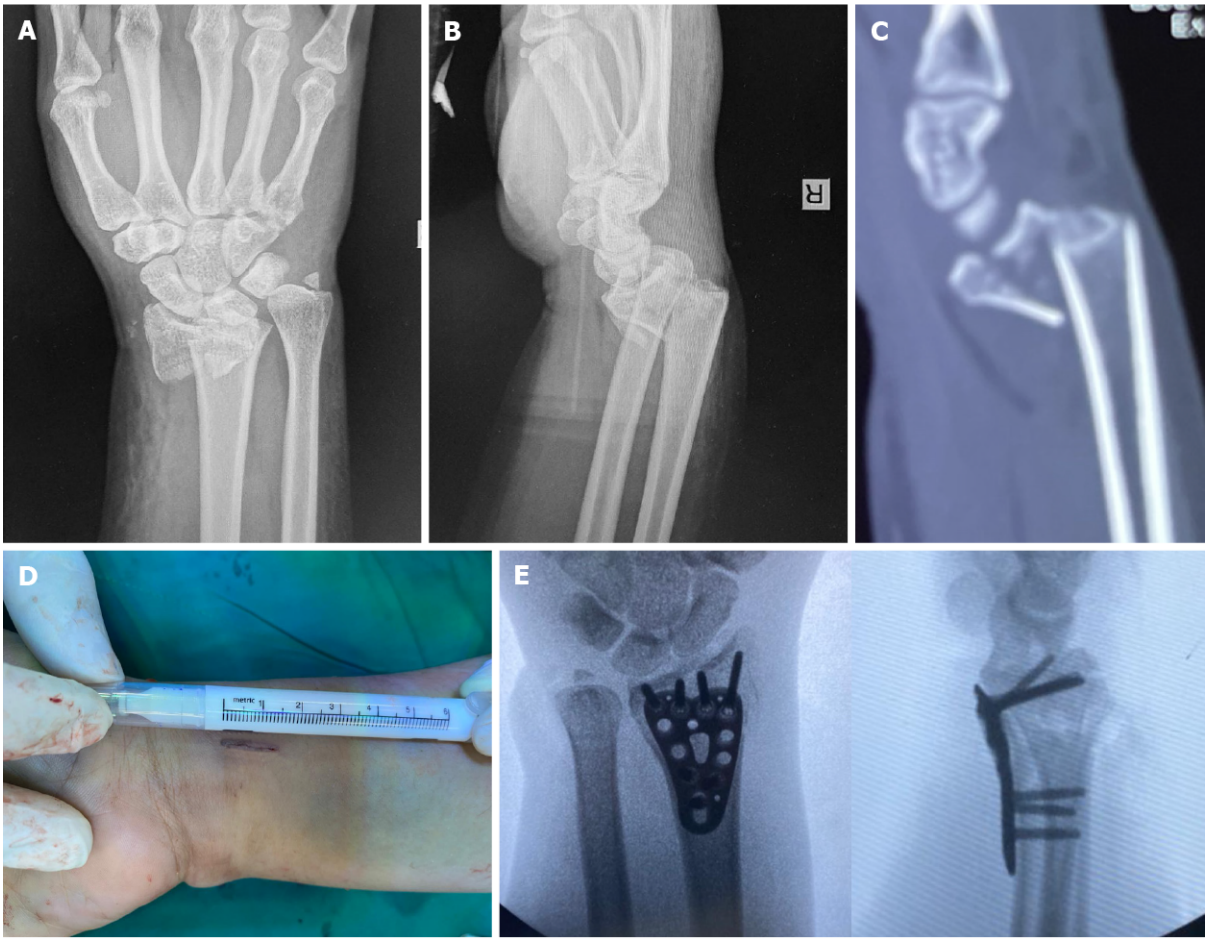
CONCLUSION

When surgeons began debating whether meniscal surgery of the knee could be done arthroscopically 40 years ago, the phrase "open meniscectomy" was likely only used in the dictionary. If the result can be shown to be equivalent or superior to open surgery, then minimally invasive arthroscopic surgery would be the optimum and preferred therapy. Because it has only been in development since 1986, wrist arthroscopy will still benefit from improvements. In fact, we learned from the literature that most traditional open wrist surgery has been attempted arthroscopically with varying degrees of success over the last 15 years. While diagnostic arthroscopy has established itself as the gold standard, most novel therapeutic studies had small numbers of clinical subjects and insufficient controlled randomized prospective study methods and lacked long-term evaluation. Well-designed clinical trials confirm the therapeutic significance in diverse wrist ailments. Wrist arthroscopy as an office diagnostic technique may become a reality in the future, with a considerably broader clinical applicability. Future advancements will most likely be restricted only by surgeons' imaginations and skill. Nonetheless, further controlled randomized prospective studies are needed to determine the genuine efficacy of each arthroscopy treatment approach in the future.



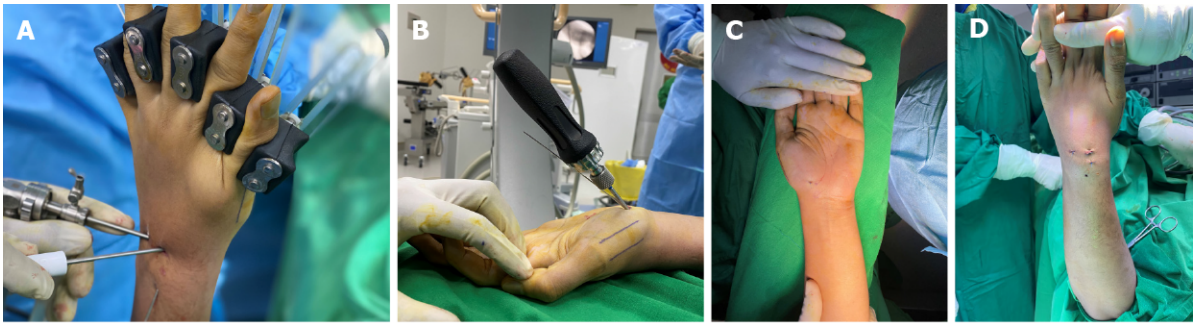
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Figure 3 Arthroscopic-assisted intra-articular reduction of a distal radius fracture. A: Finger traction was applied to the wrist; B and C: Image of intraarticular step before reduction, B1 and C1: After intraarticular reduction.



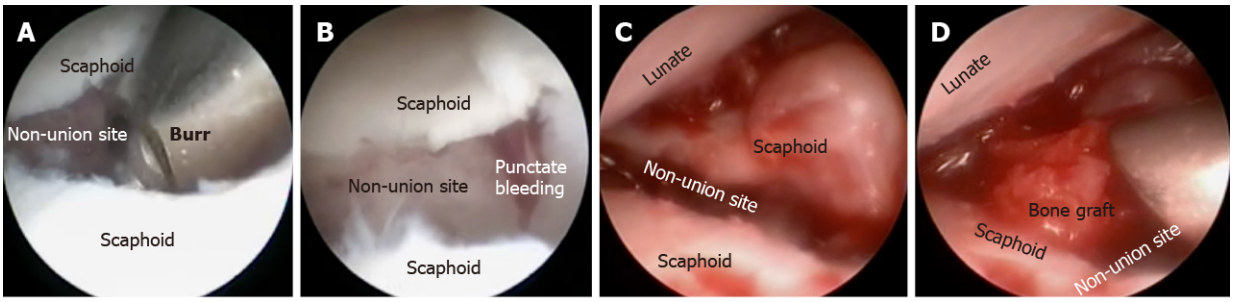
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Figure 4 Preoperative X-ray and computed tomography scan showed intra-articular fragment of a distal radius fracture and postoperative X-ray of the minimally invasive plate osteosynthesis technique with a 15 mm incision. A: Postero-anterior plain X-ray of the right wrist; B: Lateral plain X-ray of the right wrist; C: Sagittal view of computed tomography scan showed displaced intra-articular fracture of the right wrist; D: A 15 mm incision was used for the procedure; E: Postero-anterior and lateral views showed the result after plate and screw fixation.



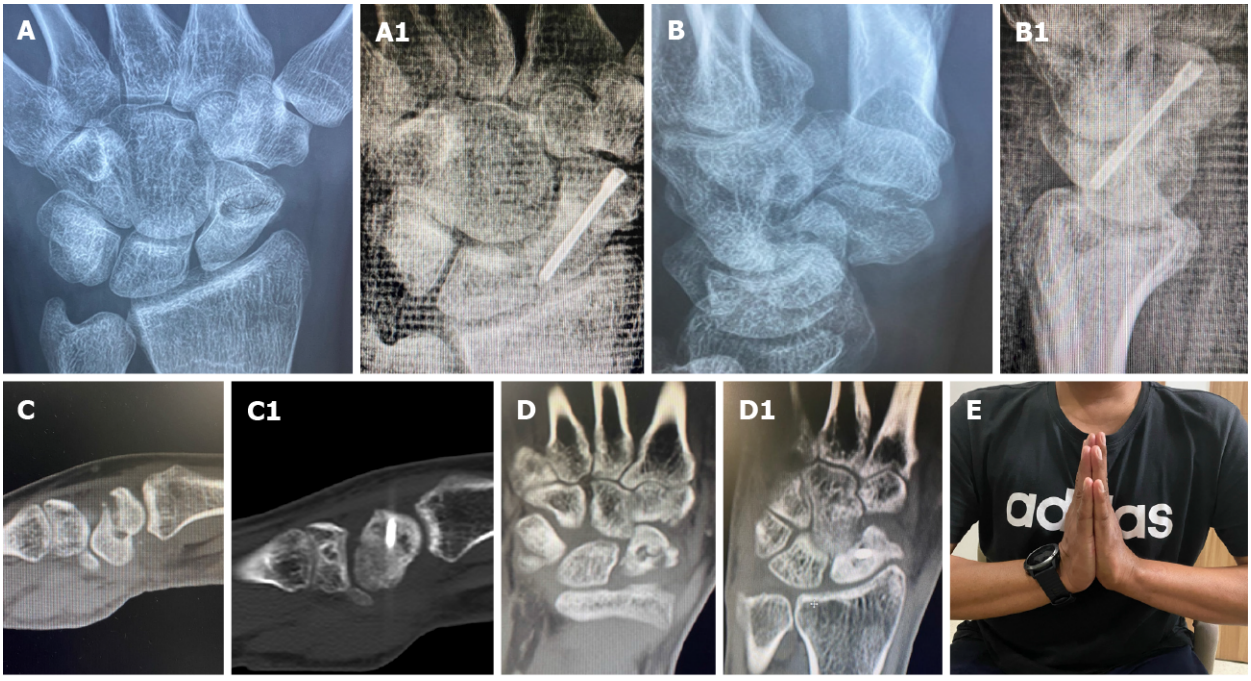
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Figure 5 Intraoperative technique of arthroscopic treatment of scaphoid nonunion. A: Arthroscopic procedure in scaphoid nonunion graft and fixation; B: Headless screw insertion through volar percutaneous approach; C and D: Minimal wound from the arthroscopic procedure.



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Figure 6 Arthroscopic view of nonunion scaphoid treatment. A: The nonunion site was debrided; B: Debridement continued until punctate bleeding was observed; C: Nonunion site was clearly visible; D: The nonunion site was packed with bone graft.



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Figure 7 Arthroscopic fixation and bone grafting in scaphoid non-union. A and B: Pre-operative X-rays; C and D: Computed tomography scans of nonunion scaphoid, showing no bony bridge and humpback deformity. The nonunion and humpback deformity was successfully healed and corrected (A1, B1, C1 and D1); E: Post-operative clinical image after five months demonstrating good and painless range of motion.



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Figure 8 Arthroscopic assisted osteotomy of distal radius intra-articular malunion. A: Arthroscopic-assisted intra-articular osteotomy; B: Pre-operative X-ray, showing volar shear intra-articular malunion with arthroscopic-assisted intra-articular osteotomy through the fracture line, and post-operative X-ray showing anatomical reduction; C: Post-operative clinical image after five months showing good and painless range of motion.

FOOTNOTES

Author contributions: Satria O and Hadinoto SA contributed equally to this work; Satria O and Hadinoto SA reviewed external sources, discussed, and wrote the article; Fathurahman I formatted the article and revised grammatical errors; and all authors have read and approved the final manuscript.

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MINIREVIEWS

Two-stage revision in periprosthetic knee joint infections

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Abstract

Periprosthetic joint infection (PJI) following total knee arthroplasty is one of the most catastrophic and costly complications that carries significant patient wellness as well as economic burdens. The road to efficiently diagnosing and treating PJI is challenging, as there is still no gold standard method to reach the diagnosis as early as desired. There are also international controversies with respect to the best approach to manage PJI cases. In this review, we highlight recent advances in managing PJI following knee arthroplasty surgery and discuss in depth the two-stage revision method.

Key Words: Periprosthetic joint infection; Knee arthroplasty; Two-stage revision; Spacer; Reimplantation

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Core Tip: Two-stage revision for management of periprosthetic joint infection (PJI) following total knee arthroplasty has been widely used with satisfactory outcomes. In this review, we provide comprehensive discussion of the treatment of knee PJI with the two-stage revision method.

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INTRODUCTION

Owing to recent advancements in medicine, the life expectancy of the general population has increased. With changes in modern lifestyle, there is an increased expectation for retention of physical activity and mobility; therefore, the number of joint replacement surgeries has surged[1,2]. Around 1 million knee and hip arthroplasty procedures are performed annually in the United States, and this number is anticipated to double by 2030[3]. In addition to this increase in the number of surgeries, the incidence of PJI also continues to rise[2]. Currently PJI occurs in 1% to 2% of primary and 4% of revision arthroplasties[1,2,4,5]. Kurtz *et al*[1] suggest that there will be over 260,000 revision total knee arthroplasties (TKAs) performed in the United States by 2030. Compared to hip arthroplasty, the risk of PJI is higher after knee arthroplasty[6,7]. For example, the rate of PJI reported after TKA varies from 0.5%-2%, while a range of 0.5%-1.0% is reported after total hip arthroplasty. A higher risk of PJI following TKA may be attributed to less protective soft tissue coverage and higher joint mobility in the knee[8,9]. Delanois *et al* [10] report that PJI alone accounted for 20.4% of all revisions after TKA, and this is considered the most common etiology leading to revision surgery. A number of risk factors are associated with developing PJI including the operative setting, patient comorbidities, and implant-related factors[2]. Additionally, the longer the implanted prosthesis is expected to last, the greater the cumulative risk is for developing infection. Diagnosing PJI early can reduce the significant physical and emotional burden on the patient and the financial pressures on society. However, early diagnosis is still challenging due to the lack of tests that are highly sensitive and specific for this complication. However, early clinical suspicion in parallel to the use of existing serological markers, radiological examination, joint aspirate evaluation, and biopsy continues to be the mainstay for diagnosing PJI[11,12]. The management of PJI remains controversial and requires a complex therapeutic approach, prolonged antimicrobial therapy, and the use of a variety of surgical techniques. Selecting the optimal treatment strategy to eradicate the infection requires proper diagnosis of the infecting microorganisms and identification of their antibiotic susceptibilities. When PJI is missed or inadequately treated, the patient will likely need to endure several operations due to the persistence of infection, negatively impacting function and quality of life[13]. An interdisciplinary approach is crucial to reaching the best patient outcome, and this requires the involvement of orthopedic and plastic surgeons, infectious disease physicians, and microbiologists[2, 14]. The greatest difficulty in managing PJI is the formation of the so-called biofilm, which enables the responsible pathogens to remain on the implant surface, making them resistant to most systemic intravenous antibiotics. Understanding this phenomenon helps in diagnosing and treating PJI[2]. For example, the use of modern diagnostic methods such as sonication for biofilm detection increases the sensitivity for diagnosing PJI, especially in chronic infections caused by low-virulence pathogens[2].

In this review, we provide an updated summary of the current concepts surrounding the two-stage revision procedure in the management of periprosthetic knee joint infections.

DEFINITION & CLASSIFICATION OF PJI

As there currently exists no single test that is capable of diagnosing PJI with complete accuracy, this surgical complication continues to be extremely challenging to tackle[15-17]. The Musculoskeletal Infection Society (MSIS) and the Infectious Diseases Society (IDSA) have proposed criteria to help physicians diagnose PJI[18,19]. In 2018, a second consensus meeting validated the MSIS definition of PJI, but made a few minor modifications[20]. Whilst the major criteria for PJI are the same across all definitions, the minor criteria and supporting evidence are less universally agreed upon. Lately, new tests and biomarkers have evolved and become increasingly available[21-23], including serum D-dimer [24], synovial leukocyte esterase[25], synovial alpha-defensin[26], synovial C-reactive protein (CRP) [27], and molecular techniques such as next-generation sequencing[28]. However, recent research has demonstrated the variability in the sensitivity and specificity of these tests[29]. Therefore, such advancements in PJI diagnosis demanded revision of the existing diagnostic criteria to incorporate the new testing and take into account the relative importance of the different tests included. Thus, a multi-institutional study was published in 2018 in the Journal of Arthroplasty and included new diagnostic criteria[17]. This new PJI scoring system outperformed the IDSA and MSIS criteria in terms of sensitivity and specificity.

The timing in which infection occurs can aid the identification of the infecting organism. Toms *et al* [30] propose a classification consisting of four modes of presentation of PJI: Stage 1 - acute infections occurring within 6 wk; Stage 2 - late onset with chronic indolent infection; Stage 3: sudden-onset in an otherwise well-functioning prosthesis with an acute presentation of infection secondary to hematogenous spread; Stage 4 (proposed by Tsukayama, Estrada, and Gustilo[31]) - positive culture at the time of surgery without previous evidence of infection.

PATHOPHYSIOLOGY OF PERIPROSTHETIC JOINT INFECTION

Most PJI cases are iatrogenic due to inoculation of microorganisms intraoperatively[13]. Based on the virulence of the infecting microorganisms, PJI could either have an early presentation (during the 1st 4-6 wk postoperative) or be delayed (usually 3 mo to 3 years). Early infection usually presents with distinct local and systemic signs of inflammation and is typically caused by highly virulent microorganisms (*e.g.*, *Staphylococcus aureus, Streptococci spp., Enterococci spp.*). On the other hand, less virulent organisms (*e.g.*, coagulase-negative *Staphylococci* or *Cutibacterium spp.*) are the culprits of most delayed infections, which usually present with milder signs and symptoms[2,13] (Figure 1). The presence of foreign bodies such as orthopedic implants increases the infection risk, largely owing to the establishment of the so-called biofilm on prosthetic surfaces[32]. The biofilm formation process consists of several steps: (1) Adherence of the microorganisms to the implant; (2) Multiplication and elaboration of exopolysaccharides ("glycocalyx"); and (3) Coalescence of microcolonies encased in the glycocalyx to form a film [33]. Near the biofilm's surface, microorganisms are generally metabolically active and have free access to nutrients. However, deep within the biofilm, microorganisms have less nutrient access and become metabolically inactive or exist in different states of dormancy, making them more immune to host defenses[34]. Hence, the success of antimicrobial therapy may be negatively impacted by the microenvironment within a biofilm, as diffusion of drugs through the biofilm may be limited[33]. Furthermore, due to the high vascularity of periprosthetic tissue, all implants are at high risk of hematogenous seeding from a distant primary focus. While the risk of this is high during the life of the implant, the highest risk of hematogenous infection occurs in the first few years after implantation[2,35].

TREATMENT PLAN

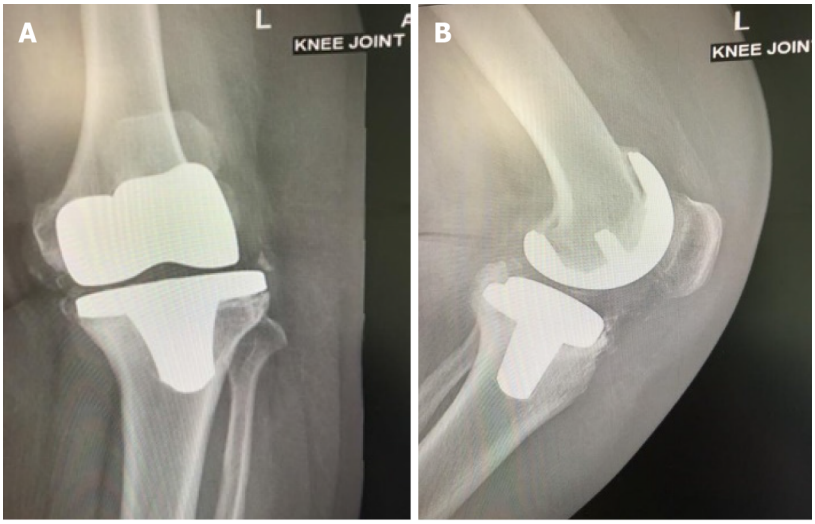
The management of PJI remains controversial; therefore treatment plans should be tailored for each patient individually. Eradication of the infection, reduction of pain, and restoration of joint function are the primary goals of treatment[12]. In general, management of PJI consists of antimicrobial therapy alone or antimicrobial therapy combined with single or staged surgeries. The approach depends on several factors, including the timing and microbiology of infection, condition of the joint and implant, and the individual patient circumstance. Surgical options include debridement and retention of the prosthesis, resection arthroplasty with reimplantation in a single or staged procedure, resection arthroplasty alone, or in extreme cases, amputation[36]. Two-stage revision remains the favorite surgical option, with overall higher rates of eradicating PJI in comparison to single-stage revision. For example, Elson *et al*[37] report 3.5% failure rates with two-stage revision *vs* 12.4% using a single-stage strategy. Similarly, Garvin *et al*[38] report a failure rate of 5.6% *vs* 10.1%, respectively. For the purposes of this review article, we will focus mainly on the two-stage revision method.

TWO-STAGE REVISION

The two-stage revision procedure is considered to be the gold standard for the management of PJI[12]. This method was described in 1983 by Insall *et al*[39] and in 1995, Garvin *et al*[40] conducted a literature review that highlighted the success associated with this approach. The first stage of the procedure includes the removal of the in-situ prosthesis, thorough debridement of the infected bone and soft tissue, and the implantation of antibiotic-loaded cement (ALC) spacers for temporary fixation. The interim period between the two stages includes administration of intravenous antibiotics and close monitoring of the patient clinically and serologically for resolution of infection. Once the infection has resolved, the second stage, which comprises the use of antibiotic-loaded cement for reimplantation of the definitive prosthesis[12,41]. The time between stages can range from 6 wk to several months. Both stages necessitate aggressive debridement of all infected and necrotic tissue[41]. The following are indications for using a two-stage rather than a single-stage revision procedure[12]: (1) Systemic infection (sepsis) with signs of infection but an unidentified causative microorganism; (2) Antibiotic-resistant microorganisms identified by preoperative cultures; (3) Presence of a sinus tract; and (4) Insufficient soft tissue coverage to allow a single-stage procedure.

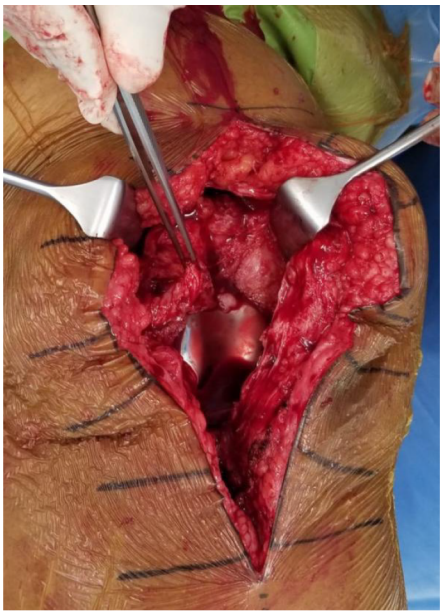
1st stage

The first stage of the procedure entails a thorough and vigorous debridement of the whole effective joint space after the removal of all implanted materials and cement[41] (Figure 2). Whenever possible, the use of antibiotics is postponed until all microbiological samples have been collected. To increase the likelihood of arriving at a conclusive diagnosis, it is recommended to obtain both aerobic and anaerobic cultures; at least three and as many as six intraoperative periprosthetic tissue samples or the explanted prosthesis itself may be sent for testing[42]. The sensitivity, specificity, positive predictive value, and negative predictive value with a minimum of two positive samples have been reported to be 94%, 97%,



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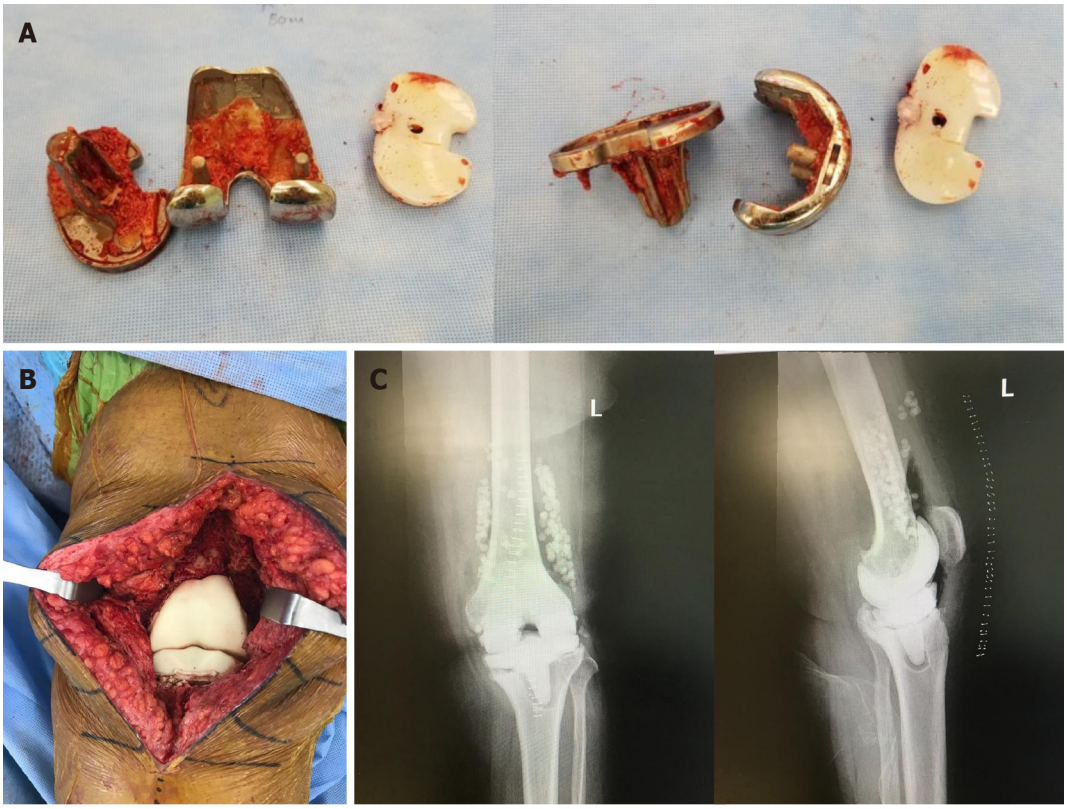
Figure 1 Anteroposterior and lateral plain radiographs showing septic loosening of a left total knee arthroplasty in a 65-year-old female patient who underwent the primary procedure 5 years previously. A: Anteroposterior view; B: Lateral view. Preoperative aspiration confirmed *Staphylococcus aureus* infection and serum and synovial fluid inflammatory markers were elevated.



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Figure 2 First stage revision of the case shown in Figure 1. Synovial tissue surrounds the prosthesis. Total synovectomy was performed and samples sent for culture confirmed the growth of *Staphylococcus aureus*.

77%, and 99.9%, respectively[43]. It is advised to excise the old scar and the sinus tract if present. Sending the prosthetic parts for sonification is an option, but this should be planned prior to surgery as it requires special packaging[41]. It is crucial to remove any cement, even if it is firmly affixed to the underlying bone, in addition to any soft tissue that is grossly involved by the infection[44]. Osteotomes, specialized chisels, drills, and taps, as well as various methods that make use of ultrasound-based extraction instruments, can all be used to remove the cement[45]. During this stage, the surgeon must proceed cautiously, since iatrogenic bone injury is possible[44] (Figure 3A). It is important to perform extensive lavage with a high-pressure pulsatile lavage system using at least 6 L of fluid. Normal saline is usually favored, and lavage provides a significant mechanical action that eliminates sequestra, necrotic tissue, and microorganisms. Several studies have investigated adding antibiotics to the normal saline, but no therapeutic advantage over plain lavage solution has been shown[41]. Following the removal of the implants and thorough debridement, new sterile drapes are applied followed by a spacer with ALC (Figure 3B and C). Spacers are either static or dynamic, prefabricated or handcrafted and hemiarthroplasty spacers can replace both sides of the joint. Preoperative culture and sensitivity testing of the



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Figure 3 First stage revision. A: Explanted prosthesis with minimal bone loss; B: Articulating spacer implantation at the end of the procedure containing vancomycin and tobramycin; C: Anteroposterior and lateral plain radiographs of the left knee after the first stage showing the spacer in situ with antibiotic beads.

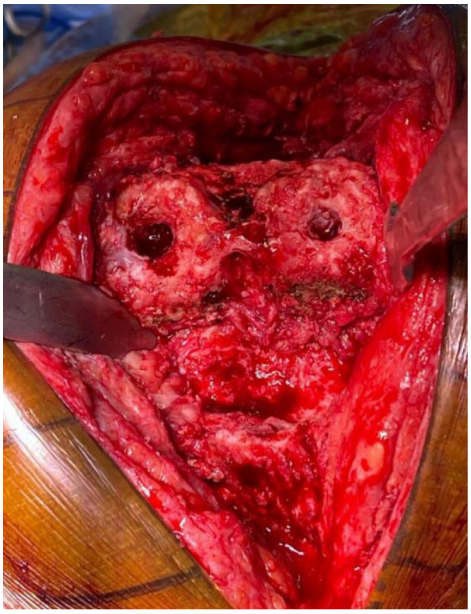
infecting microorganisms helps to decide the best antibiotics to be added preoperatively to the cement used for construction of the spacer. A discussion with a microbiologist is also necessary to agree on the best choice of antibiotics[41].

Interim period

At this point, antibiotic therapy is the cornerstone and should be tailored depending on the microorganism's antimicrobial sensitivity. With the help of a microbiologist, empiric therapy should be started if the organism or sensitivities are unknown. To identify an organism, all reasonable efforts should be made[41]. The most popular regimen is intravenous antibiotics for 4-6 wk followed by discontinuation of the antibiotics for a period of 2-8 wk prior to the second stage, as this results in a high rate of infection control[46,47]. The best results are usually obtained when the infecting microorganism is sensitive and systemic antibiotics are used in the interim period[48,49]. Prolonging the interim period has been linked with suboptimal infection control rates and poor function restoration[12]. However, a single study concluded that there were no differences in functional outcome in patients who had undergone a two-stage revision with an interim period of less than 6 mo *vs* those with more than 6 mo between resection and reimplantation[12,19]. Deciding to move forward with prosthesis reimplantation depends on clinical, serological testing, and joint aspirate assessment. Residual infection requires further debridement and a new spacer insertion[41]. Normalization of the CRP and erythrocyte sedimentation rate (ESR) alone does not guarantee eradication of the infection, especially in coagulase-negative staphylococcal infections, as these may not trigger a significant inflammatory response[12]. Kusuma *et al* [50] reported that synovial white blood cell (WBC) count is the most reliable predictor of infection control, and a decision to proceed to the second stage depends on attaining a WBC count of less than 3000/μL with less than 80% polymorphonuclear cells from the joint aspirate. Negative intraoperative frozen sections and tissues grossly appearing noninfected are other criteria which are utilized in the second stage to support the decision of proceeding with reimplantation, as there is a high risk of false positive or false negative preoperative cultures. The joint aspirate is mainly used for cell count assessment[50].

Spacer

Spacers are categorized as articulating (dynamic) or non-articulating (static). Between staged procedures, dynamic spacers maintain ambulation and joint range of motion, which protect against muscle wasting; evidence has shown them to be as or more effective at eliminating infection as static



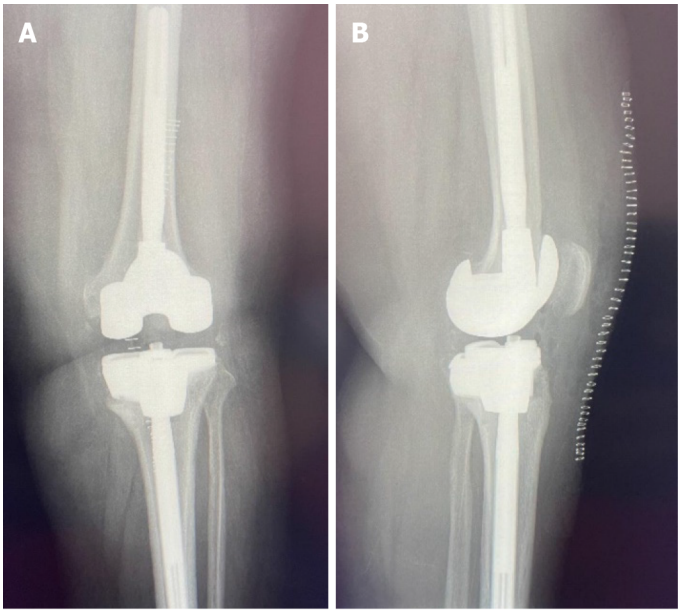
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Figure 4 Second stage revision. After the removal of the spacer, the joint is prepared for reimplantation of the prosthesis. This joint shows minimal bone loss.

spacers[51]. Being able to maintain a range of motion also prevents against the formation of soft tissue and muscle contractures, which facilitates the reimplantation procedure[12,52,53]. Brunnekreef *et al*[54] found a better and quicker recovery of knee function with dynamic spacers, resulting in shorter operation times. Furthermore, compared to static spacers, the use of a dynamic spacer appears to increase the rate of infection eradication (91.2% *vs* 87%)[55]. Moreover, using a static spacer may result in bone loss due to migration of the spacer[56,57]. Despite the above, static spacers may be preferrable in certain circumstances, such as massive bony and soft tissues loss, ligament laxity in the knee, and deficiency of the abductor muscles of the hips[41,44]. Prosthesis with Antibiotic-Loaded Acrylic Cement (PROSTALAC) is an example of an articulating spacer that delivers high concentration of broad-spectrum antibiotics locally. A common regimen used with PROSTALACs is the inclusion of 3 g of vancomycin and 2 g of gentamicin in each sachet of Palacos R cement (Schering Plough Ltd, Labo nv, Belgium). However, antibiotics in spacers may also be prepared according to the sensitivities of the infecting micro-organisms if detected preoperatively[12]. Spacers are usually augmented with a post-operative course of intravenous antibiotics until the definitive antibiotic sensitivities of the infective micro-organisms are detected from the intraoperative cultures taken at the first stage procedure[12]. However, spacers are not complication-free. Faschingbauer *et al*[58] reported that out of 138 patients, 27 (19.6%) developed complications, including spacer fractures in 12 cases (8.7%), dislocation in 12 cases (8.7%), 1 case of a periprosthetic femoral fracture with a spacer in situ, 1 case of a dislocation with simultaneous spacer fracture, and 1 case of protrusion into the pelvis.

2nd stage

The second stage consists of removal of the spacer, further debridement, and collection of tissue samples followed by definitive reimplantation of a new prosthesis (Figure 4). The decision to proceed with the definitive reimplantation must be made after the resolution of all infection-related symptoms and signs and improvement of laboratory results (a declining trend of CRP and ESR may be accepted as opposed to complete normalization of the values as stated earlier)[41,44]. During the second stage, the existing scar is usually utilized to approach the joint[59]. Once the joint is appropriately exposed, further samples are obtained for cultures. It is crucial to remove the cement spacer with the pseudo-synovial cavity that develops around the spacer without compromising the surrounding bone. Necrotic tissue is removed, and pulse lavage is used for extensive irrigation of the joint. This ensures the removal of any residual cement debris, which potentially can cause third body wear if left at the spacer site. If necessary, bone allografts may be utilized at this point to reconstruct any bony deficiencies followed by reimplantation of the definitive prosthesis in accordance with the preoperative plan. The use of bone allografts in revision surgery after PJI has drawn some controversy in the past[60]. Latest evidence, however, has not been able to demonstrate a substantial difference in the rate of reinfection following the use of allografts in this context. Therefore, when there is considerable bone loss, bone grafts may still be used safely[61]. Both cemented and uncemented prostheses may be utilized for the definitive implant. Modern antibiotic delivery methods like defensive antibacterial coating may also be utilized at this stage[62]. Similar reinfection rates and aseptic loosening have been reported when using cemented or uncemented prostheses in TKA revisions for infection[63]. Following surgery, antibiotics may be



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Figure 5 Postoperative anteroposterior and lateral plain radiographs. A: Postoperative anteroposterior view of the left knee after completion of the second stage revision; B: Lateral view of the left knee after completion of the second stage revision.

administered until the bacteriology results are revealed[12]. If any suspicion remains regarding infection during the second stage, a synovial leukocyte esterase strip test, synovial alpha-defensin test, or a frozen section intraoperative tissue analysis may be used to confirm. If the tests are suggestive of residual infection, aggressive debridement followed by a cemented spacer reimplantation (a repetition of the first stage) is necessary[41,44] (Figure 5).

CONCLUSION

PJI is challenging to manage, but recent advancements in laboratory testing have helped to facilitate early diagnosis when used collectively under the internationally agreed upon definition of this surgical complication. A multidisciplinary team approach is crucial when dealing with such cases. Efforts should be made to diagnose the causative microorganism as early as possible in order to start appropriate antimicrobial therapy and plan surgical intervention accordingly. In terms of surgical options, the two-stage revision procedure remains the gold standard approach in chronic cases and yields the highest PJI eradication rates.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Rural implementation of the perioperative surgical home: A case-control study

Srinivasan Sridhar, Amy Mouat-Hunter, Bernadette McCrory

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Abstract

BACKGROUND

Perioperative surgical home (PSH) is a novel patient-centric surgical system developed by American Society of Anesthesiologist to improve outcomes and patient satisfaction. PSH has proven success in large urban health centers by reducing surgery cancellation, operating room time, length of stay (LOS), and readmission rates. Yet, only limited studies have assessed the impact of PSH on surgical outcomes in rural areas.

AIM

To evaluate the newly implemented PSH system at a community hospital by comparing the surgical outcomes using a longitudinal case-control study.

METHODS

The research study was conducted at an 83-bed, licensed level-III trauma rural community hospital. A total of 3096 TJR procedures were collected retrospectively between January 2016 and December 2021 and were categorized as PSH and non-PSH cohorts (n = 2305). To evaluate the importance of PSH in the rural surgical system, a case-control study was performed to compare TJR surgical outcomes (LOS, discharge disposition, and 90-d readmission) of the PSH cohort against two control cohorts [Control-1 PSH (C1-PSH) (n = 1413) and Control-2 PSH (C2-PSH) (n = 892)]. Statistical tests including Chi-square test or Fischer's exact test were performed for categorical variables and Mann-Whitney test or Student's t-test were performed for continuous variables. The general linear models (Poisson regression and binomial logistic regression) were performed to fit adjusted models.

RESULTS

The LOS was significantly shorter in PSH cohort compared to two control cohorts (median PSH = 34 h, C1-PSH = 53 h, C2-PSH = 35 h) (P value < 0.05). Similarly, the PSH cohort had lower percentages of discharges to other facilities (PSH = 3.5%, C1-PSH = 15.5%, C2-PSH = 6.7%) (P value < 0.05). There was no statistical difference observed in 90-d readmission between control and PSH cohorts. However, the PSH implementation reduced the 90-d readmission percentage (PSH = 4.7%, C1-PSH = 6.1%, C2-PSH = 3.6%) lower than the national average 30-d readmission percentage which is 5.5%. The PSH system was effectively established at the rural community hospital with the help of team-based coordinated multi-disciplinary clinicians or physician co-management. The elements of PSH including preoperative assessment, patient education and optimization, and longitudinal digital engagement were vital for improving the TJR surgical outcomes at the community hospital.

CONCLUSION

Implementation of the PSH system in a rural community hospital reduced LOS, increased direct-to-home discharge, and reduced 90-d readmission percentages.

Key Words: Perioperative surgical home; Rural medicine; Case-control study; Total joint replacements; Health equity

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Core Tip: The study evaluated the newly implemented perioperative surgical home (PSH) at a rural community hospital using a case-control design. With limited supporting microsystems, team-based physician co-management was vital to establish the PSH system and following protocols including preoperative assessment, patient education, and longitudinal digital engagement. The surgical outcomes - length of stay, discharge disposition, and 90-d readmission - were compared between the PSH cohort and the control cohorts. The results from this study highlighted the effectiveness of PSH in improving total joint replacement surgical outcomes, especially for high-risk patients who are older and have one or more medical complications.

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INTRODUCTION

The demand for orthopedic surgeries including total joint replacement (TJR), which are primarily performed on hips, knees, and shoulders, are drastically increasing each year[1]. Yet, delivering quality surgical care to large volumes of TJR patients is a challenge to many hospitals, specifically those hospitals located in rural areas[2,3]. Rural and frontier health systems have siloed perioperative care that is spread across many disciplines and institutions, which contributes to inadequate communication, high cost, poor care continuity, and preventable complications[4]. On average, TJR patients are 65 years or older, and have one or more health conditions (*e.g.*, comorbidities). Due to generally higher risk of surgery in these populations, there is a 1% to 50% chance of adverse events in TJR surgeries including major cardiac incidents, healthcare-acquired conditions, extended length of stay (LOS), readmission to inpatient facilities, improper pain management, and side effects[4,5].

To improve surgical outcomes and patient experience, the perioperative surgical home (PSH) model of care was created by the leaders within American Society of Anesthesiologists (ASA)[6,7]. Compared to a traditional surgical system, the PSH is a coordinated interdisciplinary team providing all surgical care to patients from the preoperative phase (30 d before surgery) to recovery phase (90 d after surgery) (Figure 1)[7-11].

The components of PSH also included patient-centered coordination programs and enhanced recovery after surgery[12,13]. The implementation of PSH in larger healthcare systems and academic medical institutions has shown promising results in surgical outcomes, especially in orthopedic procedures[9]. For example, Qiu *et al*[14] and Alvis *et al*[15] observed that the PSH cohort had a day shorter LOS than the control cohort when examining hip and knee procedures. Kim *et al*[16] analyzed 1194 TJR procedures and found that the PSH cohort had higher discharges to home by 8.1% compared

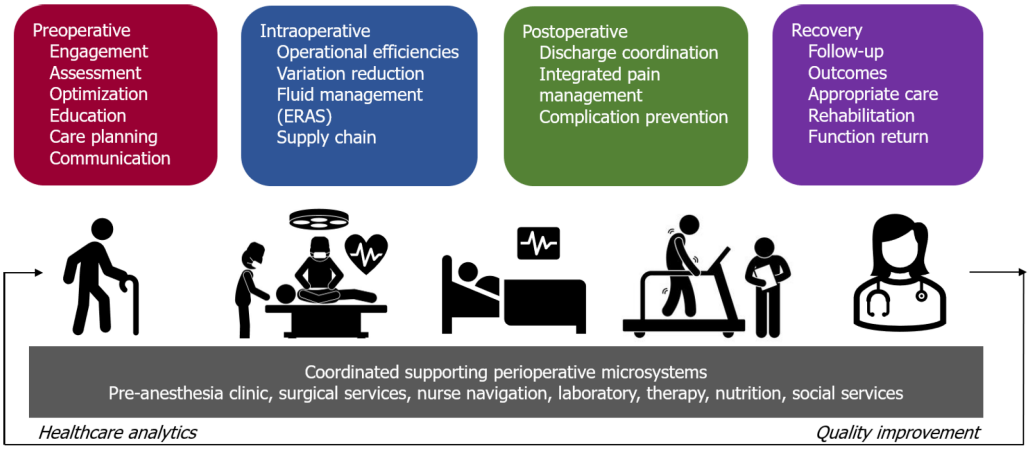


Figure 1 Perioperative surgical model (adapted from[4]).

to the non-PSH cohort. The authors also noticed the surgical cost in the non-PSH cohort was 14.9% greater cost than the PSH cohort. Yajnik *et al*[17] retrospectively analyzed 40 knee procedures and demonstrated that the PSH cohort experienced optimized post-surgical pain management with less consumption of opioids than the non-PSH cohort. Likewise, past researchers found that PSH contributed to improved surgical outcomes including, lower readmission rates, faster postoperative recovery, improved operational efficiency, and higher patient satisfaction[15,18-21].

Despite these successes, some researchers found no change in surgical outcomes with PSH in similar size urban health centers. For example, Vetter *et al*[22] and Powell *et al*[23] found no significant difference in LOS after implementing PSH for orthopedic surgeries. Qui *et al*[14] and Vetter *et al*[22] found no difference in readmission rates using the PSH system. In terms of surgery cost, Leahy *et al*[24] found there was no significant reduction for pediatric patients. These examples exhibit that there is no standard PSH program to achieve a standardized surgical outcome[9]. These PSH studies were performed in urban healthcare systems and academic-affiliated medical centers. To authors' knowledge only our pilot study has explored PSH systems in rural or frontier healthcare service area[4]. This current study addresses this gap by assessing TJR outcomes at a rural hospital with a newly implemented PSH system using a case-control study design.

Surgical care inequality is greater within rural community hospitals due to limited resources, socioeconomic differences, and poor access to healthcare[25-27]. Compared to urban hospitals, rural surgical outcomes have higher odds of in-hospital mortality and higher hospitalization cost[28]. One of the reasons for this is many rural patients are uninsured, older, and have one or more medical complications[29,30]. Rural hospitals in the United States can often be overwhelmed by the growing demand for TJR surgeries and factors such as poor coordination among clinicians, lack of patient education, poor patient care transitions, limited patient engagement (pre-operative and post-operative), and inconsistent/non-standardized care delivery affect rural orthopedic surgical care negatively[1,5].

A newly implemented PSH at a community hospital in rural Montana was created to address the factors mentioned above, which have plagued the rural orthopedic surgery system. With limited resources and supporting microsystems, the PSH was successfully initiated with the help of strong team-based coordination amongst clinicians. The PSH multi-disciplinary team consisted of the patient's selected surgeon, anesthesiologist, hospitalist, physician assistant, registered nurse, and the patient's primary care manager. This collaboration focused on improving surgical care and enhancing patient engagement perioperatively. Effective communication between clinicians was established for communal decision-making for patient-centric - "physician co-management"[31].

This research study's primary objective was to evaluate the newly implemented PSH system at a local rural, community hospital by comparing TJR surgical outcomes using a longitudinal case-control study design. Based on our preliminary study[32], it was hypothesized that the implementation of the PSH in the rural community hospital would positively impact patients' TJR outcomes (*i.e.*, shorter LOS, reduced readmissions, and increased rate of home discharge) across three distinct cohorts for the case-control design.

MATERIALS AND METHODS

The PSH clinic affiliated with the local community hospital began seeing TJR patients in November 2018. The hospital was an 83-bed, licensed level-III trauma center primarily serving three counties. However, based on initial analyses, the hospital was serving patients from more than 10 surrounding counties covering 9000 square miles and approximately 136000 residents. The research team (health

systems engineers and clinicians) retrospectively collected and analyzed all TJR data from January 2016 to December 2021. The observational timeframes were reviewed, and three distinct cohorts were determined for the case-control study design.

Data collection and pre-processing

Data were extracted from the electronic medical record for a total of 6685 orthopedic procedures that were performed on knees, hips, and shoulders between January 2016 and December 2021 (Figure 2). Six hundred and forty-eight (n = 648) procedures were included that had CPT codes - 27447 (total knee), 27130 (total hip), and 23472 (total shoulder). The remaining 6037 did not have CPT codes and were filtered for TJR procedures by searching for keywords 'arthroplasty', 'total', 'THA' (*i.e.*, Total Hip Arthroplasty), 'TKA' (*i.e.*, Total Knee Arthroplasty), and 'TSA' (*i.e.*, Total Shoulder Arthroplasty). During this filtering process, a total of 3420 procedures were excluded because they were identified as non-TJR procedures, (*e.g.*, arthroscopic procedures, reductions, nailing hip). A total of 82 TJR procedures were also excluded from the analysis because they were either duplicate records (n = 1) or missing key outcomes and demographic values (n = 81) of the patients.

A total of 3183 TJR procedures were considered for the analysis and were categorized into: the PSH cohort (case) and non-PSH cohort (control). The PSH pathway begins with visiting PSH clinic for preoperative assessment. Most patients visited the PSH clinic between 30 to 60 d before surgery for their preoperative assessment. Very few medically complicated patients needed more time for optimization and postponed their surgery 6-9 mo (not more than a year) after their preoperative assessment. Therefore, the inclusion criteria for the PSH cohort (n = 791) included if the patient visited the PSH clinic for optimization between 1 and 364 d before surgery. Those patients who visited the PSH clinic but failed to meet the inclusion criteria (*i.e.*, visited the PSH clinic a year before their surgery or after their surgery), were excluded from the analysis (n = 87). The inclusion criteria for the non-PSH cohort included the patients who did not visit the PSH clinic during their surgical process at all. The non-PSH cohort was further subcategorized based on the timeframes: Control-1 PSH (C1-PSH) cohort (before PSH implementation between January 2016 and October 2018, n = 1413) and Control-2 PSH (C2-PSH) cohort (after PSH implementation between November 2018 and December 2021, n = 892).

The study utilized two control cohorts to evaluate the importance of the PSH system in two timeframes - before and after PSH implementation. In the first evaluation, the PSH cohort was compared with C1-PSH cohort. In the second evaluation, the PSH cohort was compared with C2-PSH cohort. The baseline characteristics were compared with variables including patient age, gender, body mass index (BMI), ASA score (Class 1, 2, 3, or 4), procedure type (THA, TKA, and TSA) and insurance type (private or public payer). These variables were included in the baseline characteristics and in the analysis, as they were found to be potential confounders at PSH implemented hospitals with the surgical outcomes LOS, discharge disposition, and 90-d readmission[14,16,24,33,34].

Statistical analysis

Either the Fischer's exact test or Chi-square test for association were used to compare the categorical variables between non-PSH and PSH cohorts. The continuous variables between two cohorts were analyzed using the Mann-Whitney test or Student's t test, as appropriate. The LOS was found to be right skewed and was not normally distributed using the Shapiro-Wilk test (P value < 0.01). Therefore, a Poisson regression was performed to fit an adjusted model[14,35]. For dichotomous variables, *i.e.*, discharge disposition and 90-d readmission, the binomial logistic regression was used to fit an adjusted model. All data handling, visualization, and statistical analyses were performed using R (V4.0.3, Vienna, Austria). The statistical analyses were performed with an alpha (α) value of 0.05. All data were encrypted and were accessed only by the authors and clinicians working at the hospital.

RESULTS

Evaluation 1: Comparison of C1-PSH cohort and PSH cohort

There were no significant differences observed in the baseline characteristics for the variables gender, BMI, and procedure type (P value > 0.05) (Table 1). However, a difference was observed between cohorts for the variables age, ASA class, and insurance type (P value < 0.05). On average, patients in the PSH cohort were two years older than in the C1-PSH cohort. The PSH cohort also included more medically complex patients with a higher proportion of ASA class 3 (42%) compared to the C1-PSH cohort (36%). For insurance, there were more public insurance payers in the PSH cohort (82%) compared to the C1-PSH cohort (71%).

The LOS was lower in the PSH cohort compared to the C1-PSH cohort (median 34 *vs* 53 h, P value < 0.01) (Figure 3). Based on the Poisson regression results, the PSH clinic had a positive effect on LOS (P value < 0.01). On average, the LOS was 10% shorter in the PSH cohort compared to the C1-PSH cohort (Table 1). Other variables that also had a significant effect on patients' LOS were age, gender, BMI, procedure type, and insurance type (P value < 0.05) (Supplementary Table 1).

Table 1 Comparison of baseline characteristics between Control-1 perioperative surgical home and perioperative surgical home cohorts

Characteristics	C1-PSH (*n* = 1413)	PSH (*n* = 791)	*P* value
	mean (SD) [min, max] or *n* (%)	mean (SD) [min, max] or *n* (%)	
Age	67.3 (10) [18, 95]	69.2 (8.6) [31, 90]	< 0.01[1]
Gender			0.19[2]
Male	629 (45)	379 (47.5)	
BMI	29.7 (6.2) [17.3, 68.5]	29 (6.09) [14.67, 55.3]	0.86[1]
ASA			0.009[3]
Class 1	67 (4.7)	20 (2.5)	
Class 2	817 (57.8)	434 (54.9)	
Class 3	517 (36.6)	332 (42)	
Class 4	12 (0.8)	5 (0.6)	
Procedure			0.08[2]
THA	489 (35)	311 (39.3)	
TKA	686 (49)	356 (45)	
TSA	238 (17)	124 (15.7)	
Insurance			< 0.01[2]
Private	415 (29)	145 (18)	
Public	998 (71)	646 (82)	

[1]Mann-Whitney test.
[2]Chi-square test.
[3]Ficher's exact test.
C1-PSH: Control-1 perioperative surgical home; BMI: Body mass index; ASA: American Society of Anesthesiologist Score; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TSA: Total shoulder arthroplasty.

Discharge disposition was classified into two types: patient discharged to home or discharged to other facilities such as skilled nurse facilities, inpatient rehabilitation facilities, or other hospitals' swing beds. Discharge disposition was significantly different between the PSH and C1-PSH cohort (χ^2 = 72, *P* value < 0.01) (Figure 4). The unadjusted odds for the PSH cohort discharged to other facilities was 80% lower than the C1-PSH cohort (*P* value < 0.01) (Table 2). Using logistic regression, the adjusted odds for the PSH cohort discharged to other facilities were 91% lower than the C1-PSH cohort (*P* value < 0.01) (Table 2). Age, gender, procedure type, insurance type, and LOS were also associated with the patient's discharge type (*P* < 0.05) (Supplementary Table 1).

Readmission was categorized by if a patient was readmitted to any inpatient within 90 d post-surgery or not. The Chi-square test had no strong evidence for a difference in the readmission rates between the PSH and C1-PSH cohort (χ^2 = 1.65, *P* = 0.2) (Figure 4). The unadjusted odds for the PSH cohort readmitted after surgery was 24% lower than the C1-PSH cohort (*P* = 0.17) (Table 2). The adjusted odds for the PSH cohort readmitted after surgery was 28% lower than the C1-PSH cohort (*P* = 0.17) (Table 2). In this adjusted analysis, no variable had a significant effect on patient readmission (Supplementary Table 1).

Evaluation 2: Comparison of PSH and C2-PSH cohort

Except for variables ASA and procedure type, there was no significant difference observed between cohorts in the baseline characteristics (*P* = 0.046) (Table 3). Similar to evaluation 1, the PSH cohort had more medically complex patients with a higher proportion of ASA class 3 (42%) compared to the C2-PSH cohort (36%). For procedure types, there were more knee procedures in the PSH cohort and there were more hip and shoulder procedures in the C2-PSH cohort.

There was no significant difference between LOS in the PSH cohort and C2-PSH cohort in the unadjusted analysis (median 34 *vs* 35 h, *P* = 0.5) (Figure 5). However, in the adjusted analysis using Poisson regression, the LOS was found to be lower in the PSH cohort compared to the C2-PSH cohort (*P* value < 0.01). On average, the LOS was 10% shorter in the PSH cohort compared to the C2-PSH cohort (Table 4). Other variables that also had significant effect on patients' LOS were age, gender, BMI, procedure type, and insurance type (*P* value < 0.05) (Supplementary Table 2).

Table 2 Surgical outcomes of perioperative surgical home cohort relative to Control-1 perioperative surgical home cohort

Outcomes	Unadjusted odds ratio (95%CI)	Unadjusted, *P* value	Adjusted risk (95%CI)	Adjusted, *P* value
Length of stay	-	-	0.90 (0.88, 0.91)[1]	< 0.01
Discharge disposition	0.20 (0.13, 0.30)	< 0.01	0.09 (0.05, 0.14)[2]	< 0.01
Readmission	0.76 (0.51, 1.12)	0.17	0.72 (0.47, 1.09)[3]	0.11

[1]Poisson regression adjusted with age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA), procedure type, and insurance type.
[2]Binomial logistic regression adjusted with LOS, age, gender, BMI, ASA, procedure type, and insurance type.
[3]Binomial logistic regression adjusted with LOS, discharge disposition, age, gender, BMI, ASA, procedure type, and insurance type.

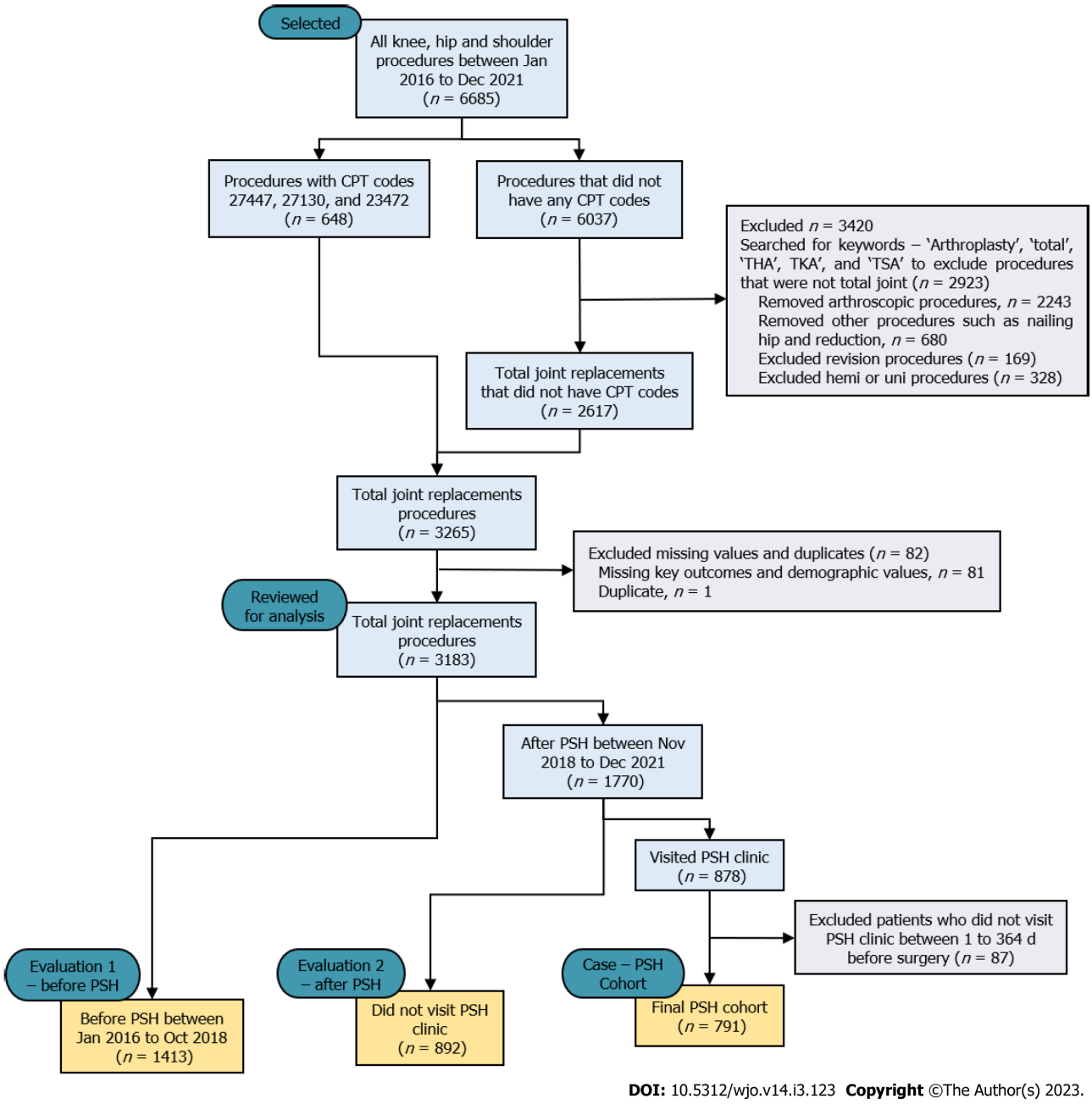
Table 3 Comparison of baseline characteristics between the Control-2 perioperative surgical home and perioperative surgical home cohorts

Characteristics	C2-PSH (*n* = 892)	PSH (*n* = 791)	*P* value
	mean (SD) [min, max] or *n* (%)	mean (SD) [min, max] or *n* (%)	
Age	69 (8.5) [37, 98]	69.2 (8.6) [31, 90]	0.2[1]
Gender			0.52[2]
Male	439 (49.2)	376 (47.5)	
BMI	30 (6.2) [17, 57.8]	30 (6.1) [14.67, 55.3]	0.76[1]
ASA			0.046[3]
Class 1	24 (2.7)	16 (3.4)	
Class 2	546 (61.2)	434 (54.9)	
Class 3	319 (35.8)	332 (42)	
Class 4	3 (0.3)	5 (0.6)	
Procedure			< 0.01[2]
THA	294 (33)	311 (39.3)	
TKA	355 (39.8)	356 (45)	
TSA	243 (27.2)	124 (15.7)	
Insurance			0.4[2]
Private	179 (20)	145 (18)	
Public	713 (80)	646 (82)	

[1]Mann-Whitney test.
[2]Chi-square test.
[3]Ficher's exact test.
C2-PSH: Control-2 perioperative surgical home; BMI: Body mass index; ASA: American Society of Anesthesiologist Score; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TSA: Total shoulder arthroplasty.

Similar to evaluation 1, the discharge disposition was found to be significantly different between the PSH and C2-PSH cohorts (χ^2 = 8, *P* value < 0.01) (Figure 6). The unadjusted odds for the PSH cohort discharged to other facilities was 49% lower than the C2-PSH cohort (*P* value < 0.01) (Table 4). Using logistic regression, the adjusted odds for the PSH cohort discharged to other facilities was 62% lower than the C2-PSH cohort (*P* value < 0.01) (Table 4). Age, gender, procedure type, insurance type, and LOS were also associated with patient discharge type (*P* value < 0.05) (Supplementary Table 2).

Similar to evaluation 1, the Chi-square test had no strong evidence for a difference in the readmission rates between the PSH and C2-PSH cohort (χ^2 = 1, *P* = 0.31) (Figure 6). However, atypical results were observed in the unadjusted analysis, where the odds of the PSH cohort readmitted after surgery was 31% higher than the C2-PSH cohort (*P* = 0.26) (Table 4). Atypical results were also observed in the adjusted analysis, where the odds for the PSH cohort readmitted after surgery was 29% higher than the C2-PSH cohort (*P* = 0.26) (Table 4). In the adjusted analysis, no variable had a significant effect on patient readmission (*P* value > 0.05) (Supplementary Table 2).



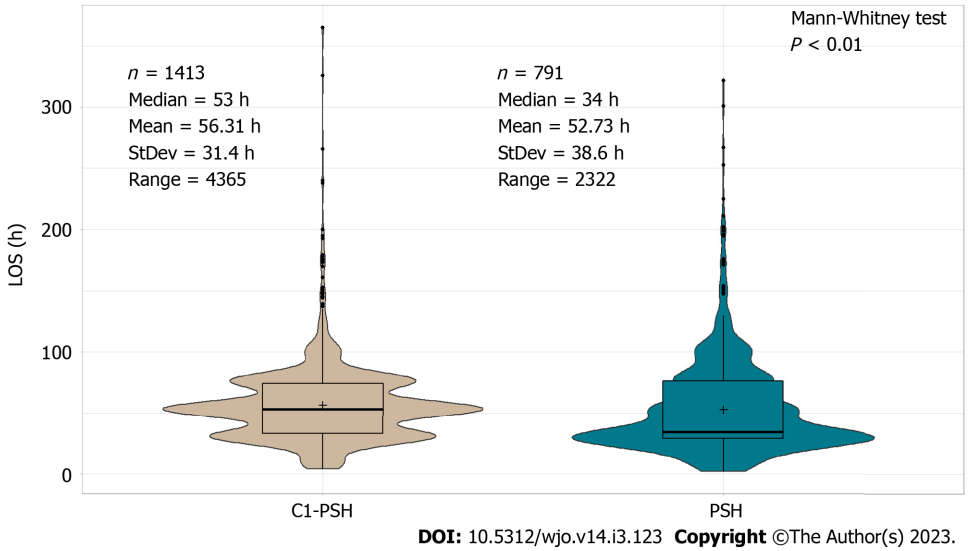
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Figure 2 CONSORT diagram for perioperative surgical home case-control study. PSH: Perioperative surgical home.

DISCUSSION

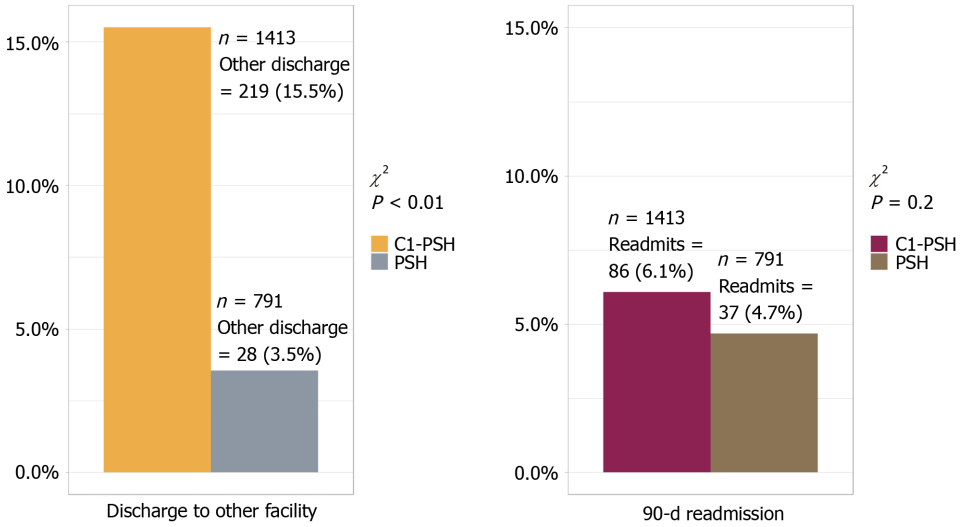
This study evaluated the importance of PSH at a rural community hospital by comparing the PSH cohort with two control cohorts. In the first evaluation, the PSH cohort was compared with the C1-PSH cohort and for the second evaluation, the PSH cohort was compared with the C2-PSH cohort. The C1-PSH cohort included patients who had TJR surgeries before the PSH was implemented. The C2-PSH cohort consists of patients, who had TJR surgeries after PSH was implemented but did not visit the PSH clinic or followed the PSH-pathway.

In both evaluations, the LOS was shorter in the PSH cohort compared to the control cohorts (median PSH = 34 h, C1-PSH = 53 h, C2-PSH = 35 h)[14,33,34]. Although there was no statistical difference in LOS between the PSH and the C2-PSH cohort in the unadjusted analysis, the LOS was significantly shorter in the PSH cohort (10% shorter) in the adjusted analysis. This is because the PSH cohort had older and more medically complicated patients than the control cohorts. Therefore, when adjusted for the variables age, BMI, ASA, *etc.*, the PSH had a significant effect in reducing LOS. Correspondingly, the PSH cohort had lower percentage of discharges to other facilities compared to the control cohorts (PSH = 3.5%, C1-PSH = 15.5%, C2-PSH = 6.7%).



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Figure 3 Length of stay distributional difference between the Control-1 perioperative surgical home and perioperative surgical home cohort. PSH: Perioperative surgical home; C1-PSH: Control-1 PSH.

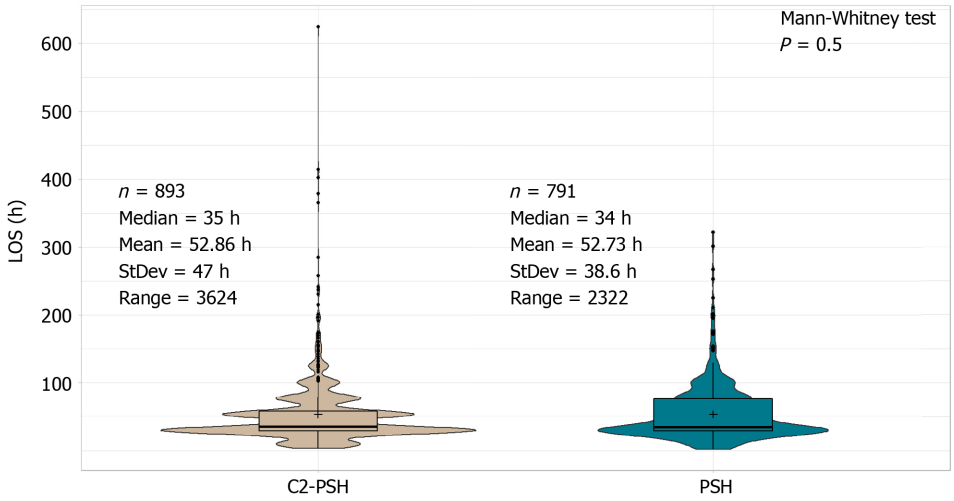


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Figure 4 Discharge disposition and readmission between the Control-1 perioperative surgical home cohort and perioperative surgical home cohort. PSH: Perioperative surgical home; C1-PSH: Control-1 PSH; C2-PSH: Control-2 PSH.

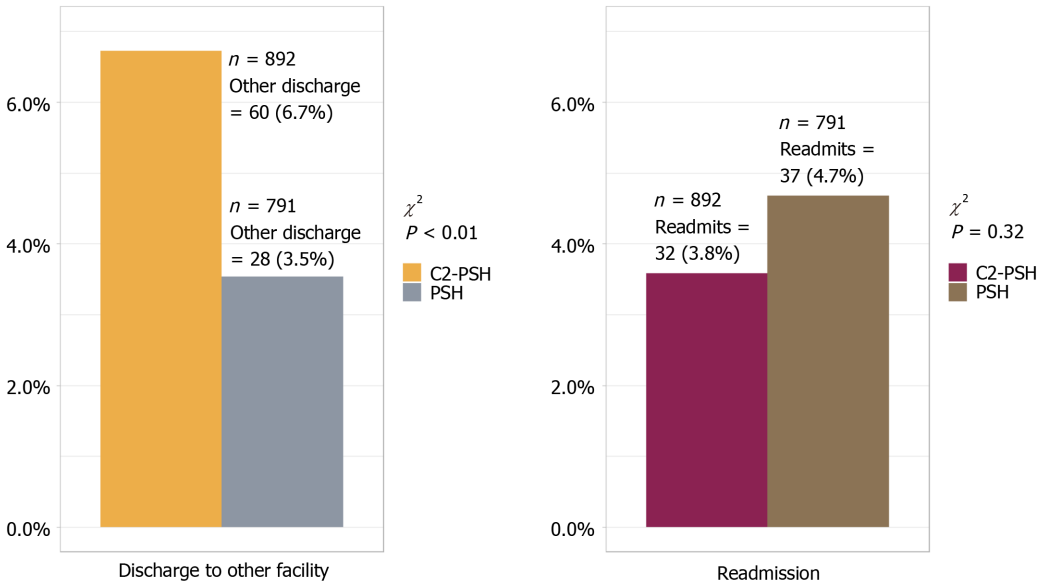
There was no statistical significance in adjusted and unadjusted analysis for 90-d readmission. The readmission percentage was lower in the PSH cohort (4.7%) than the C1-PSH cohort (6.1%). Conversely, the PSH cohort (4.7%) had slightly higher percentage of 90-d readmission than the C2-PSH cohort (3.6%). Despite a marginal increase in the PSH cohort, the 90-d readmission percentage was still lower than the national average 30-d readmission which is 5.5%[36-38]. Past studies also demonstrated similar results where despite no statistical significance, the implementation of PSH helped to lower the readmission rates after surgery[33,38,39].

Akin to other studies of urban health systems[6,9], implementing PSH at a community hospital helped to improve the TJR surgical outcomes. With only limited resources and siloed supporting microsystems, physician co-management was vital to effectively establish the PSH system at the rural community hospital. The PSH preoperative process utilized patient assessment and patient education approximately 30 d before surgery. The assessment helped clinicians identify patients with high-risk factors such as diabetes, high or low blood pressure, sleep apnea, obesity, and heart or respiratory complications[7,40]. Based on these risks, the patients were 'optimized' and received treatment to improve the overall care by minimizing existing conditions or controlling undiagnosed conditions. In addition, the total joint education class hosted by the PSH clinicians educated patients on how to prepare for surgery, manage pain, plan for postoperative discharge, and reach clinicians for postoperative assistance[6,41]. Finally, a digital platform was initiated in the recovery phase to improve



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Figure 5 Length of stay distributional difference between Control-2 perioperative surgical home and perioperative surgical home cohort. PSH: Perioperative surgical home; C2-PSH: Control-2 PSH.



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Figure 6 Discharge disposition and readmission between the Control-2 perioperative surgical home cohort and perioperative surgical home cohort. PSH: Perioperative surgical home; C2-PSH: Control-2 PSH.

patient-clinician coordination and communication after surgery. The digital platform was used to engage and assess longitudinal patient-reported outcomes (post and pre-surgical pain, satisfaction, sleep, *etc.*) from 30 d preoperative to 90 d postoperative. These factors were conducive to improving patient satisfaction, shortening the LOS, increasing discharge to home, and reducing readmission after the surgery[6,24,42].

The PSH clinic majorly saw patients who were high risk (older, high ASA score, high BMI, one or more medical complications such as diabetes, hypertension), which left the C2-PSH cohort with low to medium-risk patients. This explained why the C2-PSH had improved surgical outcomes for LOS, discharge disposition, and 90-readmission compared to the C1-PSH cohort. The PSH system was effective in optimizing medically complicated patients, delivering similar or improved surgical outcomes compared to the C2-PSH cohort. The results from this study support that more patients (especially high and medium risk) should follow the PSH pathway for an effective and improved surgical experience.

Unlike the majority of the PSH studies that were performed at hospitals or health institutions located in metropolitical areas, this research examined the dissemination of PSH system and its effectiveness at a community hospital located in a micro-statistical area (population between 10000 to 50000). According to the United States Census Bureau, 27.2 million people (8.4% of the United States population) live in

Table 4 Surgical outcomes of perioperative surgical home cohort relative to Control-2 non-perioperative surgical home cohort

Outcomes	Unadjusted odds ratio (95%CI)	Unadjusted, *P* value	Adjusted risk (95%CI)	Adjusted, *P* value
Length of stay	-	-	0.91 (0.90, 0.94)[1]	< 0.01
Discharge disposition	0.51 (0.32, 0.80)	< 0.01	0.38 (0.17, 0.77)[2]	< 0.01
Readmission	0.48 (0.22, 0.99)	0.04	0.43 (0.21, 0.93)[3]	0.03

[1]Poisson regression adjusted with age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA), procedure type, and insurance type.
[2]Binomial logistic regression adjusted with LOS, age, gender, BMI, ASA, procedure type, and insurance type.
[3]Binomial logistic regression adjusted with LOS, discharge disposition, age, gender, BMI, ASA, procedure type, and insurance type.

micro-statistical areas encompassing 660 counties[43]. Compared to metropolitical areas, patients living in micro-statistical areas are often prone to experiencing health equity issues and access to health services, including surgical care[44]. This study contributes to improving surgical outcomes using PSH system for community hospitals that are specifically located in micro-statistical areas. The authors envision that these study results will immensely help researchers and clinicians who are working to enhance surgical care in states similar to Montana demographics and social factors, including Alaska, Idaho, Wyoming, North Dakota, and South Dakota.

The limitations of this study include being a retrospective which may contain data collection biases that could alter the results and key findings[45]. Instead, a prospective clinical trial study can minimize these biases and provide better evidence-based results[46]. Second, this study was performed at a community hospital located in a rural micro-statistical area (with a population greater than 10000). The results from this study may not be generalizable to more rural places (*e.g.*, with a population of less than 5000).

CONCLUSION

To the author's knowledge, this study is first of its kind to evaluate the effectiveness of a PSH in a rural surgical system using a case-control study design. Implementing PSH at a community hospital was primarily successful because of patient-centric physician co-management to ensure continuity of care across all perioperative surgical phases. The PSH elements including preoperative assessment, patient education, and longitudinal digital engagement were imperative for improving the TJR surgical outcomes at the community hospital. Future research should include analysis of outcomes including same-day surgery cancellation, surgical cost, postoperative recovery measures, and postoperative opioid consumption. Other future research should also include advanced analytics and predictive modeling such as machine learning and deep learning to predict patient risk and improve the performance of surgical systems at rural and frontier hospitals[47].

ARTICLE HIGHLIGHTS

Research background

With increasing demand for total joint replacement (TJR) procedures, delivering quality surgical care is a challenge to many hospitals, specifically those hospitals located in rural areas. The perioperative surgical home (PSH) developed by American Society of Anesthesiologists has proven successful in large urban health centers by reducing surgery cancellation, operating room time, length of stay (LOS), and readmission rates. Yet, only limited studies have assessed the impact of PSH on surgical outcomes in rural areas.

Research motivation

Compared to urban hospitals, rural hospitals in the United States can often be overwhelmed by the growing demand for TJR surgeries and factors such as poor coordination among clinicians, lack of patient education, poor patient care transition, and inconsistent care delivery that affect rural orthopedic surgical care negatively. A new PSH system was implemented at a community hospital located in rural Montana to address these issues, which have plagued the rural orthopedic surgery system.

Research objectives

The objective of this research was to evaluate the newly implemented PSH system at a local rural, community hospital by comparing TJR surgical outcomes using a longitudinal case-control study.

Research methods

A case-control study was performed to compare the PSH and non-PSH cohorts of TJR surgical outcomes performed at a rural community hospital. Statistical tests including the Chi-square test or Fischer's exact test were performed to compare the categorical variables between non-PSH and PSH cohorts. Similarly, for continuous variables, student's *t* test or Mann-Whitney test was performed, as appropriate. The adjusted analysis was performed using general linear models; Poisson regression for the LOS, and binomial logistic regression for discharge disposition and 90-d readmission.

Research results

The LOS was shorter in PSH cohort compared to the control cohorts [median PSH = 34 h, Control-1 PSH (C1-PSH) = 53 h, Control-2 PSH (C2-PSH) = 35 h]. Correspondingly, the PSH cohort had a lower percentage of discharges to other facilities than the control cohorts (PSH = 3.5%, C1-PSH = 15.5%, C2-PSH = 6.7%). No statistically significant difference was observed in 90-d readmission between PSH and control cohorts. However, the implementation of PSH helped to lower the readmission rates after surgery.

Research conclusions

Implementing PSH at a community hospital helped to improve the TJR surgical outcomes. The patient-centric physician co-management to ensure continuity of care across all perioperative surgical phases was vital for establishing PSH system at a rural community hospital. The PSH elements including preoperative assessment, patient education, and longitudinal digital engagement were imperative for improving patient satisfaction, shortening the LOS, increasing discharge to home, and reducing readmission after the surgery.

Research perspectives

This study contributes to improving surgical outcomes using PSH system for community hospitals that are specifically located in micro-statistical areas. The authors envision that these study results will immensely help researchers and clinicians who are working to enhance surgical care in states similar to Montana demographics and social factors, including Alaska, Idaho, Wyoming, North Dakota, and South Dakota. In the long term, this research will contribute to reducing socio-economic and socio-demographic differences in delivering high-quality surgical care to patients in the United States.

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ORIGINAL ARTICLE

Retrospective Study

Inflammatory response in confirmed non-diabetic foot and ankle infections: A case series with normal inflammatory markers

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Abstract

BACKGROUND

The distinction between foot and ankle wound healing complications as opposed to infection is crucial for the appropriate and efficacious allocation of antibiotic therapy. Multiple reports have focused on the diagnostic accuracy of different inflammatory markers, however, mainly in the diabetic population.

AIM

To evaluate the diagnostic accuracy of white cell count (WCC) and C-reactive protein (CRP) as diagnostic tools for this distinction in the non-diabetic cohort.

METHODS

Data was reviewed from a prospectively maintained Infectious Diseases Unit database of 216 patients admitted at Leicester University Hospitals–United Kingdom with musculoskeletal infections over the period between July 2014 and February 2020 (68 mo). All patients with confirmed diagnosis of diabetes were excluded while only those with confirmed microbiological or clinical diagnosis of foot or ankle infection were included in our study. For the included patients, we retrospectively retrieved the inflammatory markers (WCCs and CRP) at the time of presentation. Values of CRP 0-10 mg/L and WCC 4.0-11.0 × 10^9/L were considered normal.

RESULTS

After exclusion of patients with confirmed diabetes, 25 patients with confirmed foot or ankle infections were included. All infections were confirmed microbiologically with positive intra-operative culture results. 7 (28%) patients with

osteomyelitis (OM) of the foot, 11 (44%) with OM of the ankle, 5 (20%) with ankle septic arthritis and 2 (8%) patients with post-surgical wound infection were identified. Previous bony surgery was identified in 13 (52%) patients, either a corrective osteotomy or an open reduction and internal fixation for a foot or ankle fracture with the infection developing on top of the existing metalwork. 21 (84%) patients did have raised inflammatory markers while 4 (16%) patients failed to mount an inflammatory response even with subsequent debridement and removal of metal work. CRP sensitivity was 84%, while WCC sensitivity was only 28%.

CONCLUSION

CRP has a relatively good sensitivity in the diagnosis of foot and ankle infections in non-diabetic patients, whereas WCC is a poor inflammatory marker in the detection of such cases. In presence of clinically high level of suspicion of foot or ankle infection, a normal CRP should not rule out the diagnosis of OM.

Key Words: Osteomyelitis; Septic arthritis; Surgical site infection; Inflammatory markers; C-reactive protein; White cell count

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Core Tip: Distinction between foot and ankle wound healing complications as opposed to infection is crucial for appropriate and efficacious allocation of antibiotic therapy. Multiple reports have focused on diagnostic accuracy of different inflammatory markers, however, mainly in the diabetic population. Our aim was to evaluate the diagnostic accuracy of white cell count and C-reactive protein as diagnostic tools for this distinction in the non-diabetic cohort.

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INTRODUCTION

Early stages of infection are difficult to discern from non-infected wound healing complications which warrants a different course of management and appropriate allocation of antibiotic treatment. Antibiotic treatment for non-infected wound dehiscence would kill commensal flora and may impair healing as well as possibly leading to an ensued infection with emergence of multi-drug resistance[1,2]. Conversely, delayed diagnosis of infection will lead to potentially avoidable complications which might culminate in amputation. It is therefore of paramount importance to assess strategies for differentiating non-infected from infected wounds at an early stage to begin advanced testing and treatment in high-risk patients.

Most of the literature addressing osteomyelitis (OM) of the foot and ankle focuses on patients with diabetes mellitus (DM) owing to the significantly higher rates of infection in this cohort of patients. It was established by a retrospective review on 1000 foot and ankle orthopedic surgical related infections that diabetic patients were five times more likely to experience a severe infection requiring hospitalization compared with non-diabetic patients[3]. That being said, it was further affirmed by another retrospective review on 1465 consecutive foot and ankle surgical cases that it was more specifically complicated diabetes (in terms of peripheral neuropathy and foot ulceration) that was incriminated in this significantly higher rate of infection rather than diabetes itself[4].

Diagnosis of foot and ankle OM relies on a thorough clinical examination and history taking further validated with laboratory evaluation, microbiological assessment, and diagnostic imaging. As previously mentioned, complicated diabetes adds significantly to the risk of post-operative infections and should be excluded through examination for peripheral neuropathy and ankle brachial index or other vascular examination if warranted. Plain radiographs are the initial imaging modalities to be considered and can be 67% specific and 60% sensitive for OM[5]. In equivocal cases, an advanced imaging such as a magnetic resonance imaging (MRI) especially new functional MRI modalities, including Dixon imaging, diffusion-weighted imaging and dynamic contrast-enhanced MRI or even Bone scans, such as the white blood cell labelled Indium-111 or Sulphur colloid marrow scan, may prove beneficial in distinguishing infections from other non-infective etiologies such as Charcot's

arthropathy or non-infected wound healing complications[6].

In terms of laboratory workup, acute phase reactants such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white cell count (WCC) as well as less commonly utilised surrogates for infection such as serum albumin levels, pro-calcitonin (PCT) and interleukin (IL)-6 have all been described for surgical foot and ankle infections[7].

Increased serum inflammatory markers such as CRP and ESR have been used for the diagnosis of OM with a sensitivity and specificity of > 0.70[8,9]. From the immunological perspective, a raised CRP heralds a mounting response to tumour necrosis factor-α-, IL-6- and IL-1-mediated insult. CRP should be interpreted carefully as it is routinely elevated postoperatively peaking at the second to third post-operative day and plummeting back to normal within three weeks. Therefore, any second peak in CRP level after the third postoperative day may be a sign of infection[10]. Another consideration is that CRP levels might not be elevated in a subset of patients with low virulent pathogens specifically coagulase negative Staphylococcus as well as fungal infections. This was established by diagnostic studies on shoulder and hip prosthetic joint infections showing low sensitivity for serum CRP when low-virulent organisms such as Propionibacterium acnes, coagulase negative Staphylococci and Enterococcus faecalis when compared to Streptococcal and Staphylococcal highly virulent culture diagnosis[11-14]. Leucocytosis may or may not be present and should not be used as an absolute indicator of OM. In the acute stage, elevation of the WCC may be seen. However, this condition is not true in all patients, in immunocompromised individuals, the normality of systemic temperature and WCC may be misleading in the face of an infection, making other diagnostic modalities essential[15,16].

Our study aimed to assess the diagnostic accuracy of simple and readily available inflammatory markers such as WCC and CRP as an aid to making this distinction in confirming suspected foot and ankle infections in the non-diabetic population thereby reducing morbidity and associated healthcare costs.

MATERIALS AND METHODS

A prospectively managed database for all patients discharged home on intravenous antibiotics through the University Hospitals of Leicester NHS Trust Outpatient Parenteral Antimicrobial Therapy (OPAT) service was interrogated, to identify patients who had been treated for musculoskeletal infections. The period of inclusion was from July 1, 2014 (inception of the database) until February 28, 2020 over a period of 68 mo. Patient with infections at sites other than foot and/or ankle and those with preceding confirmed diagnosis of DM were excluded. We subsequently retrieved the inflammatory markers for included patients at the time of presentation and during the perioperative period. Values of CRP 0-10 mg/L and WCC 4.0-11.0 × 10^9/L were considered normal.

The diagnosis was based on the clinical picture and confirmed by imaging and laboratory investigations. All patients presented with pain, stiffness, swelling, and erythema of the affected area. Plain radiographs were the first imaging modality requested in the investigation work-up. If no radiographic evidence was present, but clinical suspicion was high, other modalities of diagnostic studies were considered *i.e.*, ultrasonography, computed tomography and/or MRI. Laboratory investigations included WCC, CRP and blood cultures. ESR, procalcitonin and IL-6 were not routinely assessed in our hospital. Wound swabs were requested for infected surgical wounds, ulcers, or sinuses. Arthrocentesis with microscopic examination, gram staining, culture and sensitivity was performed for patients with septic arthritis. Intra-operative tissue and bone samples from OM patients acquired at the time of surgical debridement were sent to the microbiology laboratory to confirm the diagnosis, identify the causative organism and to tailor the antibiotic regimen. At least 5 samples were taken for each patient for microbiological and histological analysis.

RESULTS

A total of 216 patients were identified. Only 37 patients were identified as having foot and/or ankle infection, of those 12 had a diagnosis of DM. After exclusion of those with a confirmed diagnosis of DM at the time of the diagnosis or infections other than foot or ankle, 25 patients remained. The mean age at presentation was 48 years (range = 26–74) and 14 (56%) were males while 11 (44%) were females.

Of those 25 patients, 11 (44%) were admitted for foot OM, 7 (28%) for ankle OM, 5 (20%) patients with septic arthritis of the ankle joint, and 2 (8%) cases were diagnosed of having surgical site infection (SSI). A history of previous bony surgery, whether an elective osteotomy for deformity correction or fracture fixation was identified in 13 patients (52%) while 12 patients (48%) had non-surgical infections. The clinical summary of these patients is shown in Table 1.

Of those 21 patients (84%) showed raised inflammatory markers at the time of presentation. CRP was elevated in 21 patients with a sensitivity of 84% (range = 13–417, median = 108), whereas WCC was raised only in 7 patients with a poor sensitivity of 28% (range = 10.8–20, median = 16.5). Four patients (16%) did not mount an inflammatory response: 2 with foot OM and 2 with ankle OM. All of them

Table 1 Distribution of included patients as regards different presentations and preceding history of surgical risk factor

Diagnosis	No	Surgery related	Not surgery related
OM foot	7	1	6
OM ankle	11	10	1
Septic arthritis ankle	5	0	5
Postsurgical wound infection	2	2	0

OM: Osteomyelitis.

showed normal inflammatory markers at the time of presentation and during the perioperative period. None of these patients had a history of DM and all had normal blood glucose levels (BGL) at the time of presentation (random BGL < 11.1 mmol/L). All these patients had a history of previous bony surgery, either a corrective osteotomy (25%, n = 1) or an open reduction and internal fixation (ORIF) (75%, n = 3) for a foot or ankle fracture with the infection developing on top of the existing metalwork. Methicillin sensitive Staphylococcus aureus (MSSA) was isolated in all 4 patients. Even after implant removal and subsequent debridement for those patients, their inflammatory markers remained normal and their response to treatment was monitored clinically by successful control of local signs of infection. No significant systemic illness was noted in any of those patients and no immunosuppressive aetiology was identified. Recurrence of infection was noted in only 1 patient of those 4 (25%). The demographics of these 4 patients, their clinical and microbiological data are shown in Table 2. A more detailed history for each of those 4 presentations is described below.

Case 1: A 46-year-old female patient was admitted for debridement of a-4-week-old ulceration on right big toe, complicated by septic 1st metatarsophalangeal joint on a background history of arthrodesis 2 years prior with uneventful postoperative period. She had normal inflammatory markers with CRP and WCC values of 7 and 6.9 respectively. MSSA and Corynebacterium were isolated from all surgical specimens. Post debridement and implant removal, postoperative inflammatory markers remained within normal range, with CRP of < 5 and WCC of 7.7. One year later, she was admitted with recurrent OM, and underwent multiple procedures with the aim of infection eradication and achieving union (Figure 1). Throughout all these procedures, CRP and WCC remained within the normal range.

Case 2: A 54-year-old female patient diagnosed with OM of the right distal fibula 5 mo following ORIF for closed Weber-B lateral malleolus fracture. This infection did not mount an inflammatory response with normal values of CRP and WCC at time of presentation (CRP < 5 and WCC 6.3), and even after metalwork removal and debridement (CRP < 5 and WCC 5.4). The diagnosis was based on clinical findings, radiographs, and MRI scans (Figures 2 and 3). Tissue specimens grew MSSA and Coagulase –ve Staphylococcus.

Case 3: A 56-year-old female patient presented with infected left medial malleolus metal work and OM 5 mo after the index procedure. Pus was draining from the medial wound on presentation; however, with normal inflammatory markers (CRP 6, WCC 6.6). She was admitted for IV antibiotics with repeated inflammatory markers 3 d later still within the normal range (CRP 6 and WCC 4.3). Removal of all metalwork was done a week later with tissue and pus samples growing MSSA.

Case 4: A 48–year-old male patient presented with OM of right 5th metatarsal 2 mo following a closed fracture to the right 5th metatarsal bone managed with ORIF. On presentation, his WCC and CRP were normal with values of 8.4 and < 5 respectively. The clinical diagnosis was confirmed by MRI showing sinus tract extending from the head of the fifth metatarsal to the skin. He underwent washout and debridement with excision of the distal right 5th metatarsal followed by 5th ray amputation. Intra-operative bone and tissue samples grew MSSA. His CRP and WCC results were within the normal values from the date of presentation till the date of his last operation.

DISCUSSION

SSI following ankle surgery is one of the most common complications usually with substantial sequalae on both the patient such as permanent disability and eventually amputation if not addressed promptly, and the healthcare costs with estimated increase more than 300% for subsequent procedures[17-19].

Despite that surgical foot and ankle infections in diabetic patients is significantly higher than in their non-diabetic counterparts, OM in non-diabetics is not uncommon[2,3]. The population-based study by Kremers *et al*[20] reported the incidence of OM during a 41-year period; there was a 15% incidence of OM of the foot in patients without diabetes. Similarly, Haji Zaine *et al*[21] reported an 18.8% incidence of OM among non-diabetic patients. Although advanced imaging such as MRI and leucocyte-labelled bone scans can provide high sensitivity and specificity in diagnosing these infections, they are expensive and

Table 2 Patient demographics, index procedures and microbiological diagnosis for those 4 patients with normal inflammatory markers

No.	Diagnosis	Procedure	Gender	Age (years)	Surgery-infection interval (months)	Isolated organism
Case 1	OM 1st metatarsal	SCARF and Akin osteotomy for hallux valgus	Female	46	22	MSSA and *corynebacterium*
Case 2	OM distal fibula	ORIF lateral malleolus fracture	Female	54	5	MSSA and Coagulase-ve Staphylococcus
Case 3	OM ankle	ORIF medial malleolus fracture	Female	56	5	MSSA
Case 4	OM 5th metatarsal	ORIF 5th metatarsal fracture	Male	48	2	MSSA

OM: Osteomyelitis; ORIF: Open reduction and internal fixation; MSSA: Methicillin sensitive Staphylococcus aureus.



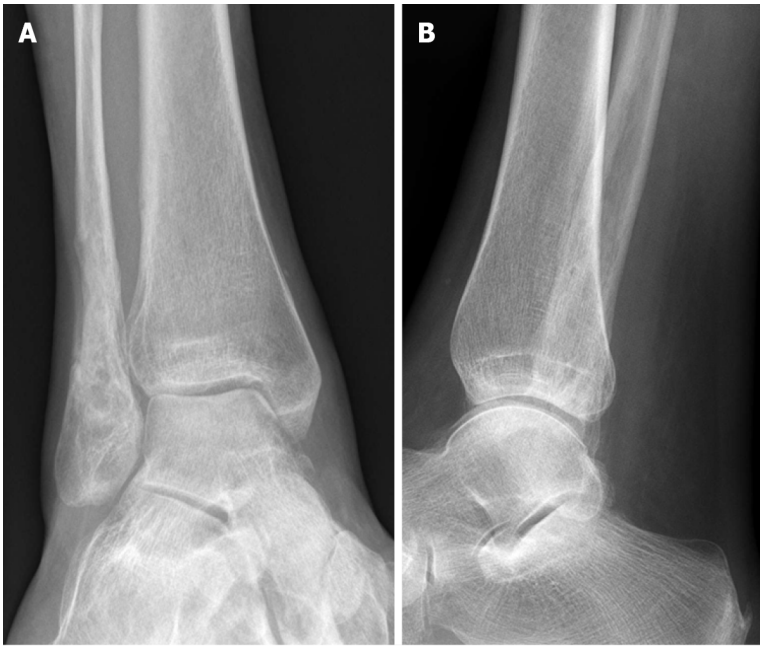
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Figure 1 Foot radiographs of case 1. A: Anteroposterior radiographs showing metalwork failure, non-union and medial ulceration soft tissue shadow; B: Removal of infected metalwork, placement of anti-biotic laden calcium beads and temporary fixation; C: Two years later with union at the fracture site and no recurrence of infection. Throughout all these procedures, C-reactive protein and white cell count were within normal range.

might not be readily available in some centres[22,23] That warranted better understanding of the reliability and sensitivity of different readily available surrogate markers for infection in that population for early diagnosis and mitigation of associated healthcare costs.

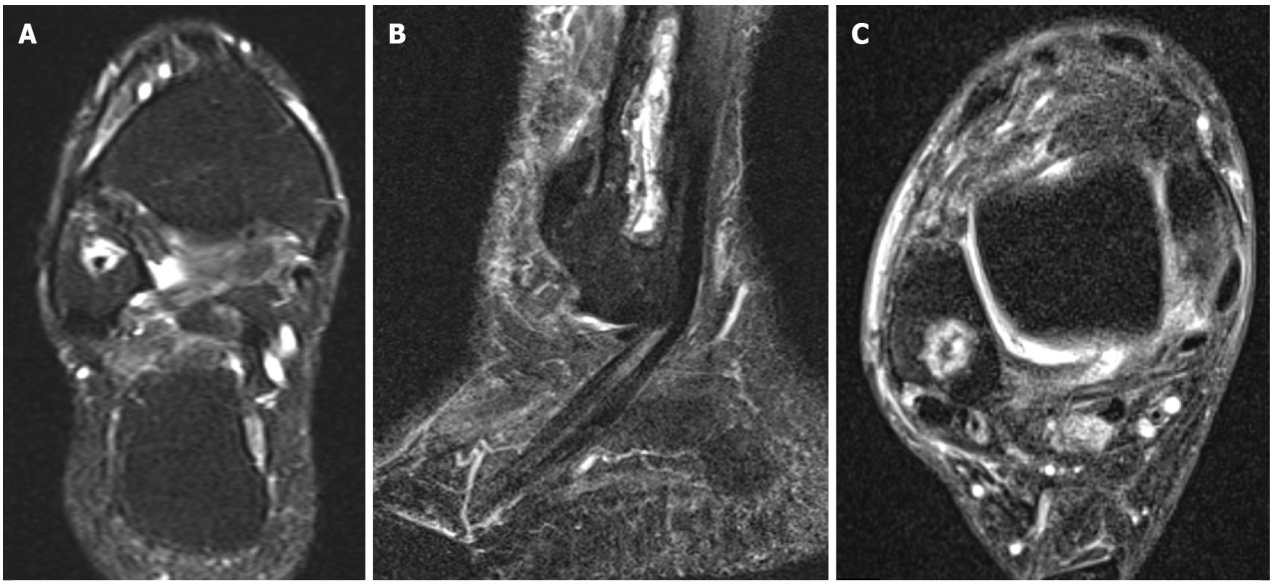
A readily available and cost-effective laboratory tests for OM diagnosis are WCCs and CRP[24]. In the presence of infection, bone marrow accelerates white blood cells production with resultant increases in WCC which is used to signify severity of infection[25]. CRP is an acute phase reactant produced by hepatocytes that increases significantly in concentration in response to infection particularly bacterial infections[26,27].

In our case series, we found that CRP > 10 mg/L had a sensitivity of 84% in the diagnosis of non-diabetic foot and ankle infections, whereas WCC had a poor sensitivity of 28% in the diagnosis of such cases. Other authors have shown similar high sensitivity of CRP diagnosis of OM. Fleischer *et al*[28] showed in their diagnostic study that CRP > 32 mg/L has a sensitivity of 0.85 and specificity of 0.65 for the diagnosis of OM. In another retrospective cohort study on 102 surgical foot and ankle infections, it was shown that CRP had a sensitivity of 71% in differentiating between superficial wound infection and OM[29].



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Figure 2 Ankle radiographs of case 2. A: Anteroposterior; B: Lateral radiographs of ankle after removal of metalwork for infected Weber-B fracture.



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Figure 3 Ankle magnetic resonance imaging of case 2 showing a Broadie's abscess. A: Coronal; B: Sagittal; C: Axial T2-magnetic resonance imaging images showing a hyperintense intra-osseous collection consistent with Broadie's abscess. The patient did not show any elevated inflammatory markers throughout the treatment.

In our cohort, a small subset of confirmed infections (16%, n = 4) did not seem to mount any inflammatory systemic reaction with resultant normal CRP and WCC levels. In their review article, Harris *et al* [30] concluded that for patients with risk factors for OM or a clinically high level of suspicion, values of ESR < 30 mm/h or CRP < 10 mg/L should not rule out the diagnosis of OM, especially in patients with puncture wounds or foot ulcers/infections. This finding has been corroborated by our results with 16% of radiologically/microbiologically confirmed infections having a CRP < 10 mg/L on presentation. In a study by Armstrong and colleagues[31], 54% of the patients with acute OM presented with normal WCC. Our series reported even higher percentage with 72% of confirmed infections presenting with normal WCC. Thus, we recommend corroborating the results with different radiological investigations as well as also considering other emerging biochemical markers for diagnosis of infection.

Those other biochemical markers are increasingly being embedded in the diagnostic panel of investigations. PCT was found in a meta-analysis to be more sensitive than CRP for differentiating bacterial from non-infective causes of inflammation (88% *vs* 75%)[32]. In another study on 93 diabetic foot ulcers, a CRP cut-off value of 17 mg/dL was found to be the single most sensitive marker for confirming infection with sensitivity 0.727, specificity 1.000, positive predictive value 1.000, and negative predictive value 0.793 while total leucocytic neutrophil count was found to be non-predictive[33]. Moreover, combining CRP with PCT yielded higher diagnostic accuracy than solely relying on only one parameter. Serum IL-6 has been described as a more sensitive marker of acute periprosthetic infection particularly in hips and knees with high accuracy, sensitivity, and specificity (97%, 100% and 95% respectively) but has not been specifically investigated in foot and ankle infections[34-36]. Measurement of bacterial load with a critical level of bacteria ≥ 10^4 to 10^6 colony-forming units per g of tissue has been also described to objectively confirm an infective aetiology[37,38].

The retrospective nature of our study has inherent limitations. It may not have included all patients with foot and ankle infections, since not all patients may have been discharged on OPAT and therefore would not have been captured by the database. The proportion of deep infections preceded by a superficial infection was not recorded however eventually all deep infections in our series were identified and reported. Our data relied on different biochemical markers but no attempt to identify a cut-off value or to quantify bacterial load was done. We agree that bacterial load is a reliable indicator of infection in acute infections but has been shown to be less reliable in early subacute or chronic infections as well as in healing wounds[39,40].

Our case series also lacked the assessment of the diagnostic sensitivity of other inflammatory markers for the diagnosis of foot and ankle infections *e.g.*, ESR, PCT and IL-6 as they are not routinely performed in our hospital. Further evaluation of these biochemical markers is recommended.

CONCLUSION

In conclusion, CRP has good sensitivity in the diagnosis these non-diabetic infections, whereas WCC is a poor inflammatory marker in the detection of such cases and should not be used as an absolute indicator of OM. In a subset of patients, relying on these inflammatory markers solely can delay diagnosis as they can be normal, and no inflammatory response mounted. We recommend incorporating other inflammatory markers such as PCT, IL-6 and bacterial load as well as radiological diagnosis when there is a high index of suspicion despite negative CRP and WCC in this subset of patients. A noteworthy finding in our study is that CRP is a readily available, cost-effective, and reliable indicator for ankle and foot infections, directing appropriate antibiotic therapy for those likely to benefit from it.

ARTICLE HIGHLIGHTS

Research background

Non-diabetic foot and ankle infections are not uncommon. Despite this, there is a paucity of the literature investigating the diagnostic accuracy of different inflammatory markers in the diagnosis of these infections as opposed to the diabetic population.

Research motivation

Defining the reliability of inflammatory markers in the diagnosis of non-diabetic foot and ankle infections can aid in early diagnosis and mitigate associated healthcare costs for delayed treatments.

Research objectives

Our aim was to define the reliability of the commonly utilized inflammatory markers such as white cell count (WCC) and C-reactive protein (CRP) in the diagnosis of non-diabetic foot and ankle infections as well as to highlight the shortcomings of those markers in a small subset of patients with normal inflammatory markers despite a microbiologically confirmed diagnosis of infection.

Research methods

This was a retrospective cohort study looking into microbiologically confirmed foot and ankle infections in the non-diabetic population presenting to our hospital (University Hospitals Leicester-United Kingdom) over the period of 6 years (2014-2020).

Research results

A total of 25 non-diabetic patients with confirmed foot or ankle infections were identified. Previous bony surgery was identified in 13 (52%) patients. Inflammatory markers were raised in 21 (84%) patients

while 4 (16%) patients did not mount an inflammatory response even with subsequent surgical procedures. CRP sensitivity was shown to be 84%, while WCC sensitivity was only 28%.

Research conclusions

CRP had a relatively good sensitivity whereas WCC is a poor inflammatory marker in the detection of non-diabetic foot and ankle infections. In a subset of non-diabetic foot and ankle infections, inflammatory markers will not be raised, and a normal CRP should not rule out the diagnosis of osteomyelitis. In these cases where a high level of suspicion persists despite normal CRP, further advanced radiological and laboratory investigations should be performed.

Research perspectives

Further evaluation of different inflammatory markers in the non-diabetic foot and ankle infections (erythrocyte sedimentation rate, pro-calcitonin and interleukin-6) could improve diagnostic accuracy and avoid more expensive investigative procedures.

FOOTNOTES

Author contributions: Mangwani J and White H conceptualized the study design and aim; Ahmed AH and Ahmed S completed data collection and statistical analysis; Barakat A drafted the manuscript and reviewed it for final submission.

Institutional review board statement: This study was reviewed by the Leicester University Hospitals-NHS Trust research ethics committee. No ethical approval was required due to the de-identified anonymous retrospective nature of the published laboratory data.

Informed consent statement: There was no direct or even indirect contact between researchers and patients, with no necessity for "Signed Informed Consent Form" to carry out our study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Identifying sex-specific injury predictors as a key factor in maintaining optimal physical activity levels

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Abstract

BACKGROUND

Optimal physical activity is known to reduce cardiovascular, respiratory and endocrine system diseases and, as a consequence, improve quality of life. An important risk factor for reinjuries during normal exercise is the initial connective tissue pathology. The variety of clinical dysplastic manifestations significantly complicate the timely diagnosis of this comorbidity.

AIM

To establish pathognomonic sex-specific dysplasia phenotypes that indicate a particular sensitivity to physical exertion.

METHODS

The study involved 117 participants with recurrent musculoskeletal injuries that occurred during normal exercise. There were 67 women (57.26%) and 50 men (42.74%), which made it possible to compare the presence of the identified signs between sexes. A validated questionnaire was used to screen their connective tissue status.

RESULTS

Ranking the most commonly revealed dysplasia signs depending on their clinical significance made it possible to establish pathognomonic sex-specific phenotypes that indicated a particular susceptibility to injuries. Individualized programs of optimal physical activity are necessary for men with chest deformities, flat-valgus feet, dolichostenomelia, arachnodactylia, hemorrhoids, abdominal muscle diastasis and recurrent hernias. In women, special sensitivity to physical exertion was associated with a combination of signs such as asthenic body, joint hypermobility, overly soft auricles, thin hyperelastic skin, atrophic striae, telangiectasias and varicose veins. Of particular importance were universal signs such as gothic palate, scoliosis, kyphosis, leg deformities, temporomandibular joint crunching, and moderate to high myopia.

CONCLUSION

Participants' connective tissue condition should be considered when designing optimal physical activity programs. Identifying the established sex-specific dysplasia phenotypes will allow timely optimization of training loads, thus reducing the risk of injury.

Key Words: Injury risk; Physical activity; Connective tissue condition; Sex-specific dysplasia phenotypes; Clinical dysplastic manifestations

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Core Tip: Ranking the most commonly revealed dysplasia signs depending on their clinical significance made it possible to establish pathognomonic sex-specific phenotypes that indicate a particular susceptibility to injuries. Individualized programs of optimal physical activity are necessary for men with chest deformities, flat-valgus feet, dolichostenomelia, arachnodactylia, hemorrhoids, abdominal muscle diastasis and recurrent hernias. In women, special sensitivity to physical exertion was associated with a combination of signs such as asthenic body, joint hypermobility, overly soft auricles, thin hyperelastic skin, atrophic striae, telangiectasias and varicose veins. Identifying the established sex-specific dysplasia phenotypes will allow timely optimization of training loads and prescription of therapeutic measures aimed at connective tissue strengthening that will reduce the injury risk during physical activity and improve public health.

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INTRODUCTION

Increasing physical activity in the population and promoting a healthy lifestyle are among the priorities of preventive measures in the health-care system[1-4]. Optimal and regular exercise is known to reduce cardiovascular, respiratory and endocrine system diseases and, as a consequence, improve the quality and duration of life[5-7]. A healthy lifestyle and the desire to maintain an optimal body functional state through increased physical activity and sports are becoming an integral part of the modern person's life, even during the coronavirus disease 2019 pandemic[8-12]. However, physical activity is invariably associated with injury risk, and professional sports are associated with the possible occurrence of musculoskeletal posttraumatic chronic conditions as a result of reinjuries[13-15].

Recently, there has been an increase in the number of cases involving sprains and ruptures of the joint ligament apparatus, dislocations and tendon injuries occurring during normal physical activity[15-19]. An important risk factor for this kind of reinjury is connective tissue pathology, the prevalence of which reaches 85.4% in the population[20-24]. Connective tissue changes caused by impaired synthesis or increased degradation of its components result in its inability to withstand full mechanical load[24,25]. The clinico-morphological manifestations of this pathology are quite variable and exhibit significant differences between sexes[22,23]. In this regard, an individualized approach to connective tissue assessment and optimal physical activity program design, taking into account sex-specific features of the dysplastic signs set, becomes relevant. Therefore, the purpose of this study was to establish pathognomonic sex-specific injury phenotypes for consideration when designing exercise programs that support optimal physical activity in men and women.

A

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + kp_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

B

$$N_1 = \left\{ 1.96 * \sqrt{0.68 * 0.32 * (1 + \frac{1}{1})} + 1.04 * \sqrt{0.889 * 0.111 + (\frac{0.471 * 0.529}{1})} \right\}^2 / 0.418^2$$

$$N_1 = 21$$

$$N_2 = K * N_1 = 21$$

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Figure 1 Minimum sample size calculation. A: Formula; B: Calculation process for this study. p1, p2: Proportion (incidence) of groups #1 and #2; Δ = |p2-p1| = absolute difference between two proportions; n1: Sample size for group #1; n2: Sample size for group #2; α: Probability of type I error; β: Probability of type II error; z: Critical *Z* value for a given α or β; K: Ratio of sample size for group #2 to group #1.

MATERIALS AND METHODS

Study design and participants

The study, conducted at Sechenov University and European Osteopathic Clinical Center and in accordance with STROBE guidelines, involved 117 participants with recurrent musculoskeletal injuries that occurred during normal physical activity in the absence of a pronounced traumatic factor. Musculoskeletal injuries of varying severity included sprains and ruptures of the joint ligament apparatus, dislocations and tendon tears. All participants, aged 26 to 47 years (average 36.4 ± 6.0 years), underwent a complete clinico-instrumental examination in the period from 2019 to 2022. There were 67 women (57.4%) and 50 men (42.6%), which made it possible to compare the identified dysplasia signs between sexes. Using the statistical package G* (EM) Power (Christian Albrechts-Universität, Olshausenstr, Germany)[26], it was determined that 21 was the minimum sample size required for each group for a statistical power of 85% and alpha criterion of 0.05. The formula and the calculations are shown in Figure 1.

Clinico-instrumental examination

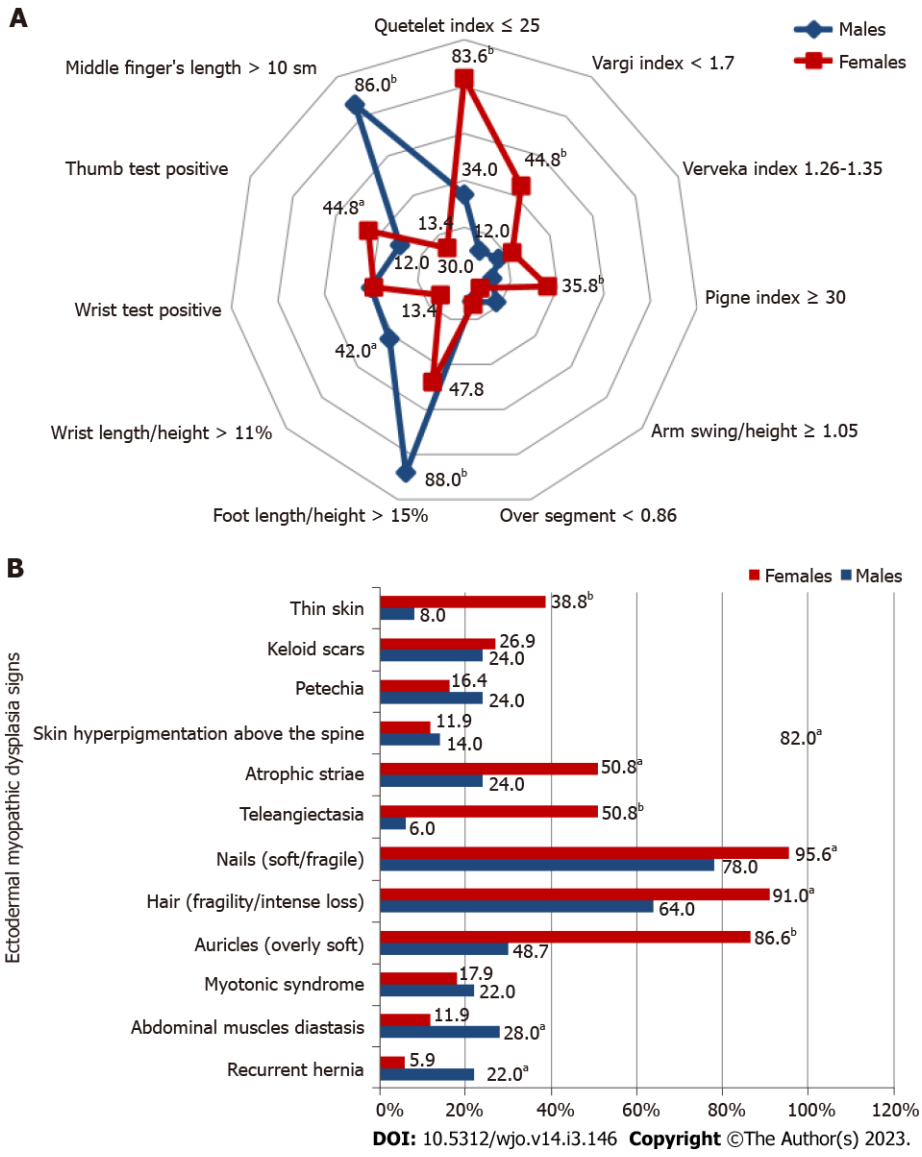
The standard clinico-instrumental therapeutic examination was supplemented with an assessment of anthropometric parameters, such as body height and weight, chest volume, arm span, lower body segment, zygomatic width, face height, and hand and foot length. The facial index (the ratio of the facial height to the zygomatic diameter) was calculated to evaluate the facial skeleton. The Verveck (the ratio of height to the sum of twice the body weight and chest circumference) and Pignet (the difference in height and the sum of body weight and chest circumference) indices were calculated to assess body proportionality. The Varga (the difference between the ratio of body weight to height and age to 100) and Quetelet (the ratio of body weight to squared height) indices were calculated to reveal body weight deficiency. The indices of hand length/height ratios, foot length/height ratios, arm span/height ratios, and upper body/lower body ratios made it possible to diagnose dolichostenomelia features[20,21]. Middle finger length and thumb and wrist tests were used to detect arachnodactyly, and Bayton's criteria were used to establish joint hypermobility[27-29]. Examinations also included ophthalmic consultation, fibrogastroduodenoscopy, ultrasound, and radiography. The revealed dysplasia signs were registered in a specially developed validated questionnaire[21] based on the Kadurina and Abbakumova[29] scale, in which each sign is assessed from 0 to 4 points.

Ethical considerations

The study complied with the Helsinki Declaration norms and was fully approved by the Local Ethics Committee of the I.M. Sechenov First Moscow State Medical University under protocol No. 08-19 on 05.06.2019. All participants gave informed consent before the study.

Statistical analysis

Comparative analysis and ranking of the revealed signs of dysplasia were carried out using RStudio Desktop (RStudio, Boston, MA, United States). The minimum sample size required for this study was calculated by power analysis. Intergroup qualitative indicators were compared using Pearson's χ-square test and Fisher's exact test. Differences were considered to be significant when $P < 0.05$. The results were counted twice by two independent researchers.



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Figure 2 Body proportionality assessment, ectodermal and myopathic sign assessment in persons with musculoskeletal reinjuries. A: Body proportionality assessment; B: Ectodermal and myopathic sign assessment. [a]*P* < 0.05, the differences are significant; [b]*P* < 0.001, the differences are highly significant.

RESULTS

Body proportionality assessment

One of the leading clinico-morphological manifestations of connective tissue pathology is the asthenic body type identified by calculating special indices (Verveck, Pignet, Varga, and Quetelet indices) and characterized by significant longitudinal size predominance and mass deficit. This constitutional type was reliably more common among women with musculoskeletal reinjuries (Figure 2A).

The data presented in the chart show that men with musculoskeletal disorders were significantly more likely than women to have disproportionately long hands and feet, indicating the presence of dolichostenomelia. Arachnodactyly manifested by long, thin, "spider" fingers was also significantly more common in men in terms of middle finger length. Notably, there was a higher rate of positive thumb tests in women with musculoskeletal reinjuries.

Osteoarticular dysplasia sign assessment

The results of this study are summarized in Figure 3A. Skeletal connective tissue damage in most persons with musculoskeletal reinjuries manifests sex-independent changes such as gothic palate, scoliosis, kyphosis, and X- and O-shaped legs. Spinal pathology, altered leg shapes and, as a consequence, incorrect motor patterns caused pronounced biomechanical disorders and led to shoulder and shoulder blade asymmetry in most subjects regardless of sex. The majority of women, in contrast to men, also had pelvic bone asymmetry. Over half of the participants reported joint crunching during

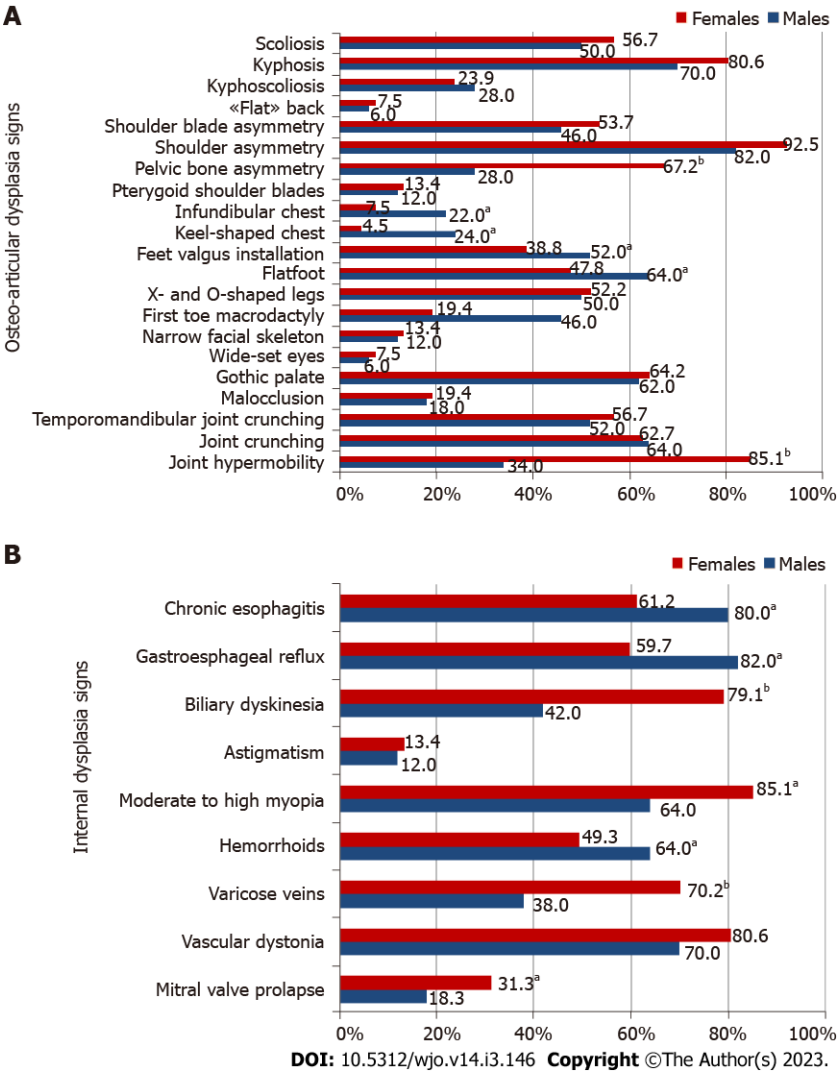


Figure 3 Assessment of osteoarticular dysplasia signs and internal dysplasia signs in persons with musculoskeletal reinjuries. A: Assessment of osteoarticular dysplasia signs; B: Assessment of internal dysplasia signs. [a]*P* < 0.05, the differences are significant; [b]*P* < 0.001, the differences are highly significant.

their movements, and half of the patients were affected by TMJ crunching. Compared to that in women, the external phenotype in men with musculoskeletal postexercise disorders was significantly more often formed by chest deformities, first toe macrodactyly, and flat feet in combination with valgus foot placement. Women, in turn, were more likely to have joint hypermobility.

Assessment of ectodermal and myopathic dysplasia signs

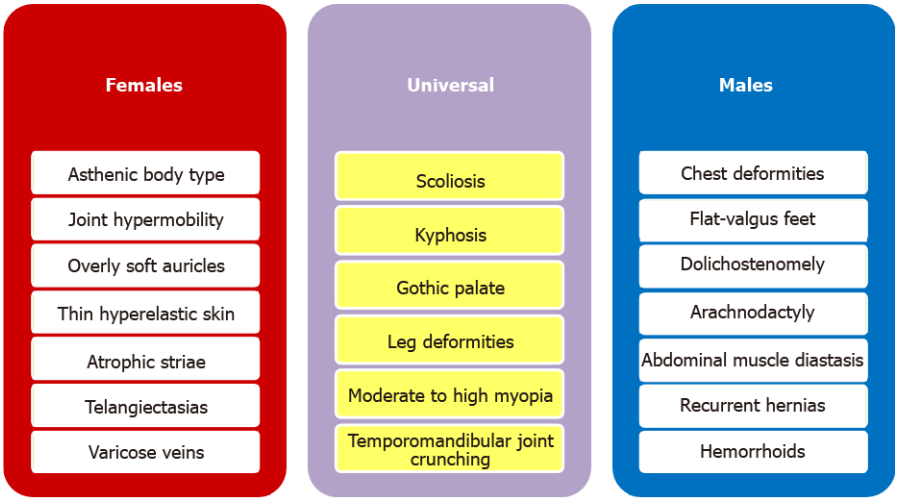
Ectodermal dysplasia signs such as thin hyperelastic skin with a well-visible vessel network, overly soft auricles, atrophic striae, telangiectasias, and nail and hair pathology were more prevalent in women. In addition, abdominal muscle diastasis and recurrent hernia were more typical for men (Figure 2B).

Internal dysplasia sign assessment

The results indicated that most participants with musculoskeletal reinjuries presented vascular dystonia, the incidence of which was shown to have a sex-independent distribution. Mitral valve prolapse, varicose veins and biliary dyskinesia were more common in women, while hemorrhoids, gastroesophageal reflux and chronic esophagitis were often observed in men. A specific sign of connective tissue pathology is moderate to high myopia, which was diagnosed in most men and women with postexercise musculoskeletal disorders, with a significant prevalence in the second subgroup (Figure 3B).

Ranking clinical significance of revealed dysplasia signs

Ranking the most common revealed dysplasia signs depending on their clinical significance made it possible to establish pathognomonic sex-specific phenotypes that indicate a particular susceptibility to injuries. Individual programs of optimal physical activity are necessary for men with chest deformities,



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Figure 4 Pathognomonic sex-specific and universal injury predictors.

flat-valgus feet, dolichostenomelia, arachnodactylia, hemorrhoids, abdominal muscle diastasis and recurrent hernias. In women, special sensitivity to physical exertion was associated with a combination of such signs as asthenic body, joint hypermobility, overly soft auricles, thin hyperelastic skin, atrophic striae, telangiectasias and varicose veins. Of particular importance are universal signs such as gothic palate, scoliosis, kyphosis, leg deformities, temporomandibular joint crunching, and moderate to high myopia (Figure 4).

DISCUSSION

At present, sports medicine is of particular importance in the regular medical-biological support of people engaged in physical exercise and sports[30-33]. The main tasks of sports physicians and physical education specialists are a reasonable choice of sports activities, timely correction of training load, and prevention of injuries and posttraumatic conditions[34-37]. The optimal physical activity program is individually designed for each person and primarily depends on their initial health state. Of particular importance is the detection of connective tissue pathology, which determines the increased sensitivity to mechanical stress, creates injury predisposition and impairs connective tissue recovery in the posttraumatic period, causing further injury recurrence[20,21].

For the first time, significant sex differences in the prevalence of certain connective dysplasia signs were revealed in persons with musculoskeletal reinjuries. Indeed, while bone and myopathic dysplasia signs were significantly more common in men, the prevalence of skin dysplasia signs and joint hypermobility was noted in women. There is evidence that sex differences in dysplastic phenotypes are largely due to exposure to sex hormones: If testosterone gives greater strength to the connective tissue by stimulating fibroplastic reactions, then estrogen causes its excessive elasticity and extensibility, contributing to the appearance of deformity. This explains the greater percentage of overly soft auricles, thin hyperelastic skin, and atrophic striae in women. Vascular wall failure is manifested by telangiectasias and varicose veins. Overstretching of the most powerful ligaments connecting the lumbar spine and the pelvic bones leads to their inability to firmly fix articular surfaces and form pelvic bone asymmetry, which is more common in women.

The influence of female sex hormones is also responsible for the higher incidence of joint hypermobility in the female population, as confirmed by other studies[25]. Increased amplitude of movement in the carpometacarpal and metacarpophalangeal joints in women causes more frequent positive wrist tests in them. The presence of pathological mobility in the joints naturally leads to the appearance of unnatural movements in most loaded joints during increased physical activity and chronic injury[36].

The pathogenetic mechanism of musculoskeletal reinjury in men with connective tissue dysplasia is more associated with skeletal system involvement in the dysplastic process and pathological motor stereotype formation, leading to degenerative-dystrophic changes in the joints and a tendency toward chronic injuries. Significant changes in the composition of glycosaminoglycans and type I and III collagen of the anterior abdominal wall cause an increase in the proportion of muscle diastasis and recurrent hernias[25].

The obtained data necessitate the development of a differentiated approach to dysplasia sign assessment and connective tissue pathology diagnosis in men and women engaged in physical exercise

and sports. At the same time, the current recommendations for identifying dysplastic phenotypes do not take into account the sex of the examined subject[22,37].

One of our study limitations was the relatively small number of participants, which may affect the reliability level of the results. In future studies, we will recruit more subjects. Another limitation is that the study was conducted in one clinical center and among individuals with a large age range. For this reason, this study and its results must be understood as the initial stage of multicenter research for developing measures to prevent sports injuries.

CONCLUSION

The connective tissue condition should be taken into account when attempting to design an optimal physical activity program. It is advisable to develop a differentiated approach to dysplasia sign assessment and connective tissue pathology diagnosis in men and women engaged in physical exercise and sports. Identifying the established sex-specific dysplasia phenotypes will allow timely optimization of training loads and prescription of therapeutic measures aimed at connective tissue strengthening that will reduce injury risk during physical activity and improve public health.

ARTICLE HIGHLIGHTS

Research background

At present, sports medicine is of particular importance in the regular medical-biological support of people engaged in physical exercise and sports. Of particular importance is the detection of connective tissue pathology, which determines the increased sensitivity to mechanical stress, creates injury predisposition and impairs connective tissue recovery in the posttraumatic period, causing further injury recurrence.

Research motivation

This study was created because existing methods often do not take into account differentiated approaches to dysplasia sign assessment and connective tissue pathology diagnosis in men and women and is therefore aimed at filling this gap and creating approaches that complement existing ones.

Research objectives

The purpose of this work was to establish pathognomonic sex-specific injury phenotypes for consideration when designing exercise programs that support optimal physical activity in men and women. The results of the study were conceived as an addition to the existing methods of assessing the risk of further injury recurrence.

Research methods

In our study, we measured 117 participants with recurrent musculoskeletal injuries that occurred during normal physical activity in the absence of a pronounced traumatic factor. Musculoskeletal injuries of varying severity included sprains and ruptures of the joint ligament apparatus, dislocations and tendon tears. Anthropometric parameters and indices indicating the presence of signs of connective tissue dysplasia were studied. An analysis was also performed to identify differences in the presence of signs between sexes. A validated questionnaire was used to screen the connective tissue state.

Research results

In our research, we studied the ranking of the most commonly revealed dysplasia signs depending on their clinical significance, making it possible to establish pathognomonic sex-specific phenotypes that indicate a particular susceptibility to injuries.

Research conclusions

The study results are of particular importance in the context of physical culture and sport safety and emphasize the importance of a differentiated approach of medico- biological support of sports activities in men and women.

Research perspectives

To further develop these findings, it is possible to conduct a larger-scale study with a larger number of participants. Further refinement of the sex-specific dysplasia phenotypes is needed for clarification and, possibly, expansion of these findings. With satisfactorily refined results, it is possible to introduce the proposed methodology into practice for a clinical trial.

FOOTNOTES

Author contributions: Sankova MV, Oganesyan MV, and Vovkogon AD involved in the conceptualization of the manuscript; Sankova MV, Nikolenko VN, Oganesyan MV, Vovkogon AD, and Zharikov YO contributed to the methodology of this article; Sankova MV, Oganesyan MV, Vovkogon AD, and Gadzhiakhmedova AN participated to the resources; Sankova MV analysed data; Sankova MV and Oganesyan MV wrote the original draft preparation; Sankova MV, Oganesyan MV, Zharikova TS and Zharikov YO wrote the review and editing; Nikolenko VN, Oganesyan MV, Vovkogon AD and Zharikov YO involved in the project administration; and all authors have read and agreed to the published manuscript version.

Institutional review board statement: The current research study was approved by the Ethics Committee of I.M. Sechenov First Moscow State Medical University (Sechenov University) under protocol No. 08-19 on 05.06.2019.

Informed consent statement: Informed consent was obtained from the participants included in this study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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SYSTEMATIC REVIEWS

Prenatal radiographic evaluation of congenital transverse limb deficiencies: A scoping review

Neeraj Vij, Luis F Goncalves, Aaron Llanes, Sean Youn, Mohan V Belthur

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Abstract

BACKGROUND

Congenital transverse deficiencies are horizontal deficiencies of the long bones that occur with a reported incidence as high 0.38%. They can occur alone or represent a manifestation of a various clinical syndromes. Diagnosis has traditionally comprised of conventional radiography and prenatal imaging studies. There has been much advancement regarding prenatal imaging modalities to allow for early diagnosis and appropriate treatment.

AIM

To summarize the current state of knowledge on congenital transverse limb deficiencies and to provide an update regarding the radiographic evaluation of congenital transverse limb deficiencies.

METHODS

This IRB-exempt scoping review followed the PRISMA-ScR checklist for scoping reviews strictly. Five search engines were searched for a total of 265 publications. Four authors reviewed these during the screening process. Of these, 51 studies were included in our article. Prenatal magnetic resonance imaging (MRI), 3D Ultrasound, and multidetector Computed tomography (CT) exist are emerging modalities that have the potential to improve diagnosis.

RESULTS

Use of the appropriate classification system, three-dimensional ultrasonography with a maximum intensity projection, and appropriate use of prenatal MRI and prenatal CT can improve diagnosis and inter-provider communication.

CONCLUSION

Further scholarly efforts are required to develop improve standardized guidelines regarding the pre-natal radiographic evaluation of congenital limb deficiencies.

Key Words: Terminal deficiencies; Roentgenographic evaluation; Pediatric skeletal deficiencies; Early diagnosis; Patient-centered care; Prenatal imaging

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Core Tip: Early diagnosis can lead to early, appropriate, family-centered care strategies with the current literature supporting both non-operative and surgical management.

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INTRODUCTION

Congenital transverse deficiencies are horizontal deficiencies involving the long bones. The incidence of congenital limb abnormalities is reported between 0.035%[1] and 0.38%[2], of which transverse limb deficiencies account for approximately half[3]. Congenital transverse limb deficiencies can occur in isolation or as a part of a clinical syndrome. These include femoral and fibular deficiencies[4], Adams-Oliver syndrome[5], Dandy-Walker syndrome[6], and Opitz trigonocephaly[7]. Congenital transverse limb deficiencies can occur in any long bones of the body, though an upper limb and left sided predominance have been demonstrated[8,9]. In the upper extremity, the most common deficiency is the transverse terminal deficiency at the upper third forearm[10].

Diagnosis of congenital transverse limb deficiencies is traditionally thought to be largely supported by conventional radiography[11]. In recent years there has been advancement regarding the use of prenatal imaging to assist in early diagnosis. This includes two-dimensional ultrasound (2D US) (Figure 1A and B, Figure 2A), three-dimensional ultrasound (3D US) (Figure 1C and Figure 2B), fetal magnetic resonance imaging (fetal MRI) (Figure 1C and E, Figure 3A) and low-dose multidetector computerized tomography with 3D reconstruction (3D-CT). The purpose of this scoping review article is to summarize the current state of knowledge on congenital transverse limb deficiencies and to provide an update regarding the radiographic evaluation of congenital transverse limb deficiencies.

MATERIALS AND METHODS

General

This was an IRB-exempt scoping review. The scoping review checklist available at the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews Checklist was followed strictly. The International prospective register of systematic reviews (PROPSERO) was contacted regarding our intention of this article and advised that scoping views do not require registration with PROSPERO.

Search strategy

The following search engines were used: Medline, PubMed Advanced Search, Cochrane library, Embase, and Scopus. Cochrane Reviews was also searched per the recommendations of Pautasso *et al* [12]. The following search items were used: 'Pediatric Transverse Limb Deficiencies', 'Radiography transverse limb deficiencies', 'radiographic evaluation' AND 'pediatric transverse limb defects', 'transverse' AND 'limb' AND 'defects', '*radiographic* AND *evaluation*' AND '*transverse*' AND '*limb*' AND '*deficiencies*', 'MRI' AND 'transverse limb deficiencies', and 'prenatal diagnosis' AND 'transverse limb deficiencies.' This resulted in a total of 265 articles.

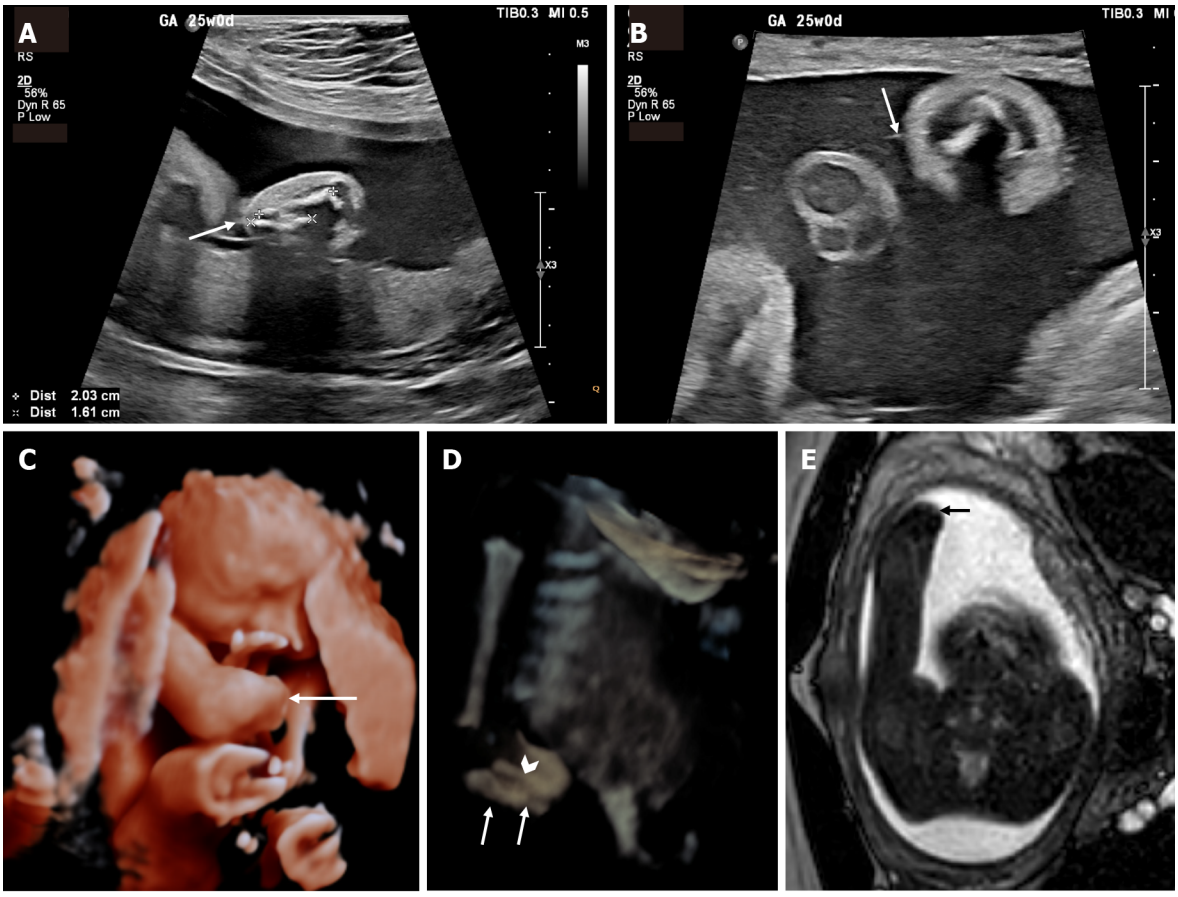
Study Screening and Selection

Four of the authors (Neeraj Vij, Aaron Llanes, Sean Youn, MV Belthur) screened the article by title and abstract. A preliminary decision to include or exclude an article was made based on relevance of the information within the abstract as determined by our inclusion/exclusion criteria (Table 1) This resulted in a preliminary list of 112 articles. This preliminary list of articles was organized into the following

Table 1 Our inclusion and exclusion criteria as applied independently by 3 of the authors during the initial title/abstract review

Inclusion criteria	Exclusion criteria
Pediatric population (ages 0 – 18)	Absence of etiologic, classification system, radiographic, or outcome data in the abstract
Date of publication 1950 – 2022[1]	
Mention of the diagnosis of terminal transverse or intercalary transverse limb deficiencies	Insufficient description of patient characteristics to reasonably draw inferences

[1]The date of publication was chosen per the recommendations of Pautasso *et al*[12].



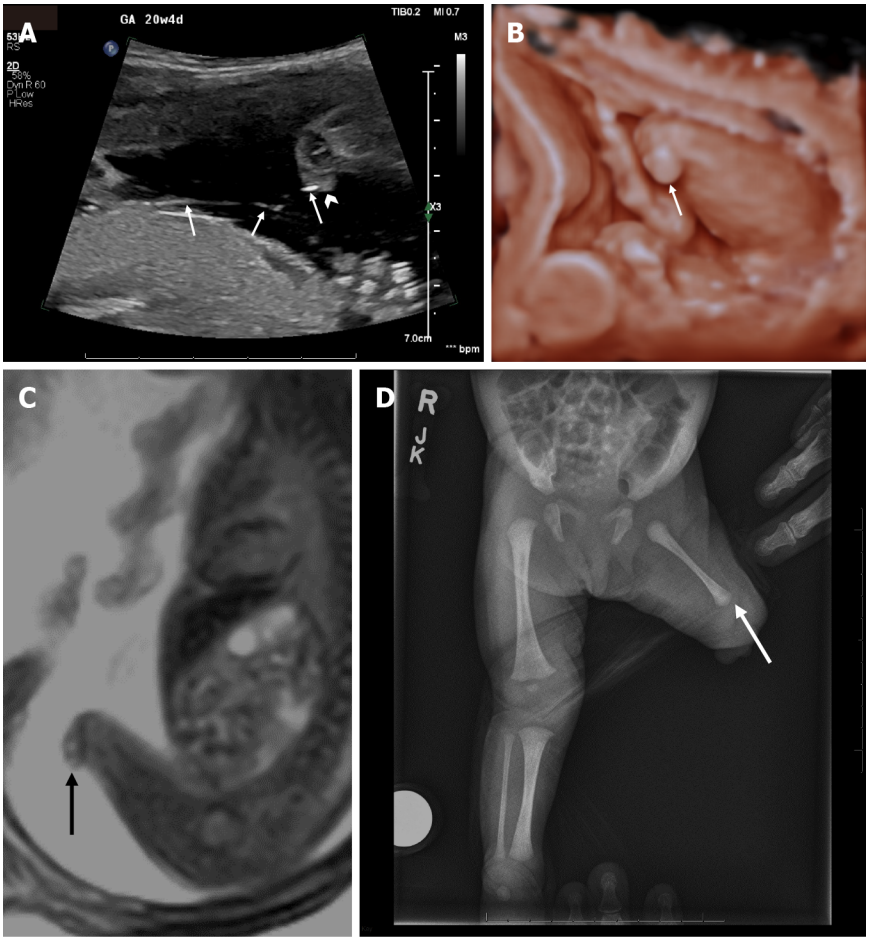
DOI: 10.5312/wjo.v14.i3.155 **Copyright** ©The Author(s) 2023.

Figure 1 Prenatal imaging at 24 wk and 5 d demonstrating a transverse limb deficiency of the right forearm. A: Two-dimensional ultrasound (2D US) showing markedly shortened right ulna (bone between "+" crosshairs) and radius (bone between "x" crosshairs) secondary to a transverse limb reduction defect (arrow); B: High-resolution 2D ultrasound with high-frequency 4-18 Megahertz probe demonstrating a hyperechogenic thin line (arrow) representing a visualized amniotic band attached to the forearm defect; C: 3D US rendered image showing the terminal transverse limb defect below the elbow (arrow); D: 3D US reconstructed image using the maximum intensity projection to demonstrate the markedly short ulna (arrows) and radius (arrowhead). The advantage of 3D US in this case is that the normal humerus and elbow (which are not in the same plane of section in Figure 1A) as well as their relationship with the amputated distal forearm can be appreciated in a single image. The 3D rendered images (Figure 1C and D) are easier to understand for both the referring providers and parents; E: Axial balanced turbo field echo fetal magnetic resonance imaging slice showing the deficiency (arrow).

subheadings: Embryology, Etiology, Natural History, Classification Systems, Prenatal Imaging, Non-surgical treatment, and Surgical treatment.

Full-Text Screening

These articles then underwent a full-text screening process by the same four authors (Neeraj Vij, Aaron Llanes, Sean Youn, MV Belthur). The primary purpose of the full-text screening was final inclusion based on the inclusion/exclusion criteria, and placement of the article in a given section. This resulted in a total of 51 included articles. The references of the selected articles were also hand-searched to identify any missing articles. This did not reveal any additional articles. The include articles were then imported and stored into the most up-to-date stable release Mendeley (v2.57.0)[12].



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Figure 2 Prenatal images at 20 wk and 4 d and postnatal images demonstrating a congenital transverse limb deficiency below the left knee. A: Two-dimensional (2D) ultrasound demonstrating the amniotic bands (arrows) that attach to the residual nubbin (arrowhead); B: 3D ultrasound rendered image showing the transverse reduction defect at the level of the knee (arrow); C: Sagittal balanced turbo field echo slice on prenatal MRI of the left lower extremity showing a terminal transverse limb defect (arrow); D: Postnatal AP x-rays of the lower extremities demonstrating the left transverse reduction defect at the left of the knee, residual nubbin (arrow) and shorter left femur compared to right.

Funding statement

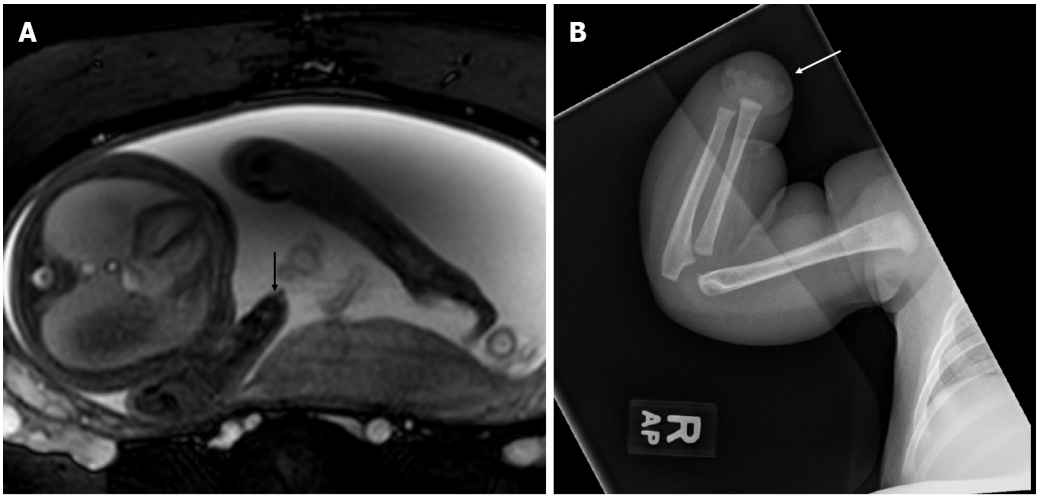
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RESULTS

Etiology & embryology

Limb development begins through paired primordial limb buds at 4 wk of intrauterine development. This is enabled by the undifferentiated mesenchymal cells that underlay the ectoderm on both the forelimb and hindlimb[13]. This structure is referred to as the apical ectodermal ridge and permits both proximodistal development through fibroblastic growth factor, anteroposterior development through the sonic hedgehog protein, and dorsoventral development through the Engrailed-1 protein[14]. The main mechanism of the etiology and embryological level is the disruption of growth of the Apical Epidermal Ridge (AER) along the proximodistal plane[14]. The subsequent result is that the interaxial signaling that is responsible for normal limb development is disrupted and causes a deficiency in the plane orthogonal to the developing limb bud, that is, transversely.

There are several proposed causes for this disruption of the AER. The leading theory includes hypoperfusion, which leads to apoptosis of the AER. This is generally thought to be due to a vasoocclusive event[15] including and other vascular etiologies including thrombosis, vasospasm, and embolism[5,16-18]. Decongestants, non-aspirin non-steroidal anti-inflammatory drugs, and smoking are significantly associated with terminal transverse limb deficiencies[16]. Other etiologies include maternal thrombophilias[9], alpha-thalassemias[19], and amniotic band sequence[16] (Figure 1).



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Figure 3 Prenatal and post natal images of a transverse limb deficiency at the level of the right wrist. A: Axial balanced turbo field echo slice on fetal MRI at 28 wk and 5 d demonstrating a terminal transverse limb defect (arrow); B: Postnatal radiographs confirming the diagnosis (arrow).

Natural history

Congenital transverse limb deficiencies are non-progressive disorders. These disorders result from apoptosis failure (usually secondary to a vascular insult). Thus, the condition is of maximum severity at its presentation and does not progress. Though congenital transverse limb deficiencies are characterized by decreased mobility and function, the symptoms do not worsen as the child grows older.

While the deformity itself cannot worsen, there are malformations associated with limb defects that need to be monitored. Preaxial limb defects were shown to occur more frequently with esophageal atresia, heart defects, and unilateral kidney dysgenesis; postaxial defects with hypospadias; transverse defects with craniofacial defects and ring constrictions; and amelia with anorectal atresia, omphalocele, gastroschises, and ring constriction[20]. Therefore, close attention to associated congenital anomalies is necessary to ensure the health and proper growth of the child.

In a significant proportion of congenital transverse limb deficiency cases, surgery and prosthetics are unnecessary and sometimes contraindicated due to the possibility of complications and the lack of functional gain. Therefore, supportive treatment along with aid from occupational therapists can be a viable option[21].

Classification systems

The first classification of congenital limb deficiencies was described in 1961 by Frantz *et al*[22] The International Society for Prosthetics and Orthotics anatomical classification for congenital limb deficiencies represented a significant expansion of the originally published classification[23]. In this system, congenital limb deficiencies are first described as either longitudinal or transverse. Longitudinal limb deficiencies refer to the complete absence or reduction of the long axis of a limb, whereas transverse limb deficiencies refer to the abrupt absence of an otherwise normally developing limb. Limb deficiencies can be described to specify the affected limb and the extent to which it is affected. By convention, longitudinal limb deficiencies name the bone that is affected such as the ulna or tibia whereas transverse limb deficiencies name the anatomical location that is affected such as the shoulder or leg. The degree of deficiency for both longitudinal and transverse deficiencies can be described as total or partial.

More recent classification systems have expounded upon the anatomy and etiology of congenital limb deficiencies. For instance, McGuirk *et al*[24] considered an additional category of limb deficiency termed intercalary defects, which refers specifically to the absence or hypoplasia of the middle portion of a long bone with intact distal features.

The most recent classification includes both an anatomic and etiologic component[25]. This greatly expands on that of Day *et al*[23] and McGuirk *et al*[24] to include an etiologic component that includes chromosomal abnormalities, Mendelian inheritance, syndromes, teratogenic exposures, vascular disruption defects, or unknown causes[25]. This classification also includes other congenital limb deficiencies, can be used to succinctly describe the location, and allows modification for the presence of nubbins. By allowing subclassification by syndromic, teratogenic, vascular, or other etiologies and by distinguishing between phenotypes within the family of transverse limb deficiencies, the classification proposed by Gold *et al*[25] can provide improved communication between providers and guide genetic testing[26].

Prenatal imaging findings

Prenatal 2D US has become the mainstay of the diagnosis of transverse limb deficiencies (Figures 1A and B, 2A) In much of the developed world, prenatal evaluation involves the mid-trimester scan[1,27]. However, a comprehensive cross-sectional study in 12 European countries for a total of 7758 cases found a prenatal detection rate of 22.7% for isolated terminal transverse deficiencies[1]. Another large study from England, demonstrates a second trimester detection rate of 25%[27]. These large studies in the developed world demonstrate a significant barrier to early intervention and counseling for patients' families.

Of note, is the potential utility of the first-trimester ultrasound scan that has shown to be useful in the detection of transverse limb deficiencies. Liao *et al*[2] demonstrated a detection rate of 77.8% for all fetal limb abnormalities through the first trimester scan. The first trimester scan may have greater role in diagnosis of these limb deficiencies than previously thought.

Fetal MRI is also used as a secondary diagnostic modality (Figures 1C and E, 3A) It is particularly useful in cases that do not image well by ultrasound including cases of maternal obesity, advanced gestational age, oligohydramnios, and unfavorable fetal position[11]. MRI may uncover other associated soft tissue anomalies that may not otherwise be diagnosed prenatally. 3D US (Figures 1C and D, 2B) and multidetector computed tomography are also emerging as modalities to improve diagnosis and lead to earlier treatment[28]; however, low-dose 3D CT is, in general, more useful in cases of suspected skeletal dysplasias. A set of radiographic pearls have been developed by our institutional experts for the reader (Table 2). However, no standardized algorithm incorporating their use is available.

DISCUSSION

Caring for individuals with congenital transverse limb deficiencies

Non-surgical therapies: Non-surgical management of congenital limb deficiencies is comprised of physical therapy, orthoses, and prostheses (Figure 4). Quality of life, functionality, and the degree of limb deficit should all be considered in deciding an appropriate non-surgical strategy[29-31]. Timely implementation of a multidisciplinary strategy is required for reducing pain, function loss, and improving quality of life[32-36].

While there are no clinical guidelines regarding the timeline of treatment, most studies recommend prosthetic fitting before the age of 2 years as the prosthetic rejection rate increases drastically after the age of two[37,38]. It is important to note that children who have treatment can achieve satisfactory degrees of movement and function.

An important facet to treatment is appropriate counseling of the family. This begins with a thorough conversation about the diagnosis, prognosis, natural history, treatment options, and alternatives. Providing an opportunity for the family to meet the family of another affected child has been shown to be very helpful. Doing so can reduce parental anxiety and improve compliance with treatment recommendations[39,40].

Special considerations in upper extremity defects – prosthesis timing and choice

Location of the defect is a very important determinant in the treatment strategy (Figure 3B). While lower extremity prosthetic intervention is widely used, the treatment strategy around upper extremity defects is more nuanced[21]. Upper extremity defects are more common and the choice and fit of prosthesis is rapidly evolving[41].

The ideal time range for prosthesis fitting for trans-forearm and trans-humeral deficiencies is between six and twenty-four months of age[42]. This improves the performance of activities of daily living (ADL's) and minimizes prosthetic rejection. Generally, the outcome of prosthesis use in patients with proximal upper limb deficiencies is good[43]. There is evidence to suggest that early myoelectric prosthesis devices between 2.5 and 4 years of age may have potential therapeutic benefit[42]. However, it is important to consider that prosthesis choice and fit needs to be individualized based on the level of amputation and stump choice to prevent the nerve entrapment syndromes associated with prosthesis overuse[44].

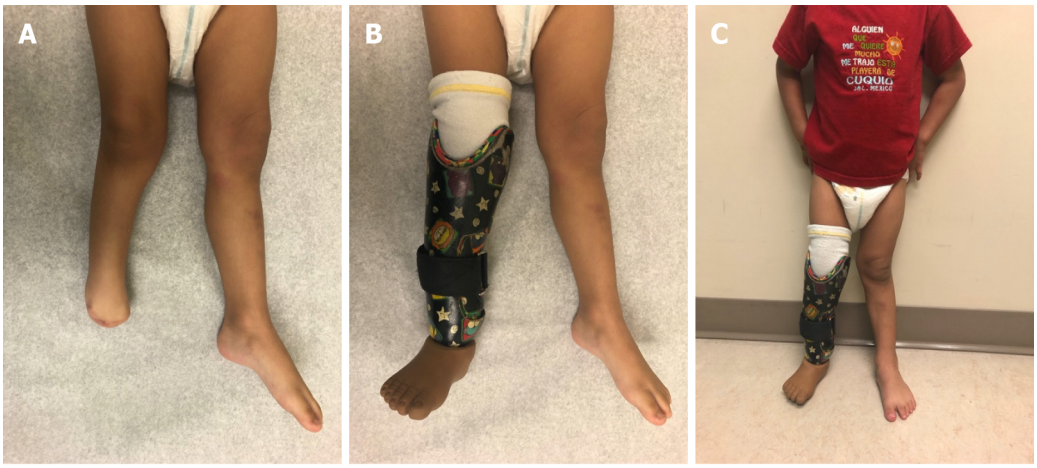
There is a reported underuse of upper limb prosthesis in children with congenital transverse reductions[45]. Children tend to use their prostheses for specific activities and not others[45]. A recent study has shown that there is a direct correlation between the number of activities that children perform and daily use of the upper extremity prosthesis[46]. Addressing the issue of sporadic use may lead to better performance on activities of daily living and increased independence[38].

Though the current literature supports the use of prostheses, there are no long-term reports that compare the outcomes of prosthetic treatment in terms of patient-reported or functional outcomes. Further studies are needed to determine the functional outcome for upper extremity prosthesis users and non-users and thus allow clinicians to make evidence-based recommendations.

Table 2 The radiographic pearls and pitfalls as identified by our literature search and our institutional musculoskeletal radiology experts

Pearl or pitfall	Reasoning and evidence
Use the appropriate classification system	Many classification systems exist[25,26]. However, the most recent classification system by Gold *et al*[27] provides improved communication. When these fail, description of the location and use of modifiers can be helpful to radiologists and non-radiologists, alike
Prenatal ultrasound pearl	Three-dimensional ultrasonography using both maximum intensity projection (MIP), thick slabs with MIP, or surface rendering greatly complements the examination using two-dimensional ultrasound. Scanning with new generation high-frequency broad band probes (up to 22 MHz in some cases) allows greater confidence in the identification of amniotic bands compared to standard obstetrical probes[11]
Prenatal fetal MRI pearl	MRI is not superior to ultrasound for imaging fetal bones. However, it may prove useful in cases where ultrasonography windows are limited, such as maternal obesity, advanced gestational age, oligohydramnios, and unfavorable fetal position. It also provides an additional opportunity to diagnose associated congenital anomalies for which MRI is more sensitive than ultrasound (*i.e.*, CNS anomalies)
Prenatal CT	Current literature supports the use of low-dose CT with 3D reconstruction for the evaluation of skeletal dysplasias[30]. The use of CT for the evaluation of transverse limb deficiencies has not been fully evaluated. The use of CT may be considered when both ultrasound and MRI failed to characterize the phenotype and only after thorough evaluation of benefits versus risks in individual cases

MRI: Magnetic resonance imaging; CT: Computed tomography.



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Figure 4 Clinical photographs of a terminal transverse deficiency of the right leg. A: Supine photograph of the transverse deficiency below the right knee; B: Supine photograph demonstrating proper prosthesis fit; C: Standing photograph demonstrating comfortable standing with the prosthesis.

Social resources

An important topic of discussion is rehabilitation options for young adults. These management resources are often underutilized. A low rate of referral to the affected child and an interdisciplinary management team has been noted from the Regional Disablement Service in Northern Ireland[47].

Ultimately, this has led to progressive social strains that further worsen the quality of life of individuals with transverse limb deficiencies. Many young adults with transverse upper limb deficiencies have difficulty in finding suitable housing and employment[48]. Further, most young adults with upper limb transversal deficiencies are unaware of available resources and have perceived limited benefit of said resources[49]. Increased focus on age-relevant information as well as dedicated training programs could increase benefit to young adults with upper limb transverse limb defects[49]. These findings suggest that an emphasis on the availability and use of these resources could have a great impact on the quality of life of individuals with transverse limb deficiencies. It remains unclear as to what the ideal age, modality of education, and the role of the physician would be to better utilize these options. More research is required to identify what measures can be taken to increase both awareness and use of available resources.

Surgical treatment

Surgical treatment is reserved for a minority of patients and ranges from 16.9%[50] to 25%[3] of patients. Generally, surgical treatment involves intermediary correction for prosthesis placement[42]. However, there is a role in corrective surgeries[3] and lengthening procedures[42,51-52] for some patients.

Surgical treatment pursued varies based on the location of the deficiency[3]. An epidemiological study in Japan noted that in both the upper and lower extremity, surgical treatment was more commonly pursued than prosthesis and orthosis combined in the setting of transverse deficiencies at or distal to the level of distal to the carpals. However, in proximal upper and lower extremity defects, surgery was rarely pursued.

When considering surgical options, they can be broadly classified as one of the following: amputation/constriction ring procedures[3], lengthening procedures[42,51], joint reconstructions[52], and digit transfer surgeries[53]. The literature on outcomes in lower extremity transverse limb surgery is sparse; however, the outcomes for upper limb defects in the hand and wrist are summarized below.

Hand and wrist upper limb deficiencies

To treat upper limb deficiencies at the level of the metacarpal or distal to the metacarpal, finger resurfacing procedures are performed. Amputation and constriction ring release procedures are also performed in preparation for the complete articulation of the limb and prosthetic[3]. However, there are a few surgical options that have been described around the topic of improving orthotic use and increasing functional ability without the need for prostheses.

Reconstruction of the wrist articulation with an iliac crest autograft has been described in the setting of terminal deficiencies. In two patients, these were shown to have cartilage formation on MRI and improved functional abilities[52].

Microsurgical toe-to-hand transfers have also been described with good radiographic outcomes at a mean follow-up of 21 months; however, no patient-reported outcomes have been noted with this surgical option. In the setting of cleft hand, transverse limb deficiencies respond well to cleft hand reconstruction with both radiographic and functional outcomes[53]. Importantly, 4 out of the 11 cleft hands due to underlying transverse limb deficiencies did require additional surgery[54]. Lengthening with either an on-top resurfacing procedure or distraction lengthening has been described with good radiographic outcomes and improved inch function[51].

Though there is some good data regarding radiographic outcomes, the literature is sparse for success rates and re-operation rates when considering these surgical options. Overall, when considering upper extremity transverse deficiencies, a re-operation rate of 5%-20% has been reported. More studies with long-term clinical and functional outcomes of these surgical options and studies investigating causes for re-operation are needed to assist in surgical decision-making.

Limitations

As a scoping review, this manuscript is limited by the quality of the evidence of the studies included. The lowest quality of evidence included was level IV. Further as a scoping review, this article uses summary date to draw conclusions about the current state of a topic. As such, it is vulnerable to selection bias. This may also result in the inability of our search findings to be completely generalizable.

CONCLUSION

Transverse limb deficiencies are rare and display an upper limb predominance. Conventionally, the diagnosis was made through radiography; however, 2D US emerged as a prevalent technology with the potential to improve our diagnostic capabilities. Prenatal 3D US, fetal MRI, and low-dose 3D CT are newly emerging modalities that could also potentially improve diagnosis; however, are not routinely employed in diagnosis. To date, there are no standardized international guidelines regarding the pre-natal radiographic evaluation of congenital limb deficiencies. A systematic method would allow for enhanced interdisciplinary communication, early diagnosis, and integration of family values into treatment plans. Management with prosthesis is commonly pursued, especially in the upper extremity, with highly variable use rates. Surgical treatment is less commonly sought out. Though some studies demonstrate good radiographic and clinical outcomes for hand/wrist surgical options, these are limited by the number of patients and quality of evidence. Further long-term studies are needed for both the conservative and operative treatment options to assist in clinical decision-making.

ARTICLE HIGHLIGHTS

Research background

Congenital transverse deficiencies are horizontal deficiencies of the long bones that occur with a reported incidence as high 0.38%.

Research motivation

There has been much advancement regarding prenatal imaging modalities to allow for early diagnosis

and appropriate treatment.

Research objectives
The purpose of this scoping review article is to summarize the current state of knowledge on congenital transverse limb deficiencies and to provide an update regarding the radiographic evaluation of congenital transverse limb deficiencies.

Research methods
This IRB-exempt scoping review followed the PRISMA-ScR checklist for scoping reviews strictly. Five search engines were searched for a total of 265 publications.

Research results
Of these, 51 studies were included in our article.

Research conclusions
Prenatal magnetic resonance imaging (MRI), 3D Ultrasound, and multidetector computed tomography (CT) exist are emerging modalities that have the potential to improve diagnosis. Use of the appropriate classification system, three-dimensional ultrasonography with a maximum intensity projection, and appropriate use of prenatal MRI and prenatal CT can improve diagnosis and inter-provider communication.

Research perspectives
Further scholarly efforts are required to develop improve standardized guidelines regarding the prenatal radiographic evaluation of congenital limb deficiencies.

FOOTNOTES

Author contributions: Vij N, Belthur M, Llanes A, Youn S, Goncalves LF contributed equally to his work. Vij N, Belthur M, Goncalves LF designed research. Vij N, Belthur M, Llanes A, Youn S, Goncalves LF performed research. Vij N, Belthur M, Llanes A, Youn S, Goncalves LF contributed to the analytic tools. Vij N, Belthur M, Llanes A, Youn S, Goncalves LF analyzed data. Vij N, Belthur M, Llanes A, Youn S, Goncalves LF wrote the paper.

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CASE REPORT

Can we suppress excessive post-surgical scar formation: A case report

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Abstract

BACKGROUND

Hypertrophic scars (HSs) formation is a complication that occurs after wounds heal with secondary intention and sometimes after clean surgical incisions. Many treatments are in vogue now with varying successes. Although the mechanism or mechanisms that cause a HS to form are not clearly understood, one thing that is clear is that once scar tissue matures, any intervention will not be successful. In this paper, we report on a case where a patient who was known to develop HS was treated with a new combination of ingredients (Phyto-chemicals + Silicone JUMI) to suppress HS formation.

CASE SUMMARY

A 68-year-old female of African descent presented a severe HS post total knee replacement (TKR), which the patient describes as itchy and painful. Due to complications caused by the scar, she was apprehensive about undergoing TKR on her other knee. However, after the TKR of the contralateral side post-removal of skin clips, JUMI anti-scar cream (JASC) was used to suppress excessive scar formation.

CONCLUSION

JASC appears potent and efficacious at suppressing excessive scar formation. We believe that this warrants further studies on larger patient groups and on different surgical sites.

Key Words: Hypertrophic scars; Photo-chemicals; JUMI; Keloid; Case report

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Core Tip: Hypertrophic scars are common after surgery and often result in social, emotional, and psychological effects. Many treatments have been tested and the most prominent one is silicone gel. However, this form of treatment has complications related to hot weather. JUMI anti-scar cream is a phyto-chemical based silicone gel that was found to be quite efficacious in reducing post-surgery scars.

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INTRODUCTION

Hypertrophic and excessive scars are common occurrences that often result in social, emotional, and psychological effects[1], in addition to exorbitant costs to manage such complications[2,3].

Hypertrophic scars (HSs) develop due to excessive collagen formation, which can regress slowly[4], but in certain circumstances may continue to deposit collagen, causing HSs[5]. We observed that scarring post joint arthroplasty occurs commonly and that scars in these areas are devoid of hair follicles and sweat glands; excessive scarring can even feel itchy and uncomfortable. Occasionally, HSs result in keloid formations, indicating that there is a dysregulation of the normal healing process, which results in excessive production of collagen, elastin, proteoglycans, and extracellular matrix proteins[6]. This demonstrates that early HS prevention could prevent keloid formation.

In this paper, we report on a case where a patient who was prone to hypertrophic scarring was treated with JUMI cream, which successfully suppressed the post-surgical scar.

CASE PRESENTATION

Chief complaints

Excessive scar formation post total knee arthroplasty of the left knee.

History of present illness

A 68-year-old female of African descent presented with pain in left knee, difficulty to walk due to severe osteoarthritis of left knee. Total knee replacement (TKR) was recommended. She was very apprehensive that the post-surgical scar will become hypertrophic and painful as the right side.

History of past illness

She had undergone TKR of her right knee 12 mo earlier and experience HS post-surgery (Figure 1A). She complained of persistent itching and pain in around the scar and sometimes depressed her became depressed because of it. She had many treatments, including using silicone gel to reduce the scar, which all failed. The patient insisted that she needed to delay surgery on her other knee because she was afraid of another scar forming with the same outcome.

Physical examination

Nothing abnormal except she had 15 degrees of varus deformity of the left knee.

Laboratory examinations

All values within normal range.

Imaging examinations

X-rays show Grade IV Kellgren-Lawrence osteoarthritis in left knee.

FINAL DIAGNOSIS

Suppression of the scar formation post TKR.



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Figure 1 Post operative picture. A: Post operative scar after 12 mo of total knee replacement (TKR); B: Post operative picture after removal of surgical clips on the other knee after TKR; C: Post surgery clinical picture after six weeks of use of JUMI anti-scar cream (JASC); D: Post surgery clinical picture after 12 wk of use of JASC.

TREATMENT

As her pain grew and her mobility deteriorated, she decided to undergo total knee arthroplasty on her left side. During the second surgery, the same procedure and closure methods from the first surgery were used again (*i.e.*, the subcutaneous layer was closed using 2-0 vicryl sutures and the Covidien Appose Single Use Skin Stapler 710 from Medtronic Parkway Minneapolis, MN 55432 United States). Standard rehabilitation hospital protocol for post-TKR was followed after both surgeries.

Two weeks post-surgery, the surgical clips were removed (Figure 1B). The patient was advised to apply JUMI anti-scar cream (JASC) twice a day for 3 mo, which she did regularly.

OUTCOME AND FOLLOW-UP

After 6 wk of applying JASC, the patient was quite happy with the effect on her scar (Figure 1C). Figure 1D shows the scar at 12 wk post suture removal, which is when she expressed having no pain or itchiness in the scar.

DISCUSSION

This case report shows that JASC [a combination of silicone gel and Phyto-Extracts (*e.g.*, Centella asiatica extract, Curcuma Longa, lavender oil, marshmallows, Musa Paradisiaca, pineapple extract, and tea tree oil)] was quite effective at suppressing scar formation. After an extensive review, Hsu *et al*[6] reported that the majority of studies that evaluated silicone gel's ability to prevent HS and keloids were poor quality with high risk of biases. Kong *et al*[7] performed a randomized study of scars after TKR and reported that silicone gel had no beneficial effects on scar pain and itching. In addition, when silicone gel was exposed to hot weather, the researchers observed incessant pruritus (80%), skin rash and maceration, and poor patient compliance[8]. HS and keloid management has improved over the years, but has not achieved the zenith of success; therefore, more trials and more effective drugs are required.

Phyto-chemicals from medicinal plants that can be used to treat HSs have been studied and found to be highly effective[9-11]. Centella asiatica extract is an important phyto-chemical used in JASC that has been proven to contain bioactive constituents, such as triterpenoid saponins, flavonoids, phenolic acids, triterpenic steroids, and amino acids. These improve skin health by increasing hydration and decreasing transepidermal water loss with anti-inflammatory effects[12-14]. JASC is a combination of optimum phyto-chemicals and silicone gel, which has been proven to be efficacious at suppressing post-operative scars.

HSs cause great discontentment and psychological and emotional issues when the scars are close to the joint. Our patient was so depressed because of the scar from the previous surgery that she decided to live with the intolerable pain rather than risk another ugly scar. Our case report demonstrates that there are many ways to suppress post-operative scars, and JASC is one of them. We believe more studies are necessary to confirm the efficacy of JASC for all types of post-operative scars.

CONCLUSION

JASC appears potent and efficacious at suppressing excessive scar formation. We believe that this finding warrants further studies on larger patient groups and different surgical sites.

FOOTNOTES

Author contributions: All authors contributed equally in the work; The literature search, writing was performed by Sadat-Ali M and Al-Mousa SA; Operated by Al-Anii FM and Al-Tabash KW; The patient was followed by Abotaleb MM, Abotaleb MM was blinded what was used for the wound after sutures were removed; All authors have read and approve the final manuscript.

Informed consent statement: Informed consent has been taken prior to surgery and publication of data and pictures thereof.

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REVIEW

Meniscus tears treatment: The good, the bad and the ugly-patterns classification and practical guide

Roberto Simonetta, Arcangelo Russo, Michelangelo Palco, Giuseppe Gianluca Costa, Pier Paolo Mariani

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Abstract

Over the years, several studies demonstrated the crucial role of knee menisci in joint biomechanics. As a result, save the meniscus has become the new imperative nowadays, and more and more studies addressed this topic. The huge amount of data on this topic may create confusion in those who want to approach this surgery. The aim of this review is to provide a practical guide for treatment of meniscus tears, including an overview of technical aspects, outcomes in the literature and personal tips. Taking inspiration from a famous movie directed by Sergio Leone in 1966, the authors classified meniscus tears in three categories: The good, the bad and the ugly lesions. The inclusion in each group was determined by the lesion pattern, its biomechanical effects on knee joint, the technical challenge, and prognosis. This classification is not intended to substitute the currently proposed classifications on meniscus tears but aims at offering a reader-friendly narrative review of an otherwise difficult topic. Furthermore, the authors provide a concise premise to deal with some aspects of menisci phylogeny, anatomy and biomechanics.

Key Words: Meniscus; Meniscus anatomy; Meniscus tear; Meniscus repair; Root lesion; Ramp lesion

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Core Tip: Several studies investigated the effects of a meniscus tear and its optimal treatment. This review aims at providing a practical guide on this topic, including an overview of technical aspects, outcomes in the literature and personal tips.

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INTRODUCTION

Meniscal tears are among the most common injuries of the knee, significantly impacting on the healthcare annual expense[1-4]. It has been estimated that the frequency of arthroscopic procedures for treating meniscus tears is increased by 49% during the 1990s and 2000s[5], but it could reasonably be further expanded in the last years.

Historically, menisci were considered as vestigial remnants, with no significant impact on knee biomechanics[6]. As a result, total meniscectomy was considered the most valuable option for a long time. McMurray[7] claimed insufficient meniscus removal was the main cause of failure of meniscectomy. In 1948, Fairbank[8] reported the clinical outcomes of 107 patients after total meniscectomies and found degenerative knee changes in most of them. From then, several other studies demonstrated the detrimental effects of total meniscectomies on knee joint[9-13]. These studies significantly changed the treatment approach of meniscus tears. Feeley and Lau[14] proposed an algorithm to approach arthroscopic partial meniscectomy starting from the concept of maintaining as much meniscal tissue as possible. The authors quantified as 60% as the maximum amount of meniscus tissue that can be sacrificed. However, this concept can be questioned, since not only the size of the tears but also the location was proved to significantly affect the outcomes[15]. Save the meniscus has become the new imperative nowadays[16,17]. Several studies addressed this topic over many years, but the huge amount of data may create confusion in those who want to approach this surgery.

The aim of this paper is to provide a practical guide for treatment of meniscus tears, including an overview of technical aspects, outcomes in the literature and personal tips. Furthermore, the authors provide a concise premise to deal with some aspects of menisci phylogeny, anatomy and biomechanics. This can be useful for the reader to fully understand the factors affecting the fate of a meniscus tear.

PHYLOGENY AND ONTOGENY OF THE MENISCI

The knowledge of meniscus phylogeny and ontogeny can be useful to correlate meniscal gross anatomy to meniscal function.

Knee menisci are not unique to humans but can be found in several living tetrapods, including amphibians, reptiles, birds and mammals. In most of them, both menisci are massive structures fitted between the tibial and femoral surfaces and are connected anteriorly by an intermeniscal ligament. Only in mammals, regardless of the walking style or size, the menisci have the same semilunar shape[18]. The medial meniscus is very similar in all mammals, including primates. It is crescent shaped with two tibial insertions. By contrast, the lateral meniscus is more variable in shape and in the pattern of tibial insertions[19,20]. The presence of a double tibial insertion of the lateral meniscus is a particular feature of Homo sapiens, unique among living mammals. The second posterior insertion aids in preventing extreme anterior gliding of the lateral meniscus during frequent extension[21]. The presence of meniscofemoral ligaments reinforces the posterior fixation of the lateral meniscus, providing better stability. As a result, only humans are able to maintain a stable knee extension during bipedal stance. Other nonhuman primates cannot do likewise in bipedal walking, but only during quadrupedal gait. Therefore, humans' menisci are not only simple load distributers, but provide a fundamental contribution to knee stability during bipedal stance.

In humans, the meniscus is identifiable after about 8 wk[21,22], assuming its characteristic shape already at this stage. At no time the lateral meniscus takes a discoid shape. In the prenatal stage, the meniscus is highly cellular with a large nuclear/cytoplasmic ratio. Blood vessels are numerous throughout the substance of the foetal meniscus, mostly along the capsular attachment sites. The main postnatal change is the progressively decreasing vascularity and cellularity, with concomitant increase in collagen content[22].

MENISCI ANATOMY

The menisci are two fibrocartilaginous structures mainly composed of water (65%-75%), type I collagen (22%) and glycosaminoglycans (approximately 1%)[23]. The collagen bundles are combined in different orientations to oppose compressive, radial, and shear stresses. Specifically, radial bundles are more frequent in the inner part, which is more resistant to compression forces. Conversely circumferential bundles are mainly located in the outer two-thirds part of the meniscus, counteracting to radial tension forces. This may explain why radial tears typically start from the inner portion, whereas longitudinal tears are more frequent in the most peripheral zones of the meniscus[24]. Furthermore, fiber orientation affects the tensile properties of suture configurations. Vertical sutures showed a significantly higher pull-out strength than horizontal sutures[25-27]. It was assumed that vertical sutures captured more circumferential collagen fiber, thus providing higher failure strength. A third group of collagen fiber are located among the circumferential bundles and are called "tie fibers". These fibers are radially orientated, thus opposing to longitudinal splitting forces[24].

The medial meniscus has a stable fixation to the tibia due to the anterior and posterior root attachments, the meniscotibial (coronary) ligament around the entire perimeter of the meniscus and the deep medial collateral ligament. In 1998, Berlet and Fowler[28] described four distinct insertion patterns of the anterior horns of the medial meniscus. The type I insertion is the most common and seems to provide a very strong fixation to the tibia into the flat area called crista *areae intercondylaris anterior* by Jacobsen[29]. The type II insertion also provide a firm fixation, but more medially and closer to the articular surface. Type III insertion is very anterior and, even if firm, provides little resistance to anterior motion of the meniscus. The last one, type IV, has no firm fixation on the tibia, and the displacement of the anterior horn of the meniscus is controlled by coronary fibers. The superior part of the medial meniscus body is attached to the synovial tissue. In the posterior horn of the medial meniscus, the superior edge does not attach to the joint capsule, while the inferior part attaches to the tibia through the meniscotibial ligament. This ligament, together with the posterior joint capsule, forms the posteromedial femoral recess, defined as ramp area. The semimembranosus attachment to the posterior capsule seems to have a role on the pathogenesis of meniscus tears in this area. A fixation of the medial posterior horn to the capsule may potentially have an influence on the mobility of the medial meniscus, which subsequently might be responsible for poor long-term follow-up. A strictly anatomic medial meniscus repair with reconstruction only of meniscotibial attachment should be to be considered.

The lateral meniscus has a looser attachment to the tibia and joint capsule, because of the presence of the hiatus popliteus. In this zone, the popliteomeniscal fascicules connect the lateral meniscus to the popliteus tendon and the joint capsule. An injury or the absence of such fascicules in discoid meniscus variations may produce an unstable tear causing a symptomatic meniscus hypermobility[30] (Figure 1). Posteriorly, lateral meniscus root attachment is reinforced by one or two meniscofemoral ligaments. These ligaments seem to have a significant contribution in preventing lateral meniscus extrusion[31].

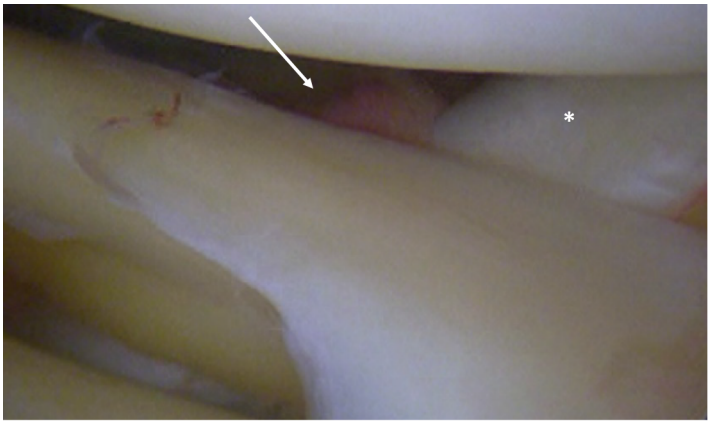
Menisci vascularization is another important factor affecting the healing process. The major vascular support to the meniscus comes from the branches of superior and inferior geniculate arteries that make a subsynovial and perimeniscal capillary network infiltrating the periphery of the meniscus. Vascular supply is limited to the peripheral 10%–25% for the lateral meniscus and 10%–30% for the medial meniscus[32], but it seems to be wider in younger individuals[33]. Vascular penetration is fairly homogeneous in the lateral meniscus, whereas there is more variation within the medial meniscus, with the medial posterior horn having a significantly smaller vascularization[33]. According to the vascular supply, three different zones can be detected within the menisci: The red-red zone (the most peripheral and vascularized zone), the red-white zone (at the inner border of the vascularized zone) and the white-white zone (the inner and avascular zone)[32]. Evidently, tears in the most vascularized zones have higher healing potential and are amenable for repair, while tears in the inner portion are frequently subject to meniscectomy.

Nerve fibers follow closely the blood vessels in their course, with the vascular outer third of the menisci being the most innervated portion[34].

BIOMECHANICS OF THE MENISCI

Menisci play a critical role in load distribution, protecting the smooth hyaline cartilage on both the distal femur and proximal tibia. The medial meniscus covers up to 50%–60% of the medial tibial plateau[35], and it is responsive of about 50% of load transmission in the medial tibiofemoral compartment[36]. The lateral compartment is less congruent, since the lateral tibial plateau has a more convex morphology when compared to the medial compartment. For that reason, the lateral meniscus has a higher contribute to ensure joint congruency, transferring up to 70% of load in its compartments[37]. Indeed, lateral meniscectomy result in worse clinical and radiological outcomes than medial meniscectomy[38].

Menisci also provide a fundamental contribute to joint stability. Specifically, the medial meniscus has been shown to be a secondary restraint to anterior translation of the tibia[39], while the lateral meniscus notably restrains tibial rotation and the pivot-shift mechanism[40]. Both medial and lateral menisci



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Figure 1 Arthroscopic view of posterosuperior popliteomeniscal fascicule injury (white arrow). The lateral meniscus is no longer properly anchored to popliteus tendon (asterisk), causing meniscus hypermobility.

translate posteriorly on the tibial plateau during deep knee flexion. The posterior translation of the lateral meniscus (8.2 ± 3.2 mm) is greater than that of the medial one (3.3 ± 1.5 mm)[41]. This asymmetry of kinematics between the medial and lateral compartment is an established characteristic of human knees, resulting in an internal rotation of the tibia relative to the femur with increasing flexion.

At last, menisci are also thought to play roles in knee joint lubrication and nutrient distribution as well as knee proprioception[42,43].

A NEW PATTERNS CLASSIFICATION FOR MENISCUS TEARS: THE GOOD, THE BAD AND THE UGLY LESIONS

An ideal classification system should be simple, all-inclusive, reliable, reproducible, and treated-oriented[44]. Actually, numerous classifications of meniscus tears have been described, but the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine classification is most widely adopted[45,46]. It is based on tear depth, pattern, length, location and rim width, as well as quality of meniscal tissue. However, some important factors are missing, including prognosis of the lesion pattern.

Taking inspiration from a famous movie directed by Leone and Tigani[44], the authors classified the meniscus tears in three categories: The good, the bad and the ugly lesions. The inclusion in each group was determined by the type of injury, its biomechanical effects on knee joint, the technical challenge, and the prognosis. The meniscus tear patterns included in each cluster and the related treatment proposed by the authors are resumed in Table 1. This classification is not intended to substitute the currently proposed classifications on meniscus tears but aims at offering a reader-friendly narrative review of an otherwise difficult topic.

The good lesions

Small stable longitudinal tears (both partial and full thickness tears), as well as small oblique/flap tears can be classified as good lesions. This is mainly due to the poor impact on knee biomechanics[10], both in terms of maximum contact pressure and tibial contact area changes. However, if the tear is more than 15 mm and involves the posterior horn of the meniscus, a significant change of knee biomechanics has been reported[47]. Moreover, longitudinal tears were found to decrease the in-situ meniscus force[48], thus potentially impacting on meniscus function. In addition to this, longitudinal tears of medial meniscus were significantly correlated with meniscus extrusion[49], especially if the tear size increases. Probably, the same traumatic force causing longitudinal meniscus tears may produce a concomitant meniscotibial ligament lesion, which has been closely related to meniscus extrusion[50]. As a result, such lesions should not be overlooked because if they become larger, the knee functionality may be irreversibly impaired.

Either partial meniscectomy or arthroscopic repair can be performed, depending on the tear location and according to the vascular zones of the meniscus. A meta-analysis comparing meniscus repair and meniscectomy found better functional scores in the first group, but meniscectomy for unstable lesions in the white-white zone offered better short-term outcomes and a lower revision surgery rate[15]. The indication for surgical repair of small stable lesions in the peripheric zone of the medial meniscus is almost mandatory, due to the high risk of secondary meniscectomy if left alone[51]. On the other hand, for the lateral meniscus with peripheric small stable lesions, “leave the meniscus alone” can be the

Table 1 The classification of meniscus lesions and the recommended treatment for each tear pattern

	Suggested treatment	Secondary treatment
Good lesions		
Stable longitudinal tears	Repair of peripheral tears	Peripheric small tears of the lateral meniscus can be left in situ because of the low risk of subsequent meniscectomy
Small flap tears	Partial meniscectomy of small lesions in the avascular zone of the meniscus	
Bad lesions		
Bucket handle tears	Repair with dedicated technique according to the lesion features	Meniscectomy of isolated medial bucket handle tears must be discussed with patients
Ramp lesions	Conservative treatment should be considered as first-line for degenerative tears	Surgical treatment of degenerative tears should be considered when conservative approach failed or in presence of mechanical symptoms
Lateral posterior root tears		
Degenerative tears (big flap tears, horizontal tears, complex tears)		
Ugly lesions		
Radial tears	Repair must be attempted aiming at preserving meniscus function	Valgus or varus osteotomy needs to be considered in case of limb malalignment
Medial posterior root tears		
Anterior root tears		

preferred approach given the low risk of subsequent meniscectomy[52].

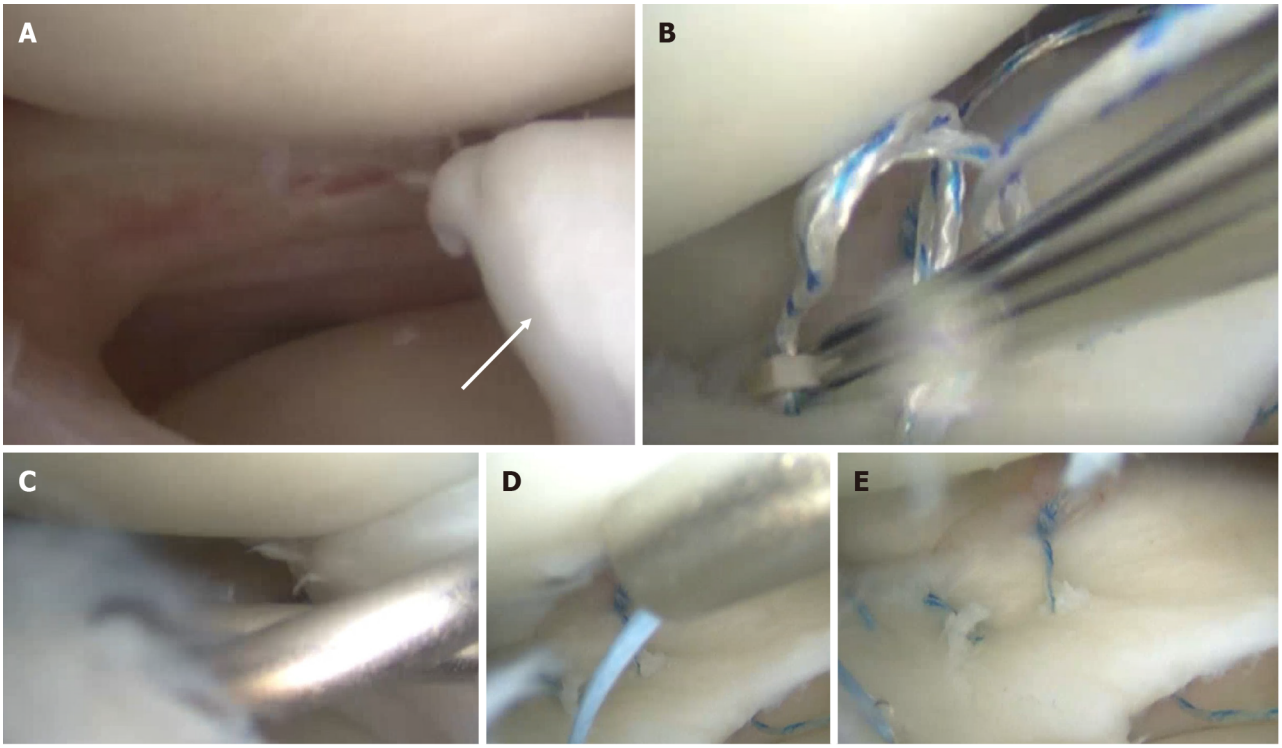
Recent systematic reviews confirmed the good healing potential, regardless of the surgical technique [53,54]. Meniscal zones and timing from trauma have been reported as predictors of meniscal repairs outcomes[55,56]. Even arthroscopic repair of the meniscus tear in the red-white zone of the meniscus showed low failure rates[57]. Biological enhancements like platelet-rich plasma and bone marrow mesenchymal stem cells were found to improve the healing process in the white-white zone in canine models[58], but these data need to be confirmed in clinical setting. Once again, location would seem to affect outcomes, since lateral meniscus repairs showed lower failure rate than medial repairs[15]. There is still controversy regarding the influence of patients' age on failure rate[59]. This is probably because cartilage status as well as activity level may play a more significant role[60].

The bad lesions

The bad lesions are defined as tears causing a significant loss of meniscus function and significantly altering knee biomechanics. However, prognosis can be good when promptly treated. Big longitudinal tears, bucket-handle tears, ramp lesions, posterior lateral root tears and complex degenerative tears can be included in this group.

Large longitudinal tears worth being counted among bad lesions for the biomechanical reasons stated above[47-49]. Arthroscopic repair of such lesions is to be attempted, since meniscectomy would result in great loss of meniscus function[14]. Bucket-handle tears are peculiar longitudinal tears with unstable fragment causing pain and mechanical symptoms. A particular variant is the ''hypermobile lateral meniscus'', that is a very peripheral longitudinal tear causing the detachment of the lateral meniscus from the capsule in the region of the popliteus tendon hiatus. Traumatic or microtraumatic rupture of the meniscopopliteal fascicles is called upon, allowing excessive meniscal mobility[30,61]. High index of suspicion is needed because diagnosis can be easily misled with the magnetic resonance imaging (MRI).

Preservation of the meniscal tissue is of utmost importance in this setting. Resection of bucket-handle tears drastically increases the mean and peak contact pressures in both medial and lateral tibiofemoral compartments, whereas arthroscopic repair of a bucket-handle tear more closely restores native tibiofemoral biomechanics[62]. However, the healing process of bucket-handle tears can be challenging because of the size and the complexity of the lesion[15]. A recent meta-analysis[63] showed that failure rate after arthroscopic bucket-handle meniscus tears repair ranges between 11.3%-18.3%, that is significantly higher than longitudinal tears. Medial tears and isolated tears are found to significantly increase the risk of failure within 2 years[63]. On the other hand, higher is the number of stitches, lower is the risk of failure[63]. Literature supports arthroscopic repair of such lesions, especially the bucket-handle tears of the lateral meniscus and during concomitant anterior cruciate ligament (ACL) reconstruction[16,17]. A combination of all suture techniques (all-inside, inside-outside and outside-inside) is desirable to improve the mechanical strength of the repair (Figure 2). The use of vertical sutures every 5 to 7 mm is preferred, because horizontal sutures are placed parallel to the meniscus collagen fibers and can easily pull out by separating such fibers. Either circumferential compression sutures[64] with dedicated devices or double-sided all-inside suture repair[65] (both in the superior and in the inferior surface of the meniscus) can produce overall compression of the tear, thus promoting



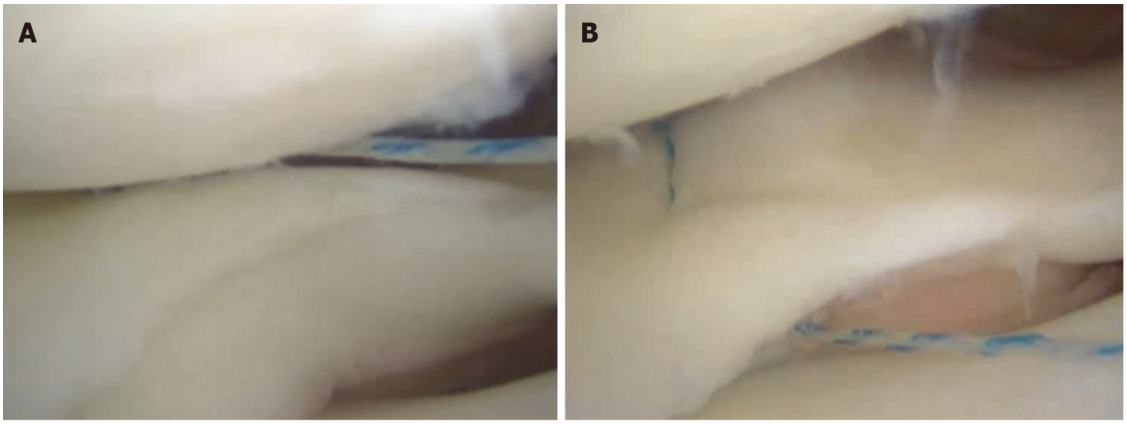
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Figure 2 Isolated lateral meniscus bucket-handle tear in an 18-year-old male patient. A: Arthroscopic findings with the unstable bucket-handle fragment (white arrow); B: Arthroscopic repair of the posterior horn using an all-inside technique; C: Repair of the anterior third using an outside-in technique; D: Repair of the meniscal body with an inside-out technique; E: Final aspect of the meniscal repair.

complete healing (Figure 3). Isolated medial meniscus bucket-handle tears pose a treatment dilemma with no easy solution[66]. The good short-term outcomes as well as the high return-to-play rates after partial meniscectomy must be balanced against the long-term degenerative consequences. Patient's age and activity level need to be taken into consideration. The decision to perform either a meniscectomy or a repair must be made in agreements with the patient, discussing risks and benefits of each option.

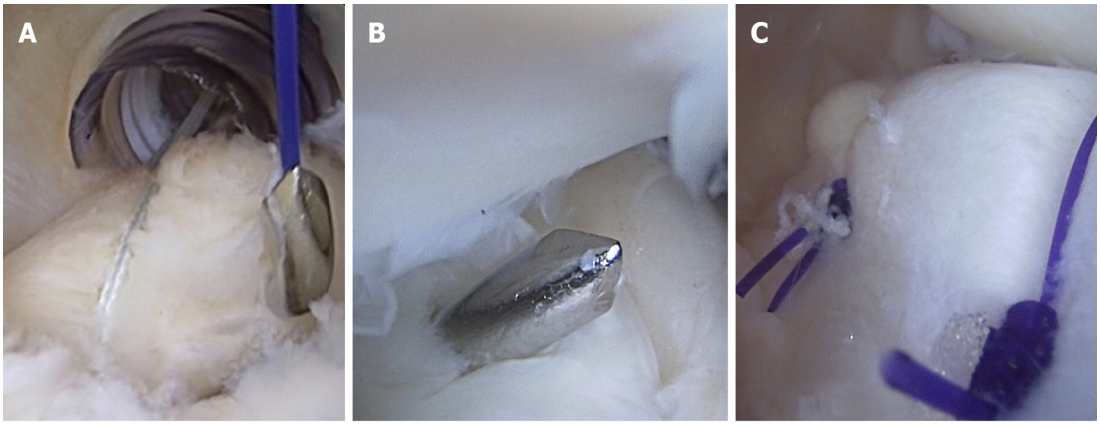
Ramp lesions represent a further variant of bad lesion. These longitudinal peripheral tears of the posterior horn of medial meniscus produce a meniscocapsular or meniscotibial disruption, increasing the anterior tibial translation, internal and external rotation, and the pivot shift in ACL-deficient knees [67]. An isolated ACL reconstruction cannot adequately restore native tibiofemoral biomechanics but requires concomitant meniscocapsular and meniscotibial repair[67]. Furthermore, it has been reported that unrepaired ramp lesions may evolve in medial bucket handle meniscus tears at long-term follow-up[68]. As a result, a proper diagnosis and treatment of such lesion is fundamental. However, this type of injury can be often missed, both during MRI reading and due to its "blind" point of arthroscopic vision. It is crucial to perform a systematic exploration of the posteromedial compartment of the knee using a specific trans-notch approach. As these lesions occur in a well-vascularized zone of the meniscus, small (less than 10 mm) and stable tears may be amenable to trephination alone[69]. For unstable tears, arthroscopic repair is recommended. Reported failure rates range between 2.6% and 12.0%[70]. Several surgical techniques have been proposed, including inside-outside technique[71], all-inside[72] technique with standard devices introduced from the anterior portals, and all-inside technique using a suture hook[73] introduced from a posteromedial portal (Figure 4). The type of suture would seem associated with failure of the ramp lesion repair, with a significantly higher risk with the all-inside device than with suture hook repair sutures[74]. A hybrid repair is recommended in large lesions involving the most medial part of the ramp area in order to enhance structural stability[75]. Even the suture material has been called into question, and an absorbable monofilament suture is advocated for such repair to reduce the risk of failure[70].

Lateral meniscus posterior root tear (LMPRT) is a further bad lesion typically occurring in ACL-deficient knees. Such lesions create altered load distribution and transmission functions[76], also contributing to increase anterior tibial subluxation of the lateral compartment[77]. Compared with the medial ones, LMPRTs occur in younger male patients with lower body mass index, less cartilage degeneration and less extrusion on MRI. The better functional outcomes after LMPRTs repair than medial root repair suggest that differences in injury and patient characteristics may contribute to differences in these results[78,79]. Repair of LMPRT can be performed with a side-to-side reconstruction or a trans-tibial pull-out technique, according to the type of the lesion. If the repair occurs during



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Figure 3 All-inside repair of a longitudinal meniscus tear. A: Superior suture placement creates a non-uniform compression of the tear; B: A second suture placed in the inferior portion of the meniscus rebalance the repair compression forces, thus correcting the superior meniscus displacement secondary to the first suture.

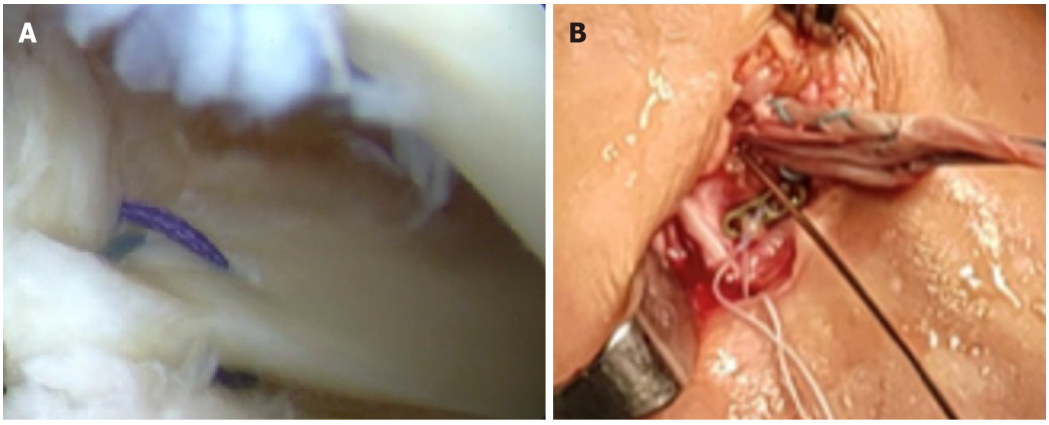


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Figure 4 Ramp lesion repair from the posteromedial portal using a suture hook. A: The suture is passed through the posteromedial capsule and the posterior meniscotibial ligament; B: The hook is advanced until reaching the posterior portion of the medial meniscus; C: A sliding-knot is used to secure the repair (view from the posteromedial portal).

concomitant ACL reconstruction, the risk of convergence of the posterior root tunnel and the tibial ACL tunnel is high. Some authors recommend drilling the meniscal root tunnel from the anterolateral tibia [80]. Other authors suggest using the ACL tunnel to fix the meniscus suture[31] (Figure 5). A personalized technique using a suture anchor[81] was previously described, in order to eliminate this risk in selected cases.

The list of the bad lesions is completed with complex tears, that are a combination of different degenerative tear patterns including oblique tears, big flaps and horizontal cleavage of the meniscus. These lesions are counted among this group because they can be indicators of early-stages osteoarthritis. Knee malalignment, obesity and functional overloading may be responsive for degenerative meniscal matrix changes, thus leading to meniscal fatigue, loss of function and extrusion. Such lesions in their turn further undermine knee joint, by increasing peak compressive and shear stress of both cartilages and menisci[82]. Degenerative tears of the medial meniscus seem to have a greater impact on knee biomechanics, by inducing larger stress and extrusion than the lateral meniscal tears[82]. There is a consensus in the literature promoting conservative treatment as the first-line approach for such lesions [83,84]. This should include activity modification, intra-articular injections, physical therapy with specific rehabilitation, gait analysis and supportive orthoses[85-87]. Surgical treatment is recommended only in case of pain no longer responsive to medical therapy or in presence of mechanical symptoms, such as clicking or briefly locking knees. Surgical indication must be confirmed with radiographic and MRI investigation, to rule out signs of advanced osteoarthritis, meniscal extrusion, extensive cartilage damage or bone marrow lesions, which may negatively impact on arthroscopy outcomes. Due to the degenerative nature of the lesion and the poor biological potential of healing, arthroscopic partial meniscectomy has been recommended as the main surgical option. Partial meniscectomy should be limited to the unstable fragments but preserving as much healthy meniscal tissue as possible. A



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Figure 5 Arthroscopic repair of the lateral meniscus posterior root repair. A: Arthroscopic view of the repair; B: The suture is passed in the same anterior cruciate ligament tibial tunnel and knotted on a dedicated plate.

complete resection of such tears would subsequently result in a subtotal meniscectomy, further accelerating the joint degenerative process[82]. This also applies in case of degenerative horizontal tears. In a biomechanical study on 10 cadaveric knees, both single leaflet and double leaflet resection was found to significantly reduce contact area and increase contact pressure in the knee[88]. Only a suture repair of such horizontal cleavage tears returns the contact area and contact pressure to nearly normal [88]. As a result, the repair of such lesions is recommended using a vertical mattress stitch configuration following minimum edge resection, if the quality of the meniscal tissue is adequate[89]. Biological augmentation has been proposed in the literature to enhance healing potential of such degenerative lesions[90,91], but further studies with higher methodologic quality are needed to confirm this option.

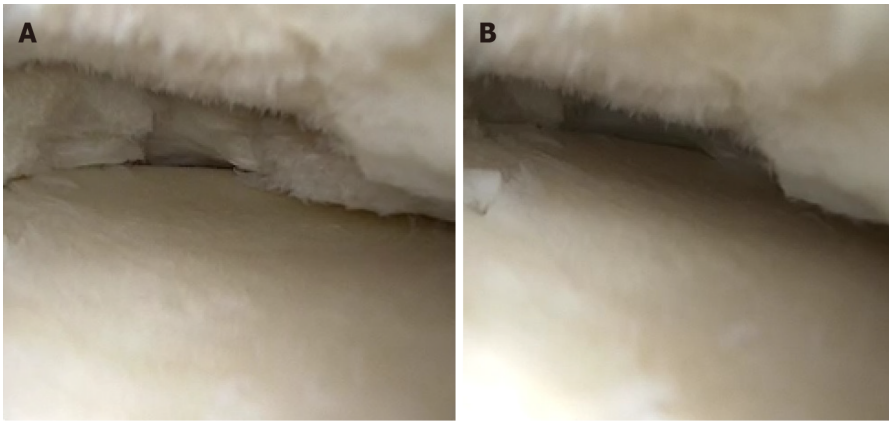
The ugly lesions

The ugly lesions represent the worst scenario for knees, since this group include meniscus tears with the poorest prognosis. All meniscus injuries causing a damage of the meniscus ring are considered ugly lesions, because the interruption of this structure means a complete loss of meniscal function.

Radial tears represent the first type of ugly lesions, because create unfavourable knee dynamic contact mechanics that are not significantly different from those resulting from meniscectomy[11,76] (Figure 6 and Video 1). Such lesions seem to have a lower potential for healing than longitudinal tears [92]. Despite this, the focus on preservation of meniscal tissue has become increasingly imperative even in this context. This has led to the emergence of several arthroscopic repair techniques. Inside-outside or outside-inside horizontal repairs have been considered for long time as the gold standard. However, a recent systematic review demonstrated that a combination of all-inside horizontal or crossed stitches reinforced with suture parallel to the tear as ripstop (defined as hashtag or crosstag technique, respectively) may improve the repair strength[93]. Radial meniscus tear repairs can be further strengthen by creating a transtibial tunnel augmentation[93]. Even a suture anchor can be used to reinforce the radial meniscus repair (Figure 7), but biomechanical data are needed to confirm the validity of this technique.

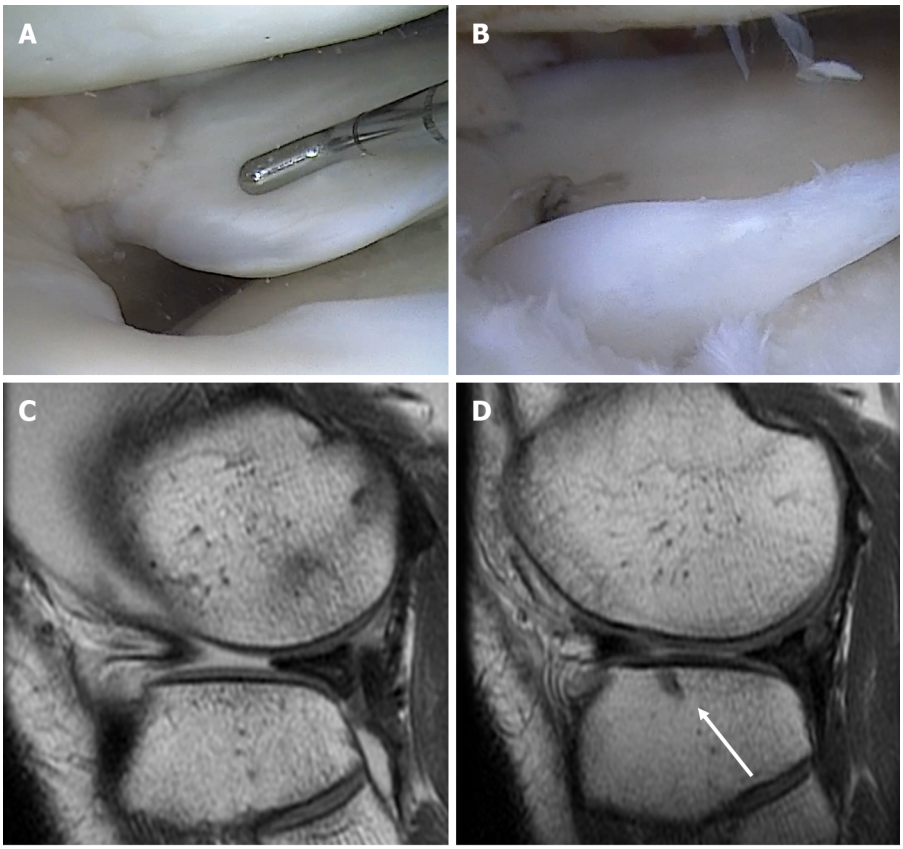
Medial meniscus posterior root tears (MMPRTs) represent a further variant of ugly lesions. This is because creates an interruption of the meniscus ring with subsequent effects on knee kinematics, load transmission and stability[94-96]. In addition, this injury can be responsive of meniscus extrusion[94] (Figure 8), thus leading to a complete meniscus loss of function. Differently to LMRTs, the medial tears are typically associated with high-grade chondral lesions and severe varus knee alignment, which are well-recognized risk factors for poor outcomes[78,97]. According to the current literature, MMPRT repairs result in favourable clinical improvements, but meniscus extrusion seems not to be significantly reduced[98]. Furthermore, the progression of joint degeneration seems to not be completely prevented [98]. The arthroscopic meniscus centralization associated with MMPRT repair has been proposed (Figure 9), resulting in good short terms outcomes and significant reduction of extrusion distance[99]. However, the beneficial long-term effects have yet to be demonstrated. In such circumstances, surgeons' efforts should not only focus on the meniscus tear, but also on limb alignment. A concomitant valgus osteotomy needs to be considered in cases of severe varus knees. This has been demonstrated to improve meniscus healing process, although clinical and radiological outcomes seem not to significantly differ from isolated valgus osteotomies[100].

Medial and lateral anterior root tears need a separate mention. Injuries to the anterior root of the menisci are less common and frequently iatrogenic, such as during arthroscopic portals creation, ACL tibial tunnel reaming or tibial nailing for traumatic fractures[96]. In the authors' experience, medial anterior root tear can be associated with medial bucket-handle tear (Figure 10). As a result, the biomech-



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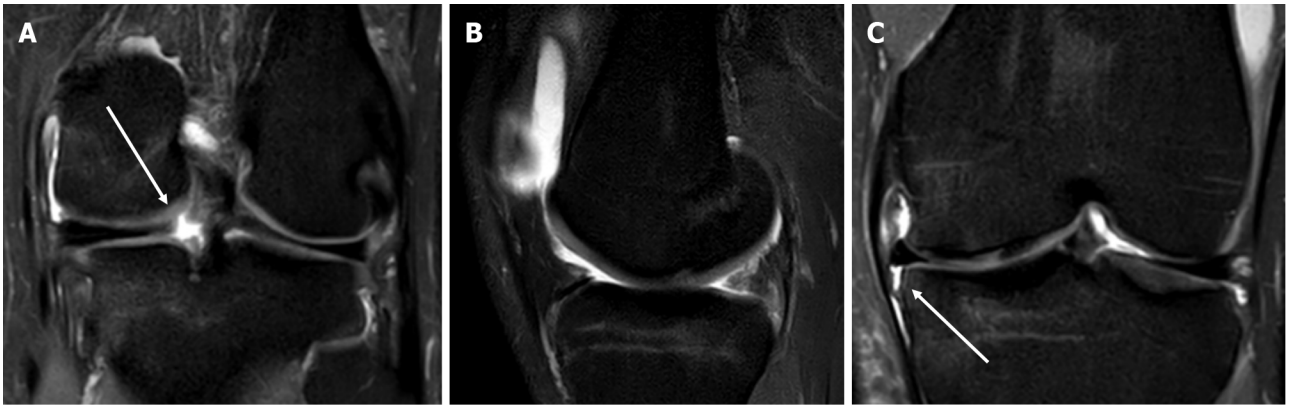
Figure 6 Arthroscopic view of a radial tear of the medial meniscus. A: Medial meniscus in no-weightbearing condition; B: After applying a compression force, the medial meniscus is totally extruded, thus losing is protective function in the knee joint.



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Figure 7 Radial tear of the lateral meniscus. A: Arthroscopic visualization of the radial tear of the lateral meniscus; B: Tear repair using an all-suture anchor; C: Preoperative T1 sagittal magnetic resonance imaging (MRI) view, showing the extrusion of the anterior portion of the lateral meniscus; D: Six-month follow-up T1 sagittal MRI view, showing the relocation of the anterior portion and the all-suture anchor used for the repair (white arrow).

anical effect of such lesions remains unclear. Although most of the reported literature refers to posterior meniscal root tears, it would stand to reason that anterior root tears will have the same fate if not anatomically repaired. Repair of such lesions can be extremely challenging. Anatomical tibial tunnel positioning or the use of suture anchor can be needed. The creation of accessory portals and the use of dedicated devices can make the procedure easier.



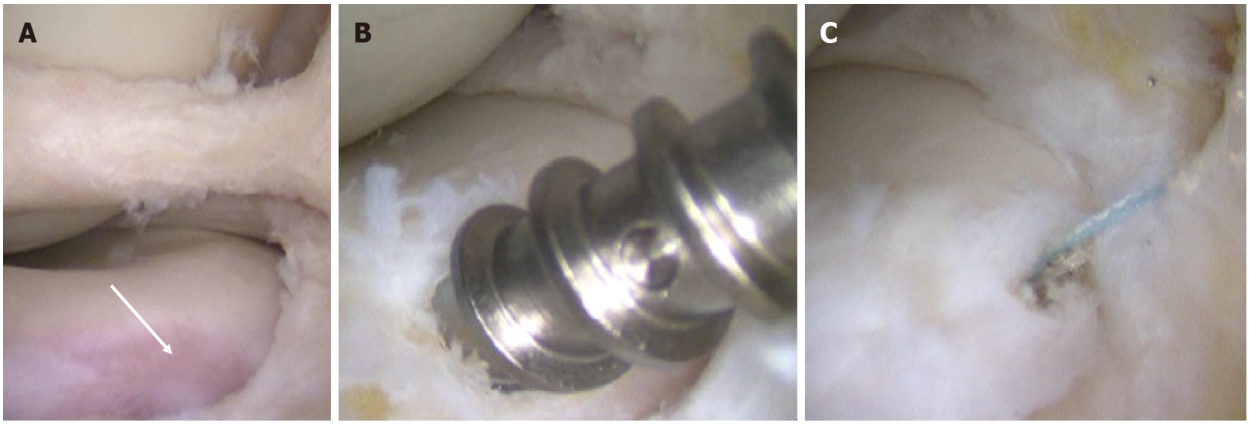
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Figure 8 Isolated posterior root tear of the medial meniscus. A: T2 Fat-Sat coronal magnetic resonance imaging (MRI) view, showing disruption of the meniscus ring (white arrow); B: T2 Fat-Sat sagittal MRI view, with the "ghost sign", highly suggestive for posterior root tear; C: T2 Fat-Sat coronal MRI view, showing detachment of the medial meniscotibial ligament (white arrow) and meniscus extrusion.



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Figure 9 Arthroscopic view of medial meniscus centralization with two all-suture anchors.



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Figure 10 Anterior root detachment of the medial meniscus, with concomitant bucket handle tear. A: Arthroscopic finding with the tibial avulsion site (white arrow); B: Repair of the lesion using a 3.5 metallic suture anchor; C: Final view of the repair.

CONCLUSION

This review aims at representing a practical and updated guide for treatment of meniscus tears. Several factors should be considered when approaching meniscus surgery. Biomechanical aspects, technical challenges and long-term outcomes need to be considered before deciding the most appropriate

therapeutic approach. Further biomechanical studies as well as rigorous clinical research with high methodologic quality are welcome to improve the current knowledge on this fascinating but challenging topic.

FOOTNOTES

Author contributions: Simonetta R and Russo A were involved in study design and images collection; Palco M and Costa GG were involved in manuscript writing and literature research; Mariani PP was involved in language editing and final revision.

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MINIREVIEWS

Effects of different pelvic osteotomies on acetabular morphology in developmental dysplasia of hip in children

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Abstract

Developmental dysplasia of hip seriously affects the health of children, and pelvic osteotomy is an important part of surgical treatment. Improving the shape of the acetabulum, preventing or delaying the progression of osteoarthritis is the ultimate goal of pelvic osteotomies. Re-directional osteotomies, reshaping osteotomies and salvage osteotomies are the three most common types of pelvic osteotomy. The influence of different pelvic osteotomy on acetabular morphology is different, and the acetabular morphology after osteotomy is closely related to the prognosis of the patients. But there lacks comparison of acetabular morphology between different pelvic osteotomies, on the basis of retrospective analysis and measurable imaging indicators, this study predicted the acetabular shape after developmental dysplasia of the hip pelvic osteotomy in order to help clinicians make reasonable and correct decisions and improve the planning and performance of pelvic osteotomy.

Key Words: Developmental dysplasia of the hip; Pelvic osteotomy; Acetabular morphology; Re-directional osteotomies; Reshaping osteotomies; Salvage osteotomies

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Core Tip: Developmental dysplasia of hip seriously affects the health of children, and pelvic osteotomy is an important part of surgical treatment. Improving the shape of the acetabulum, preventing or delaying the progression of osteoarthritis is the ultimate goal of pelvic osteotomies. This manuscript reviewed influences of different pelvic osteotomy on acetabular morphology and the acetabular morphology after osteotomy. Accurate prediction of acetabular shape after pelvic osteotomies can help clinicians to make reasonable and correct decisions and improve the planning and performance of pelvic osteotomies.

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INTRODUCTION

Developmental dysplasia of the hip (DDH) leads to loss of the normal anatomical relationship between the femoral head and acetabulum due to developmental defects of the acetabulum, resulting in abnormal morphology and position of the hip joint[1-3]. DDH is the most common hip deformity in children. The global incidence rate is 1‰–2‰. Surgical correction is still the most challenging problem for pediatric orthopedic surgeons[4,5]. Delayed diagnosis of DDH means that more complex and higher failure rates of treatment are needed, so early diagnosis and treatment are important[6]. The main goal of DDH treatment is to achieve and maintain concentric reduction of the femoral head and acetabulum, to ensure the normal development of the hip joint, and to avoid osteonecrosis of the femoral head and reoperation[7,8]. Surgical treatment of DDH is usually determined according to the age, imaging examination and clinical symptoms of the child. In patients with progressive acetabular dysplasia, pelvic osteotomyis necessary to minimize the risk of hip dislocation in adults[9]. Common surgical procedures for DDH patients include pelvic osteotomy, open reduction, capsular arthroplasty and femoral osteotomy[10]. To restore the anatomical morphology and mechanical structure of the pelvis and ensure normal development and life of children, pelvic osteotomy is almost inevitable[11,12]. Morphology of the acetabulum after pelvic osteotomy is closely related to prognosis of DDH. Many researchers have proposed their own methods of pelvic osteotomy that have their own characteristics, indications and clinical effects. There are three common types of pelvic osteotomy: Redirectional, reshaping and salvage[11]. On the basis of retrospective analysis and measurable imaging indicators, this study predicted the acetabular shape after DDH pelvic osteotomy in order to help clinicians make reasonable and correct decisions and improve the planning and performance of pelvic osteotomy.

NORMAL ACETABULAR MORPHOLOGY IN CHILDREN

The hip joint consists of a round head of the femur and a cup-shaped acetabulum, which forms a unique ball and fossa shape that helps stabilize the joint and allows a dynamic range of rotational motion[13]. The normal acetabular structure consists of the upper ilium, the anterior pubic bone and the posterior ischial bone. In early infants, the acetabulum consists of a cartilage complex composed of Y-type and acetabular cartilage. The acetabular cartilage is located at the outer two thirds of the acetabular fossa, and the Y-type cartilage is located at the junction of the pubic bone, ischium and ilium[14,15]. With the growth and development of infants, the ossification center in acetabular cartilage appears and develops successively; the pubic ossification center develops and forms the anterior wall of the acetabulum; the ossification center of the ischium develops and forms the posterior wall of the acetabulum; and the ossification center of the ilium develops and forms the superior wall of the acetabulum. The cartilage complex of the normal acetabulum fuses at the age of 12–16 years, completely forming the fossa of the joint, and covering the entire femoral head. The stress direction determines whether the growing hip joint tends to concentric growth, and determines the morphology and structure of the acetabulum under stress[16]. The acetabular cup usually faces downward, lateral and anterior, opposite to the upper, medial and lateral direction of the femoral head, forming a stable spherical joint structure of the hip joint[17]. Acetabular cartilage is interrupted in the center of the acetabular fossa and is also known as lunate cartilage because it is similar to a crescent shape. Lunate cartilage is located on the lateral and superior articular surface of the acetabulum, which is thicker and stronger than femoral head cartilage [18]. The glenoid labrum is a fibrocartilage structure that surrounds the outer edge of the bony structure of the acetabulum, which functionally deepens the acetabular cup and improves the stability of the hip joint[19,20].

ACETABULAR MORPHOLOGY DURING DDH

Morphological changes of the acetabulum and proximal femur during DDH includes acetabular cartilage degeneration, acetabular fossa shallower, acetabular roof tilted, acetabulum lost its normal and nearly round shape[21,22]. Subluxation or dislocation of the hip is characterized by widening of teardrops, loss of lateral depression of the acetabulum, elongation of the posterior upper edge of the acetabulum, increase of the ratio of long diameter to short diameter of the acetabulum, and loss of normal concentric circle relationship between the proximal femur and the acetabulum[5,23]. Due to the reduction of the contact area between the acetabulum and femoral head, the load of the acetabulum increases, and the structure of the acetabulum propagates laterally under stress, resulting in excessive anteversion of the femoral neck and varying degrees of hip varus[24,25]. The structural changes of the hip joint also cause compensatory changes in the pelvis and spine, leading to a variety of clinical symptoms. It was believed that dislocation of the hip joint during DDH was caused by insufficient depth and excessive tilt of the acetabulum, which could not accommodate the femoral head. However, recent studies have shown that the development between the acetabulum and femoral head follows the Wolff rule[26]. Accordingly, the arrangement of bone trabeculae is affected by the dynamic distribution of bone load, and the mechanical pressure on the bone is conducive to stimulating bone development. When the acetabulum loses the centripetal pressure from the femoral head, the structural development of the acetabulum is affected, and the depth, width and inclination of the acetabulum become abnormal, and even acetabular cartilage degenerates. With the development of DDH, the anatomical morphology of the acetabulum is completely lost and the hip joint is totally dislocated. In the case of total dislocation of the hip, the normal acetabulum loses the pressure from the femoral head, resulting in hypertrophy of the articular pelvis, and the hypertrophic pelvis adheres to the joint capsule and ligaments, which further affects the reduction of the femoral head.

EVALUATION OF ACETABULAR MORPHOLOGY BY COMPUTED TOMOGRAPHY

Computed tomography (CT) is a widely used method for evaluation of the hip joint. Because acetabular dysplasia is not just a simple malrotation or anterolateral defect, three-dimensional (3D) CT imaging can help doctors to determine the exact shape of the acetabulum[27]. Because of the simplicity and speed of obtaining images, CT has become an important method for the diagnosis of hip joint structural changes, preoperative evaluation and postoperative re-examination[25]. The traditional 3D reconstruction of CT can observe the acetabular morphology of DDH in many directions, accurately measuring the acetabulum, and carrying out further quantitative analysis, so as to better evaluate the pathological changes of DDH and morphology of the acetabulum after osteotomy. Some parameters that cannot be measured by conventional X-ray films can be measured by3D CT, such as bony acetabular index and anteversion. Therefore, CT and 3D reconstruction scanning have important guiding significance for clinicians. The bone reconstruction model of 3D CT provides an omnidirectional and multiangle observation index for clinicians to observe the pathological changes of the hip joint and the curative effect of surgery, and has value for guiding surgical planning and prediction of postoperative acetabular shape[28]. Li *et al*[29] used computer-aided design for quantitative dynamic analysis of hip joint morphology, and found that it was a better guide for surgical planning and evaluation of treatment results. Some clinical studies have found that the value and safety of using 3D CT to guide pelvic osteotomy is higher than that of ordinary CT[30]. In addition, 3D CT can also be combined with finite element analysis method to carry out biomechanical analysis of acetabular morphology after DDH, which has important guiding significance for the evaluation of surgical efficacy and improvement of surgical methods of DDH[31].

EVALUATION OF ACETABULAR MORPHOLOGY BY X-RAY FILM

X-ray film can dynamically observe the changes of bone structure during child growth and development, which is the most basic imaging method to evaluate the structural changes of the hip joint, and is important for guiding screening and evaluation of acetabular morphology[32-34]. The following are the main parameters in the evaluation of acetabular morphology by X-ray film[35,36]: Degree of acetabular anteversion, central edge angle (CEA), Acetabular index (AI), sharp angle, angle of iliac wall, and acetabular coverage. The normal acetabulum is usually tilted forward, and it is of clinical importance when the angle is increased by > 7° compared with normal[24]. CEA is an important index to describe the shape of the acetabulum[37,38]. It is normal when the CEA is > 25°, but abnormal when it is < 20°, suggesting that the acetabulum is incomplete. When CEA is between 20° and 25°, it is necessary to closely follow up and observe its changing trends. AI is an objective measurement index of acetabular dysplasia, which can be used to judge the severity and therapeutic effect of DDH. The normal range of AI before age 2 years is 20°–25°, and AI > 30° after 2 years is considered abnormal[38, 39]. The sharp angle reflects the development of the acetabulum and coverage of the hip joint on the

femoral head. It is used to diagnose and predict the progress of hip dislocation. The normal value is 33°–38°. Dynamic observation is needed when the value is 42°–47°, and abnormality can be diagnosed when it is > 47°[40]. The angle of the iliac wall is the angle between the line from the anterior inferior iliac spine to the outer upper edge of the acetabulum and the Y-shaped cartilage line on both sides of the acetabulum. The normal value of the infant is about 55°. The iliac wall angle increases slowly with infant age, and there is little difference between the normal value and the outlier range, so it is necessary to compare the two sides on the X-ray film[41]. The acetabular coverage rate[42] reflects accommodation of the acetabulum to the femoral head. It is the ratio of the distance from the inner edge of the femoral head to the vertical line of the upper edge of the acetabulum to the diameter of the femoral head, and the normal value is > 75%. X-ray film is a simple, fast and economic examination method, which can quickly diagnose DDH from a large number of pelvic films, effectively reduce the misdiagnosis rate and evaluating the shape of the pelvis and acetabulum after surgery.

PELVIC OSTEOTOMYAND ACETABULAR MORPHOLOGY

The ability of acetabular remodeling has an age limit, and previous studies have shown that the acetabulum can be remodeled under the age of 5 years[43]. Acetabular dysplasia over a certain age needs to be corrected by pelvic osteotomy. Different methods of pelvic osteotomy depend on the age of DDH patients and the degree of deformity[44,45]. Normal development of the acetabulum depends on the femoral head under the concentric circle position, but DDH changes the biomechanical structure of the hip joint, which limits the morphological development of the acetabulum in children, so the purpose of the operation is to restore the concentric reduction of the hip joint[46]. Pelvic osteotomy can improve deformity of the acetabulum, increase the stress area of the hip joint, restore the coverage of acetabular cartilage, and reconstruct the biomechanical relationship of the hip joint[47]. When acetabular dysplasia is associated with subluxation or dislocation, pelvic osteotomy is necessary to minimize the risk of hip dislocation in adults[11]. The older the onset of DDH, the worse the prognosis. It is generally believed that osteotomy has a lot of complications in patients aged > 8 years[48]. The effects of different pelvic osteotomy on acetabular morphology are different, which provides a basis for different patients to formulate specific osteotomy methods[49]. The current imaging technology has been able to measure the relevant indicators of acetabular morphology, but the operations process of different patients can't be total the same, so it is difficult to measure acetabular morphology accurately by different osteotomies. Previous researchers used the lateral CEA to assess acetabular developmental defects, but Daniel *et al*[50] found that acetabular deficiency in borderline hip dysplasia can be underestimated by lateral CEA alone. Some researchers used 3D printing technology to measure the relevant indexes of acetabular morphology after different osteotomies. The real proportional anatomical model can accurately measure the AI before and after surgery, and it provides conditions for optimizing the surgical plan and improving the method. Researchers had described many types of pelvic osteotomy. Different pelvic osteotomies have different advantages and indications, and the shape of the acetabulum after osteotomy is also different. There are three common types of pelvic osteotomy: Redirectional, reshaping and salvage[11]. We will describe the effects of the different types of pelvic osteotomy on the morphology of the acetabulum.

REDIRECTIONAL OSTEOTOMY

Redirectional osteotomy of the pelvis changes the direction of the acetabulum, increases the contact area between the acetabulum and the femoral head, and increases the area of hyaline cartilage in the weight-bearing area of the acetabulum. It is characterized by repositioning the acetabulum to improve the anterolateral acetabular cover without changing the size and shape of the hip, which is an incomplete osteotomy[51]. The common redirectional osteotomies include Salter, periacetabular and triple pelvic osteotomy.

Salter osteotomy

Salter osteotomy is a classic method of pelvic osteotomy, which belongs to the osteotomies that change the direction of the acetabulum. It was first proposed by Salter in 1961[52]. The osteotomy line of Salter is from the anterior inferior iliac spine to the great ischial notch, and the entire acetabulum is turned forward and outward with the pubic symphysis as the fulcrum. It changes the overall orientation of the acetabulum to increase the inclusiveness of the acetabulum to the femoral head, and the shape and volume of the acetabulum remain unchanged[3]. Therefore, Salter osteotomy is suitable for the following[52,53]: (1) Children aged 18 mo to 6 years with unossified pubic symphysis; (2) anterolateral acetabular defect as the main defect; and (3) AI is basically normal. Salter osteotomy requires internal fixation support, so the wedge-shaped bone removed from the ilium is placed into the fracture line and fixed with Kirschner wire to increase stability of the acetabulum after osteotomy. In the Salter

procedure, the rotation angle and distance of the distal iliac bone are not only the difficulties of the operation, but also the key to its effectiveness. Previous studies have shown that Salter osteotomy changes the acetabular center with the movement of the distal bone mass, and the AI decreases yearly. At 3–4 years after the operation, the AI is stable to about 15°, the CEA increases yearly, and returns to the normal range for about 5 years, and the postoperative obturator area is significantly reduced[54].

Periacetabular osteotomy

Periacetabular osteotomy, also known as GANZ osteotomy, is suitable for patients with hip pain and when the femoral head is located in the center of the acetabulum, and the degree of hip deformity and arthritis is low. It was first proposed by Ganz in 1983[55]. The periacetabular osteotomy procedure is mainly to amputate the pubic bone, ischium and ilium, and under the condition of maintaining the continuity of the pelvis, rotate the acetabulum to make the acetabulum cover the femoral head to the best extent[56]. Because periacetabular osteotomy does not destroy the acetabular blood supply and the pelvic ring, it can improve the biomechanical relationship between the acetabulum and femoral head, reduce the probability of postoperative acetabular necrosis, and avoid the occurrence of hip arthritis [45]. Andrew *et al*[57] found that among athletes with symptomatic hip dysplasia who received periacetabular osteotomy, all acetabular parameters were improved, and the return to exercise rate of competitive athletes was > 70%. Periacetabular osteotomy allows the acetabulum to be relocated in multiple directions to correct the deficiency of the anterior coverage of the femoral head, so even severe acetabular deformities can be satisfactorily corrected by accurate rotation and internal displacement of the acetabular center. Because periacetabular osteotomy maintains the integrity of the posterior column of the acetabulum, better initial stability is obtained[55,58]. Through long-term follow-up, researchers have found that in the patients treated with periacetabular osteotomy, the fracture healed well, the lateral coverage of the femoral head, AI angle and Sharp angle were significantly improved, the cartilage area of the acetabular weight-bearing area was increased, and the gait and hip joint function were significantly improved.

Triple pelvic osteotomy

Triple pelvic osteotomy, which includes osteotomy of the ilium, pubis and ischium around the acetabulum, is a complete redirected osteotomy, which solves the problems of limited movement of bone mass and lateralization of the hip joint after osteotomy[59,60]. This complete redirected osteotomy increases the range of motion of the acetabulum by cutting off the pubic bone, ischium and ilium, so that the rotated acetabulum can completely contain the femoral head and achieve concentric reduction of the hip joint. At present, there are three common triple pelvic osteotomy procedures, which are LeCoeur, Steel and Tonis[61]. By amputating the ilium and the superior and inferior branches of the pubis near the symphysis pubis, the LeCoeur procedure limits the rotation of the acetabulum because the position of the amputated pubis and ischium is far from the acetabulum[11].Steel osteotomy cuts the ischial bone at the ischial tubercle through the posterior approach, and the pubic bone and ilium through the anterior approach. Because the osteotomy is close to the acetabulum, the range of acetabular adjustment is better than that of LeCoeur. The position of the Tonnis osteotomy is closer to the acetabulum than the Steel osteotomy is, so the acetabular rotation is greater[62]. Like other redirected osteotomies, triple pelvic osteotomy is a rotational osteotomy that does not change the size and shape of the acetabulum [63]. The premise of this operation is that the structure of the hip joint is intact, which is mainly suitable for older children with more severe acetabular dysplasia, and it is an unstable osteotomy that requires solid internal and external fixation[59,64]. Triple pelvic osteotomy can improve the CEA, lateral coverage of the femoral head, and stress distribution of acetabular cartilage, and can effectively correct acetabular deformities.

RESHAPING OSTEOTOMIES

Compared with pelvic redirectional osteotomies, pelvic reshaping osteotomies are incomplete, which increases the coverage of the acetabulum and femoral head by bending acetabular vertices[65]. Therefore, this kind of operation is also called acetabuloplasty. Because it is an incomplete osteotomy, the position of the bone mass after operation is stable and usually does not require internal fixation. There are three common methods of reshaping osteotomies, namely, Pemberton, Dega and SanDiego. Researchers[49] compared the effects of these three osteotomies on acetabular morphology using 3D-printed models, and found that Pemberton and Dega increased the upper and anterior coverage of the acetabulum, resulting in retroversion of the acetabulum, while SanDiego increased the posterior coverage of the acetabulum, resulting in acetabular anteversion.

Pembertonpelvic osteotomy

Pemberton pelvic osteotomy is a periarticular osteotomy, also known as Pemberton acetabuloplasty, which was first proposed by Pemberton in 1968[66,67]. Pemberton pelvic osteotomy has a wide range of adaptation, and can be used in children under 12 years old, but because it affects development of the

pelvis and pubic symphysis, caution is needed in children under 6 years old. Pemberton pelvic osteotomy takes the Y-type cartilage around the acetabulum as the rotation fulcrum and controls the shape of the acetabulum by adjusting the position of the bone cortex on the posterior side of the ilium. It increases the coverage of the anterior edge of the acetabulum, and significantly increases the coverage of the outer upper edge and posterior edge of the acetabulum[68]. Pemberton pelvic osteotomy can adjust acetabular direction, correct acetabular deformity and increase acetabular depth according to the degree of acetabular defect. Therefore, it can reduce AI, increase the coverage of acetabulum and femoral head, stabilize the hip joint, and reduce deformity of the acetabulum[69,70]. Because the Pemberton procedure can reduce AI, it is suitable for cases where the acetabulum needs to be corrected by > 15° and the acetabulum is shallow and steep.

Degapelvic osteotomy

Dega osteotomy is one of the commonly used osteotomies in the treatment of DDH. It was first proposed and applied in clinic Dega in 1958[71,72]. The Dega procedure is a type of acetabuloplasty to change the shape and inclination of the acetabulum, mainly to increase the lateral coverage of the acetabulum, which can change the volume of the acetabulum without damaging the Y-type cartilage [73]. Dega operation uses the iliac bone of incomplete osteotomy above the Y-type cartilage as a hinge to change the direction and inclination of the acetabulum. Its advantage is that the position of iliac osteotomy can be adjusted according to the location of the acetabular defect, so that acetabular defects in different parts can be corrected[74]. A retrospective analysis[75] showed that AI decreased significantly in patients who underwent Dega acetabuloplasty, and postoperative Sharp angle was also improved, which can improve AI and inclusiveness of the femoral head.

San Diego pelvic osteotomy

SanDiego osteotomy is a modified Dega osteotomy to improve lateral and posterior acetabular coverage [11,76]. The SanDiego operation is an incomplete osteotomy. The medial iliac bone cortex is intact except for the anterior and posterior sides, and the ischial and pubic corticesare also continuous[51]. In iliac osteotomy, the wedge-shaped bone can be used to stretch the osteotomy surface, so this kind of monocortical osteotomy enables doctors to change the shape of the acetabulum by changing the size and position of the bone graft, thus solving the problem of insufficient acetabular coverage[76]. Because San Diego osteotomy mainly increases coverage of the acetabulum, the shape of the acetabulum tilts forward after osteotomy, the volume of the acetabulum decreases, and the depth of the acetabulum increases.

SALVAGE PELVIC OSTEOTOMIES

If DDH is untreated or inadequately treated, it aggravates the deformity of the hip joint, which eventually develops into a nonfunctional joint with pain symptoms[77]. At that time, the change in the bony structure of the hip joint is more serious, the shaping ability of the bone decreases, the shape of the femoral head and acetabulum are difficult to reduce by simple methods, and in severe cases, cartilage injury of the hip joint occurs[78]. At that time, surgeons should pay attention to recovery of hip joint function and perform salvage surgery, so as to delay the progress of arthritis and reduce the probability of osteonecrosis of the femoral head. The common salvage pelvic osteotomies are Chiari and Shelf.

Chiari pelvic osteotomy

Chiari osteotomy, also known as intrapelvic osteotomy, was first proposed and applied by Chiari *et al* [79] in 1974. Chiari osteotomy changes the weight-bearing line of the hip joint and increases the weight-bearing area by moving the position of iliac osteotomy. It is a type of joint capsule plasty, which belongs to single-plane osteotomy[80]. Therefore, Chiari operation is suitable for older children with abnormal acetabular–femoral head index, non concentric reduction of the femoral head, acetabular deformity and lack of plastic potential[81,82]. The Chiari procedure cuts the ilium from front to back from the area between the acetabulum and the anterior inferior iliac spine along the ischial notch, and then the bone mass of the distal end of the ilium is moved inward and upward. In this process, it is necessary to ensure the coverage of the acetabulum to the femoral head and avoid the impact between the femoral head and ilium[51,78].The coverage of the acetabulum depends on the width of the ilium. In order to achieve satisfactory coverage of the lateral acetabulum, it is usually necessary to move the distal bone completely inward to the width of the ilium. If there is insufficient containment of the anterior side of the femoral head, iliac alar osteotomy can be performed, then coverage on the anterior side of the femoral head was improved. The Chiari procedure distributes the weight-bearing area of the acetabulum by expanding the inclusion of the acetabulum to the femoral head, but the damaged acetabular cartilage and glenoid labrum may still be located in the weight-bearing area after salvage surgery. Therefore, although this operation can better restore the acetabular–femoral head index, it cannot solve the defect in front of the acetabulum, and shortens the transverse diameter of the pelvis, resulting in unsatisfactory surgical results[83].

Table 1 Summation of previous studies with their case number and conclusions

Ref.	Pelvic osteotomies	Number of cases/hip	Conclusion
Sawamura *et al* [52]	Salter osteotomy	42/50	Showed favorable outcomes with satisfactory at skeletal maturity
Scott *et al*[53]		58/78	Improve acetabular morphology, reduced the incidence of advanced osteoarthritis and the probability of THA
Tan *et al*[55]	PAO	?/225	Lead to good deformity correction for both acetabular retroversion and hip dysplasia
Ali *et al*[56]		314/?	All acetabular parameters were observed to be improved
Dornacher *et al* [63]	TPO	176/206	Acetabular parameters recovered well, intraoperative fluoroscopy increased the accuracy of the operation
Lyu *et al*[64]		43/48	Improve parameters of the acetabulum, makes the complex operation safer and more effective
Bhatti *et al*[67]	PPO	60/82	The hips with Pemberton's acetabuloplasty exhibited better acetabular coverage and progressive development of hips as compared to Salter's osteotomy
Czubak *et al* [71]	Dega osteotomy	45/52	It is a safe and adequate operation to restore the acetabulum to normal or close to normal
Badrinath *et al* [76]	San Diego osteotomy	?/45	It is a safe and effective alternative to treat acetabular dysplasia in patients with typical DDH and can solve specific acetabular defects
Ito *et al*[82]	Chiari pelvic osteotomy	31/32	Improve acetabular index, relieve pain and reduce hip replacement rate
Dammerer *et al* [81]		12/12	Improve the acetabular coverage of the hip joint and suitable for some specific older children
Yoo *et al*[84]	Shelf pelvic osteotomy	14/14	Improve the depth and coverage of acetabulum and can stimulate the growth of acetabulum
Benad *et al*[85]		56/61	Relieve pain symptoms, improve joint function and delay THA in patients

PAO: Periacetabular osteotomy; TPO: Triple pelvic osteotomy; PPO: Pemberton pelvic osteotomy; THA: Total hip arthroplasty; DDH: Developmental dysplasia of the hip.

Shelf pelvic osteotomy

Shelf osteotomy, also known as acetabular extension, is mainly suitable for older children with femoral head and acetabular mismatch and hip dislocation. The anterior, posterior and lateral weight-bearing surface of the acetabulum is enlarged by osteotomy of the ilium and bone grafting at the fracture line, so the acetabular coverage of the femoral head is increased[11]. Shelf operation is a salvage operation, which is suitable for older children who have failed nonoperative treatment of DDH[84]. Shelf acetabuloplasty has a favorable, stimulatory effect on acetabular growth[85]. The operation does not change the direction or biomechanical structure of the acetabulum, but increases the volume, so it can improve stability of the hip joint. After Shelf osteotomy, the central marginal angle of the hip joint increases, the coverage of the acetabulum to the femoral head increases, and the acetabular shaping is improved[86].

CONCLUSION

Pelvic osteotomy is an important method for surgical treatment of DDH. There are three common types of pelvic osteotomy: redirectional, reshaping and salvage. The choice of pelvic osteotomy depends on the patient's age, acetabular development and disease severity. No operation is the best, and no operation is suitable for all cases. It is particularly important for pediatric orthopedic surgeons to choose the osteotomy with which they are most familiar and which is most suitable for patients. Different methods of pelvic osteotomy have different effects on acetabular morphology, and the acetabular morphology is closely related to prognosis (Table 1). It is still one of the most challenging problems for pediatric orthopedic surgeons to master the principles of various pelvic osteotomies and to understand the morphological changes in the acetabulum after pelvic osteotomy. At present, the evaluation of acetabular morphology after pelvic osteotomy mainly depends on ordinary X-ray or 3D CT reconstruction, but the measurement of acetabular morphology is not accurate because of the non-replicability of different patients and the individual differences of observers. In the future, the acetabular morphology of different pelvic osteotomy methods will be measured by 3D printing, and the morphological changes in the acetabulum before and after surgery will be accurately measured by real proportional anatomical models, so as to provide a basis for optimizing the surgical plan and improving the osteotomy method.

FOOTNOTES

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MINIREVIEWS

Background, techniques, applications, current trends, and future directions of minimally invasive endoscopic spine surgery: A review of literature

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Abstract

Across many of the surgical specialties, the use of minimally invasive techniques that utilize indirect visualization has been increasingly replacing traditional techniques which utilize direct visualization. Arthroscopic surgery of the appendicular skeleton has evolved dramatically and become an integral part of musculoskeletal surgery over the last several decades, allowing surgeons to achieve similar or better outcomes, while reducing cost and recovery time. However, to date, the axial skeleton, with its close proximity to critical neural and vascular structures, has not adopted endoscopic techniques at as rapid of a rate. Over the past decade, increased patient demand for less invasive spine surgery combined with surgeon desire to meet these demands has driven significant evolution and innovation in endoscopic spine surgery. In addition, there has been an enormous advancement in technologies that assist in navigation and automation that help surgeons circumvent limitations of direct visualization inherent to less invasive techniques. There are currently a multitude of endoscopic techniques and approaches that can be utilized in the treatment of spine disorders, many of which are evolving rapidly. Here we present a review of the field of endoscopic spine surgery, including the background, techniques, applications, current trends, and future directions, to help providers gain a better understanding of this growing modality in spine surgery.

Key Words: Endoscopic; Spine Surgery; Applications; Minimally invasive surgery; Endoscopy; Spine

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Core Tip: Endoscopy is a rapidly evolving minimally invasive technique in the field of spine surgery. This review aims to summarize the history, current techniques, and discuss the benefits, limitations, and future directions of this minimally invasive technique.

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INTRODUCTION

Minimally invasive surgery (MIS) with integration of endoscopic techniques has continued to expand its application across various surgical specialties due to its applications of smaller surgical corridors and cannulas[1]. Modern endoscopic approaches allow surgeons to reduce incision size, decrease blood loss, and report less postoperative pain, however, a significant learning curve associated with its adoption does exist[2-6]. Currently, most endoscopic procedures are performed within either an existing 3-dimensional (3D) cavity or the enlargement of a potential space, including endoscopy of the gastrointestinal tract, nasal sinuses, cerebral ventricles, and thoraco-abdominal compartments. However, spinal endoscopy involves a different approach as surgical manipulation within confined spaces is performed. Endoscopic spine surgery has been developed as a MIS technique for decompression in patients with lumbar disc herniation and lumbar stenosis, as decompression by lumbar spinal fusion is the gold standard treatment for a variety of lumbar degenerative diseases[7,8]. Reports as early as 2008 describe the first use of endoscopic technology in fusion surgeries, specifically for transforaminal lumbar interbody fusion (TLIF) procedures[9], as previous approaches reported limitations. The first TLIF approach was described as an open technique in 1998 by Harms *et al*[10]. This was a unilateral approach to the disc space through the ipsilateral facet joint, enabling the placement of an interbody spacer to achieve indirect decompression of impinged nerve roots[11]. With technical refinements and the development of a tubular retractor, the first MIS TLIF was performed and reported as a combination of less tissue disruption and shorter recovery time resulting in reduced postoperative pain, improved clinical outcomes, and lower costs[9-12]. However, recent research has identified potential limitations in the use of MIS TLIF procedures, as it has been suggested that the retraction of muscles during surgery may lead to muscle degeneration and long-term weakness.[8]. Although, MIS endoscopy in spine is a novel technique that may distinguish itself from other approaches, it is still in its nascency and several limitations are important to recognize such as: the steep learning curve when transitioning from traditional open surgery to endoscopic techniques[13], limited field of view and lack of resolution, thus making identification of anatomic structures difficult[1,14], and disorientation due to indirect visualization, resulting in the surgeon being unable to accommodate orientation and perspective[1]. It has been proposed that the implementation of advanced optical systems and the refinement of surgical instruments could effectively mitigate the aforementioned challenges[15]. As endoscopic spine surgery becomes increasingly prevalent, it is critical to understand the applications, progression and continued safety and efficacy of endoscopy in minimally invasive spine surgery. This review addresses previous and current techniques of endoscopic applications in MIS, specifically TLIF procedures, and discusses benefits, limitations, and future perspectives.

History of endoscopic spine surgery

The use of endoscopes in spine surgery dates back to the early 20th century, when they were first utilized for diagnostic purposes (Table 1). In 1931, Burman used arthroscopic tools to perform "myeloscopies" in cadavers which allowed direct visualization of the spinal cord and nerve roots[16]. In 1936, Stern developed a tool called the "spinascope", which was used by Pool in 1938 to visualize nerve roots of the cauda equina and their accompanying blood vessels in patients using an incision "not over 2.5 mm"[17,18]. The breakthrough of fiber optic technology revolutionized the field of endoscopy during the 1970s. Prior to the 1970s, endoscopes were limited by their ability to transmit light and image quality was poor. The use of fiber optic cables in endoscopes allowed for the transmission of bright, high-quality images and enabled surgeons to visualize the inside of the body in greater detail. It also made it possible to design smaller and more flexible endoscopes, which made it easier for surgeons to access and maneuver within small and confined spaces in the body, such as the spinal canal. The foundation for endoscopic spine surgery was formed by the evolution of a needle–based technique called percutaneous endoscopic discectomy in the 1970s. In 1973, Kambin demonstrated a technique for percutaneous nonvisualized indirect spinal canal decompression—percutaneous nucleotomy-through a posterolateral approach using a Craig cannula[19]. Two years later, Hijikata ran an independent study

Table 1 Chronological timeline showing the technical and procedural advancements of endoscopic spine surgery

Decades	Events
1930's	1931: Burman's "myeloscopies" in cadavers, successfully visualized the spinal cord and the nerve roots
	1936: Stern's development of new instrumentation, termed "spinascope"
	1938: Pool's myeloscopies through incisions "not over 2.5 mm", visualized the nerve roots in great detail
1940's-1950's	Technological advancements in optical lens systems and the development of fiber-optics
1960's	1963: Smith's injection of chymopapain intradiscally called "chemonucleolysis", led to "intradiscal decompression"
1970's	1973: Kambin's and Gellmann's feasibility study of mechanical nuclear debulking by inserting Craig cannula *via* posterolateral approach
	1975: Hijikata preformed first percutaneous nucleotomy (posterolateral approach, < 2.6 mm)
	1977-1978: Gazi and Caspar introduced microsurgical techniques
1980's	1982: Harms and Rolinger introduced transforaminal lumbar interbody fusions
	1983: Forst's and Hausman's introduction of arthroscopy into intervertebral disc space
	1986: Kambin further developed percutaneous discectomy
	1988: Kambin;s first endoscopy view of herniated nucleus pulposus
	1989: Schreiber, Suezawa, and Leu were the first preformed percutaneous nucleotomy under visual control and endoscope (discoscopy)
1990's	1990: Kambin created, "Kambin Triangle", a percutaneous technique
	1990: Spine surgeons started doing minimally invasive spine surgery by magnification loupe or under microscope
	1991: Kambin and Sampson developed cannula (10 mm-23 mm) for interlaminar and transforaminal endoscopy
	1996: (Foraminoscopy) Matthew's preformed a more lateral mass route and prefomed foraminal epidural endoscopic surgery
	1997: Yeung had designed YESS endoscope and developed technique of "inside out" technique
	1998: (Foraminoascopy) Ditsworth's preformed endoscopic transforaminal procedure
	1998: Harms described the first TLIF approach as an open technique
	1998: Destandau and Foley developed tubular retractor system and endoscopy aided spine surgery through interlaminar approach
2000's	2003: Hoogland introduced the outside- in technique using transforaminal approach
	2005-2006: Rutten and Choi extended indications and developed interlaminar endoscopic discectomy
2010's	2013: Choi presented work flow to avoid risk of exiting root injury, a step forward in endoscopic spinal surgery

TLIF: Transforaminal lumbar interbody fusion.

which demonstrated the same technique using a 2.6-mm cannula[20]. The evolution of this technique was characterzied by the addition of the endoscope.

During the 1980's, advancements in technology and techniques became more prominent as the introduction of TLIF was introduced by Harms and Rolinger, which was a lateral approach to the disc space, and reduced the amount of thecal sac and nerve root retraction[21]. Furthermore, this technique afforded a less invasive alternative to traditional posterior lumbar interbody fusion. That following year, Forst and Hausman were the first to introduce the endoscope into the intervertebral disc space [22]. Over time, Kambin published the first endoscopic view of the nucleus pulposus in 1988 and it was followed by Schreiber and Suezawa in 1989, who were the first to perform a percutaneous nucleotomy using endoscopy[23-25]. In the 1990's, advancements were made in spine endoscopy techniques and technology based on two different approaches, the extraforaminal and interlaminar approaches. A deeper understanding of the "Kambin Triangle" allowed for the expansion of endoscopic spine surgery beyond the limits of percutaneous nucleotomy. Kambin's triangle provided a pathway for the use of larger instruments and channels near foraminal pathology without risking injury to the exiting nerve [19-26]. The concept of a safe zone between the exiting and traversing nerve roots in the foramen allowed endoscopic spine surgery to extend into the foramen. In 1993, Mayer and Brock introduced the use of an angled lens scope to improve visualization of annular pathology[26]. In the mid 1990's, the introduction of multichannel endoscopes with larger working channels were then introduced by Tsou *et al*[27] and were later developed and studied in the years to come.

Furthermore, the YESS endoscope was first designed for the "inside-out" technique by Yeung in 1997, and foraminoscopy was first developed which was described by Mathews in 1996 and Ditsworth in 1998 [29-31]. In the same year, Harms *et al*[10] described the first TLIF approach as an open technique, which

was a unilateral approach to the disc space through the ipsilateral facet joint, enabling the placement of an interbody spacer to achieve indirect decompression of impinged nerve roots. During that same year, Kambin and Zhou[31] described workflows for decompressing the lumbar nerve root through anulectomy and relieving lateral recess stenosis. After the turn of the new millennium, further developments and techniques in endoscopic spine surgery were further refined and unveiled. Hoogland introduced the "outside-in" technique using a transforaminal approach in 2003[32]. Two years later, Schubert and Hoogland then described a method for transforaminal endoscopic removal of a sequestered disc fragment using reamers which enlarged the foraminal window by removing the ventral portion of the superior articular process[33]. In 2007, Ruetten *et al*[34] facilitated the direct endoscopic decompression of foraminal pathology, based on the introduction of multichannel endoscopes with larger working channels by Tsou *et al*[27] in 1997 and several clinical studies including those by Yeung and Tsou in 2002.

More recently, studies have further examined techniques and workflow to avoid risk of exiting root injuries. In 2013, Choi *et al*[36] reported a workflow to avoid such injury such as, measuring the distance from the exiting root to the facet at the lower disc level based on preoperative magnetic resonance imaging scans. Alternative surgical methods, such as microdiscectomy or conventional open discectomy, should be considered if the distance is too small. With current advancements in technology and refinement in techniques, risk of injury and potential barriers are underway of being well studied and understood.

Techniques in endoscopic spine surgery

There are various endoscopic techniques that can be used to treat spine disorders. These techniques involve using a camera to indirectly view the surgical area (Figure 1), with the camera being inserted into the body through a channel called a working channel (Figures 1 and 2). The size and number of working channels are used to classify different types of spinal endoscopy. The capabilities and benefits of these techniques depend on the size and number of working channels, with a trade-off between having larger or more channels, which can allow for the use of multiple instruments but may cause more tissue disruption, and having smaller or fewer channels, which may cause less tissue disruption but limit the use of multiple instruments. The three most common techniques are full endoscopy, microendoscopy, and biportal endoscopy (Table 2). Full endoscopy involves the use of a single working channel, which holds the endoscope and one surgical instrument in the same tubular device (Figure 2). The working channel only allows for the use of one instrument at a time, so the operator must change the instrument if they want to use a different one. The small size of the working channel means that the camera and the instrument must be moved together, with some modifications allowing for limited independent movement of the instrument's distal end. To create space around the surgical area during full endoscopy, an aqueous environment is typically used to separate tissues. One advantage of this technique is that it causes less collateral tissue damage compared to other techniques. However, the single working channel limits the ability to use multiple instruments concurrently and independently control the camera and instrument movements, which can be limiting during spine procedures. In order to retract tissue during surgery, some full endoscopy techniques use beveled working channels that allow the surgeon to use the working channel as a retractor. The size of the working channel can also limit the ability to implant devices.

Microendoscopy involves the use of a single, larger working channel that allows for the concurrent use of multiple instruments and independent control of the endoscope. In this category of techniques, a rigid endoscope (microendoscope) is attached to a tubular retractor that includes tissue dilators to reduce the need for muscle retraction. The most common system in this category is the METRx tube assembly. This increased flexibility allows the surgeon to use multiple instruments simultaneously and have both hands free. The larger working channel size also allows for the use of a wider range of tools and the implantation of devices such as interbody cages and bone graft. The main disadvantage of microendoscopy is that it may cause more tissue disruption due to the larger portal size, though the clinical impact of this is not well understood. Another disadvantage is that it is currently performed in a dry environment, without the use of an aqueous field to aid in tissue separation and visualization.

Biportal endoscopy involves the use of two working channels: one for the endoscope and one for instruments. This approach is similar to arthroscopy techniques used in other arthroscopic procedures and allows for independent control of the scope and instruments, as well as greater freedom of instrument positioning. Biportal endoscopy may be more familiar to surgeons who have experience with other peripheral joint arthroscopy techniques, as many of the principles are similar. Like full endoscopy, biportal procedures use an aqueous environment to create a space around the surgical site. The main disadvantages of biportal endoscopy are the need for multiple access portals, which can cause more tissue disruption, and the limited ability to implant devices. Additionally, the lack of a contained joint space and the need to exchange and co-locate instruments through multiple portals can make the procedure technically more challenging.

Surgical approaches in endoscopic spine surgery

There are two primary approaches most commonly used for endoscopic spine surgery: The postero-lateral (or interlaminar) approach and the extraforaminal (or transforaminal) approach. The

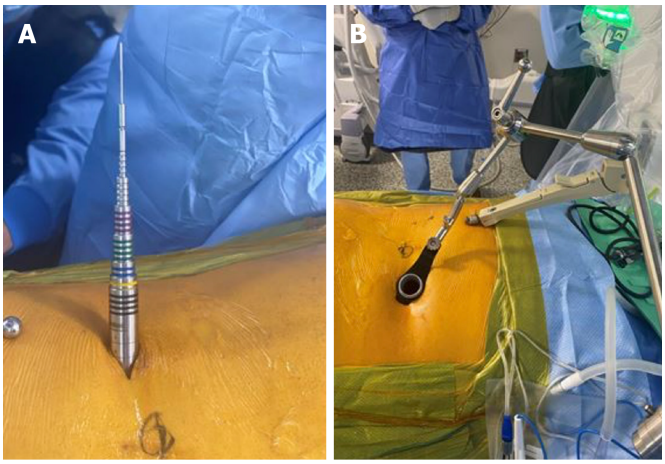
Table 2 Pros and cons of full endoscopy, microendoscopy, and biportal endoscopy

Technique	Pros	Cons
Full endoscopy	Least amount of tissue damage out of the three	Cannot move camera and tool independently
Microendoscopy	Space for more tools, space for implanting devices	Large portal size
		Dry environment only
Biportal endoscopy	Independence of tools	Most tissue damage out of the three
		Locating tools more
	Familiarly with other arthroscopic techniques	Challenging



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Figure 1 Direct endoscopic view from tubular/retractor-based camera that provides a two-dimensional image on a screen with digital zoom.



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Figure 2 Minimally invasive surgery endoscopic technique. A: Endoscopic cannula inserted in posterior lumbar region; B: Tubular/retractor-based setup where the camera can be inserted into the body through a channel called a working channel.

interlaminar approach involves making a paramedian incision to access the lamina and interlaminar space, allowing the surgeon to directly reach the spinal structures within the central canal and lateral recesses. This technique is similar to open microscopic lumbar/thoracic decompression, which is familiar to many spine surgeons. The decompression process in this technique is also similar to that of open microscopic decompression. This approach is suitable for a wide range of spinal disorders, as many of these conditions involve neural compression in the central and/or lateral recess zones. The transforaminal approach is a posterior-lateral percutaneous approach to the disc or epidural space through the foraminal window that aims to preserve normal musculoskeletal structures. The transfo-

raminal approach involves making a far lateral incision for cannula set up to allow instruments to access the transforaminal and lateral foraminal zones in an area known as Kambin's triangle (Figure 2). This approach provides direct access to the foramen and is often used for isolated, unilateral foraminal conditions or neural compression in the lateral recess or central canal due to ventral disc pathology (Figure 3). One key benefit of this approach is that it can provide direct access to the area of concern without requiring a large skin incision, extensive muscle retraction, unnecessary bone removal, or general anesthesia. However, the transforaminal approach has the disadvantage of being limited in its ability to address many types of lateral recess or central stenosis caused by dorsal pathology.

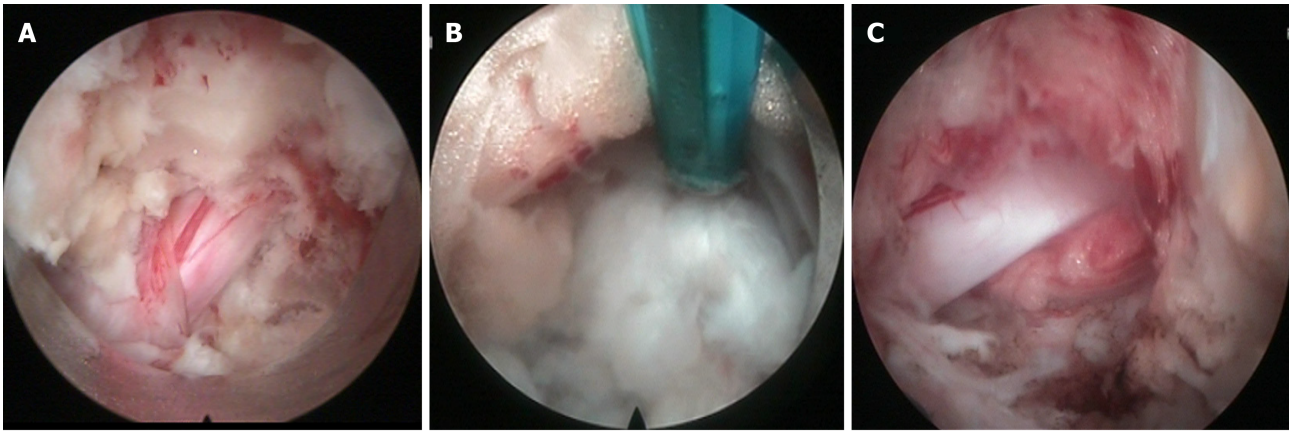
Uptick in studies on endoscopic spine surgery

In the last few years, investigation into endoscopic spine surgical techniques has erupted with over 250 related publications on the technique in 2020 compared to less than 50 in 2012[37]. The evolution of different techniques within endoscopic spine surgery such as full endoscopy, microendoscopy, and biportal endoscopy has contributed to this tremendous growth, with recent publications exploring efficacy in numerous procedures through the cervical, thoracic, and lumbar spines. Lumbar disc herniation is one of the most common spinal pathologies and numerous randomized controlled trials (RCTs) have shown similar patient pain scores and functional outcomes with microdiscectomy, the gold standard procedure, and endoscopic surgery for lumbar disc herniation[38-40]. A prominent, early clinical trial, by Ruetten *et al*[41] demonstrated similar pain and disability ratings between 178 patients randomly assigned to either endoscopic discectomy or microdiscectomy for lumbar disc herniation. Endoscopic approaches for TLIF have not been extensively studied because endoscopic techniques generally lessen collateral tissue damage and minimize the need for fusion. Moreover, the size of interbody cages used in fusions are usually too large for the endoscopic access channel, thus more expandable cages are being developed for use[37]. Kim *et al*[42] Examined 87 patients who underwent biportal endoscopic TLIF or MIS TLIF and found significantly lower visual analog scale (VAS) scores in the endoscopic group at two months but no differences in fusion or pain scores at later time points. Furthermore, a case series by Kamson *et al*[43] *d*emonstrated significant improvement in VAS scores and patient satisfaction in 85 patients who were elected for an endoscopic TLIF. Due to the lack of RCTs (likely due to prior lack of expandable interbody cages), more research is needed to deem endoscopic techniques effective for TLIF procedures. Endoscopic surgery has also been examined in the context of several other common spinal pathologies and procedures including lumbar spinal stenosis, posterior cervical discectomy and foraminotomy, and spondylolisthesis[44-46]. Many of these studies have found endoscopic techniques to be equivalent to open surgery and other MIS techniques with inconsistent benefits of shorter operative times and hospital length of stay[43,45,46].

Current trends in usage

Although literature examining endoscopic spine surgery has increased globally, the technique is still much more commonly utilized in Asia and Europe compared to the United States[47,50]. A recent study evaluating geographical usage trends in endoscopic spine surgery found that 70.3% of Asian surgeons and 55.2% of non-Asian surgeons utilized endoscopic techniques (P = 0.015). Additionally, Asian surgeons used endoscopic decompression techniques which required extensive training twice as much as non-Asian surgeons[50]. The basis of the significant difference in volume of endoscopic procedures between Asia and the United States/Europe is multifaceted. In a recent minireview, Yoon and Wang supported the statement above and discussed the reasons for the low usage rate of endoscopic spine surgery in the United States: (1) A lack of United States billing codes for endoscopic spine surgery; (2) Poor surgeon reimbursement for endoscopic procedures; (3) A lack of profit/interest for medical device companies; and (4) Philosophical differences in goals for spine surgery[47]. In the United States, it is clear financial motivation from surgeons and medical device companies is towards fusion procedures and not endoscopic techniques[37,47]. Because endoscopic procedures minimize the need for fusion, medical device companies will get less revenue (due to less plates, interbody cages, and screws sold to hospitals), and surgeons will be compensated less making United States adoption extremely challenging.

Another reason for less usage of endoscopic techniques for spinal surgery in the United States is due to a limited number of training and educational programs on the topic. In the United States, there are no formal training programs/fellowships with endoscopic techniques for spinal surgeons[47]. There are occasional cadaver workshops for interested surgeons in the United States, however Kim *et al*[48] found that these workshops simply introduce the instrumentation and basic technique. The workshops do not offer practical guidelines such as diagnostic workup, surgical indications, and specific procedural steps for management of different spinal pathologies with the endoscopic technique. Due to the training/educational behaviors and steep learning curve related to endoscopic techniques in spine surgery, even highly motivated surgeons in the United States face several challenges when attempting to familiarize and implement endoscopic spine techniques into their repertoire. Overall, financial, educational, and training barriers contribute to the limited utilization of endoscopic spine techniques in the United States.



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Figure 3 Direct two-dimensional endoscopic view (top of image as anatomically medial, bottom as lateral, left as cranial, and right as caudal) with dura mater exposed. A: Disc has compressed nerve ventrally; B: Disc irrigated, exposed, and removed to alleviate nerve compression; and C: Nerve has been decompressed.

LIMITATIONS

Although the development of enhanced lighting and visualization techniques are critical to the progression and safety of endoscopic approaches in spine surgery, particularly minimally invasive spine surgery, there are barriers to adoption that do exist. Firstly, most surgeons will experience a steep learning curve when transitioning from traditional open surgery to endoscopic techniques[13]. Secondly, the limited field of view and lack of resolution makes identification of anatomic structures difficult to view. Lastly, disorientation from indirect visualization may result in the surgeon being unable to accommodate orientation and perspective[1]. The transition from traditional open surgery to minimally invasive endoscopic surgery is associated with a steep learning curve. The air-tight and tubular approach requires surgeon manipulation and attention shift from the surgical field to indirect use of two-dimensional monitor viewing, in addition to careful hand–eye coordination[13]. Furthermore, Hirano *et al*[14] described the endoscopic surgical approach to be the opposite of open posterior lumbar decompressions, as microsurgery is done from the outside in, whereas posterior lumbar decompressions are done from the inside out. However, further development of endoscopic instruments may help improve the safety of endoscopic TLIF and reduce the learning curve[4]. In addition, it has been reported that novel surgeons may obtain hands-on training with cadaver simulation when adopting endoscopic surgery for practice[13,50-52].

Aside from the steep learning curve, another common challenge of MIS endoscopic technique is the limited field of view and lack of resolution, therefore making identification of anatomic structures difficult. As anatomical landmarks are absent, there is the possiblity of inadequate exposure during surgery with insufficient decompression, inaccurate placement of cages, and an increased risk of pedicle screw malpositioning[14]. Furthermore, multiple fluoroscopies are required to ensure accurate pedicle screw placement, which may increase the radiation exposure to patients and medical staff[9,14]. Basil *et al*[1] reported anatomical disorientation is due to the optical angle of the endoscopic generally being between 0° to 30° depending on the spinal level at which the endoscope is used. Thus, endoscopes with larger optical angles can lead to greater surgical disorientation because the human eye is accustomed to a 0° optical angle when viewing the world[1,53]. s As the next stages of developments in surgical optical systems occur visualization will improve, helpingmitigate such challenges.

CONCLUSION

Like many other surgical subspecialties in recent years, spine surgery has migrated towards minimally invasive techniques, allowing surgeons to achieve the same goals as they do with open surgery, but with decreased collateral tissue damage and better patient outcomes[13]. Many studies have illustrated adequate functional restoration and decompression of the spine with surgeons utilizing endoscopic techniques[42-47]. Regarding surgical results, the current literature suggests endoscopic techniques are in line with other MIS techniques but not clearly superior. Therefore, more long-term, RCTs comparing endoscopic techniques with other MIS spine techniques are needed to demonstrate additional benefits in the usage of endoscopic techniques. If these studies demonstrate superiority with endoscopic techniques compared to other MIS techniques, then the barriers for adoption of endoscopic techniques in the United States such as medical device company financial motivations and lack of training centers

for endoscopic spine surgery may be overcome. Medical device companies in the United States make a large portion of their money in spine surgery from selling hospitals interbody cages, pedicle screws, and rods used during fusion procedures. Historically, endoscopic spine surgery has achieved decompression while minimizing the need for fusion, thus creating an impediment for adoption in the United States. However, recent technological advancements such as biportal endoscopic surgery and expandable interbody cages have popularized endoscopic TLIF procedures. This may be an avenue to allow medical device companies to profit from selling their instrumentation while enabling better patient outcomes with endoscopic techniques. In summary, due to the migration towards minimally invasive techniques, and the ongoing focus on patient-centered care in spine surgery, it is likely endoscopic techniques will integrate even further into the United States and offer an additional MIS technique for patients and surgeons.

FOOTNOTES

Author contributions: Tang K, Goldman S, and Avrumova F did the designed the collection and assembly of data; all authors interpreted the data, writing and approved the final manuscript.

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ORIGINAL ARTICLE

Basic Study

Bridge plating in the setting of radiocarpal instability: Does distal fixation to the second or third metacarpal matter? A cadaveric study

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Abstract

BACKGROUND

Radiocarpal dislocations are rare but potentially devastating injuries. Poorer outcomes are associated with inadequate or lost reduction, such as ulnar translocation, but no consensus exists on the ideal fixation technique. Dorsal bridge plate fixation has been described for various settings in the treatment of complex distal radius fractures and can be fixed distally to the second or third metacarpal, but its application for radiocarpal dislocations has not been established.

AIM

To determine whether distal fixation to the second or third metacarpal matters.

METHODS
Using a cadaveric radiocarpal dislocation model, the effect of distal fixation was studied in two stages: (1) A pilot study that investigated the effect of distal fixation alone; and (2) a more refined study that investigated the effect of described techniques for distal and proximal fixation. Radiographs were measured in various parameters to determine the quality of the reduction achieved.

RESULTS
The pilot study found that focusing on distal fixation alone without changing proximal fixation results in ulnar translocation and volar subluxation when fixing distally to the second metacarpal compared with the third. The second iteration demonstrated that anatomic alignment in coronal and sagittal planes could be achieved with each technique.

CONCLUSION
In a cadaveric radiocarpal dislocation model, anatomic alignment can be maintained with bridge plate fixation to the second metacarpal or the third metacarpal if the described technique is followed. When considering dorsal bridge plate fixation for radiocarpal dislocations, the surgeon is encouraged to understand the nuances of different fixation techniques and how implant design features may influence proximal placement.

Key Words: Wrist; Instability; Bridge plate; Dorsal spanning plate; Radiocarpal dislocation model; Cadaveric study

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Core Tip: Radiocarpal dislocations are rare but potentially devastating injuries. Poorer outcomes are associated with inadequate or lost reduction, such as ulnar translocation, but no consensus exists on the ideal fixation technique. Dorsal bridge plate fixation has been described for various settings in the treatment of complex distal radius fractures and can be fixed distally to the second or third metacarpal, but its application for radiocarpal dislocations has not been established. In a cadaveric radiocarpal dislocation model, anatomic alignment can be maintained with bridge plate fixation to the second metacarpal or the third metacarpal if the described technique is followed. When considering dorsal bridge plate fixation for radiocarpal dislocations, the surgeon is encouraged to understand the nuances of different fixation techniques and how implant design features may influence proximal placement.

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INTRODUCTION

Radiocarpal dislocations are uncommon injuries, representing 0.2% of all dislocations[1] with the largest clinical series to date reporting only 27 cases[2]. They occur most frequently after high energy trauma, such as motor vehicle accidents or falls from height. Men in their fourth decade are at highest risk[3,4]. The proposed mechanism of injury is flexion or extension of the radiocarpal joint in combination with a rotational component[2].

Two classifications have been proposed, distinguishing between pure dislocations and those with associated fractures. The Dumontier[2] classification emphasizes the difference between pure radiocarpal dislocations, including those with an avulsion of the tip of the radial styloid (group 1), and those with an associated fracture of the styloid involving more than one third of the scaphoid fossa (group 2). Moneim *et al*[5] describes two types: Type I consists of a pure volar or dorsal dislocation, and type II describes a more complex injury, involving intracarpal fractures, dislocations and more severe ligamentous disruption.

Current published treatment options include pin fixation and external fixation, soft tissue reconstruction, and decompression of neurovascular structures when indicated[2-4]. The most common predictors for a poor outcome include pure ligamentous injuries (Dumontier Group 1 and Moneim Type I), persistent instability and non-anatomic reduction[2]. Primary or secondary ulnar shifting of the

carpus after initial reduction has been reported as a frequent finding associated with poor range of motion and function, especially in Dumontier Group 1 radiocarpal dislocations[2,6] (pure ligamentous injuries). Anatomic reduction and stable fixation, then, are of paramount importance.

The use of dorsal bridge plate fixation for complex distal radius fractures has continued to gain traction in recent years. Relying in part on ligamentotaxis, bridge plate fixation has been advocated for high-energy distal radius fractures[7], those with intraarticular and/or metadiaphyseal comminution[8,9], multiply injured patients with lower extremity trauma who require immediate platform weight-bearing[10], the elderly[11], as well as those in extremis[12,13]. Bridge plate fixation has also been described for lower energy fractures in patients who have a baseline reliance on upper extremity weight bearing assist devices[14,15].

Two major techniques have been described and advocated[8,9,16,17], each with its advantages and disadvantages. Fixation to the third metacarpal may better centralize the distal fragment and carpus with respect to the radius and have certain biomechanical advantages[18] but may also place the extensor tendons at risk[19]. Fixation to the second metacarpal, however, may improve radial height and inclination in certain distal radius fractures and avoid tendon or nerve entrapment[19].

Bridge plate fixation for radiocarpal instability has received some attention recently. Wahl *et al*[20] reported good outcomes with the use of this technique in their retrospective review of 13 patients, using fixation to the third metacarpal in all their cases[20]. Azad *et al*[21] recently shared their results of a cadaveric study and suggested that fixation to the third metacarpal may result in more anatomic alignment. The senior authors of our study (RC Srinivasan and JM Saucedo), however, have routinely used both techniques (distal fixation to the second or third metacarpals) in treating complex distal radius fractures and radiocarpal dislocations, and both techniques appear capable of achieving anatomic reduction and satisfactory clinical results.

Given the rarity of radiocarpal dislocations in the community and in the literature, there appears to be little consensus on which fixation method allows for more anatomic reduction and stable fixation in the setting of radiocarpal instability. To help answer this question, we designed a study to compare distal fixation to the second metacarpal *vs* the third metacarpal in a cadaveric radiocarpal dislocation model. We hypothesized that in a cadaveric model for radiocarpal instability, distal fixation to the third metacarpal and the second metacarpal can equally achieve anatomic alignment.

MATERIALS AND METHODS

Pilot study: Focusing on distal fixation alone

Ten matched trans-humeral cadaveric arms were obtained, whose ages ranged from 25 to 65 years old (mean 48). Four were men and one female. None had a history of previous injury or surgery. Each was examined grossly and radiographically to confirm the absence of anatomic deformity.

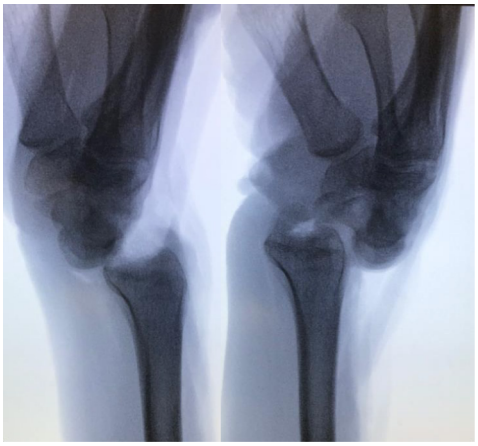
Cadaveric models were prepared through a standard dorsal approach to the radiocarpal joint. Under traction and through a dorsal incision over the radiocarpal joint, the dorsal and volar radiocarpal ligaments were transected until both dorsal and volar dislocation could be achieved with manipulation alone (defined by 100% translation of the carpus with respect to the radius on a standard lateral X-ray view) (Figure 1).

Each specimen was matched to itself to minimize confounding variables such as subtle differences in morphology. Each specimen had the plate fixed first to the radial shaft with a single screw through the fourth dorsal compartment. Then, all of the right-side specimens (group A) had the bridge plate fixed first to the second metacarpal. Once alignment was confirmed on fluoroscopy, an additional screw was placed distally and proximally. The plate was then removed from the second metacarpal and then fixed similarly to the third metacarpal with standardized X-rays obtained before and after each intervention. Group B included all of the left-sided specimens and underwent similar treatment except that distal fixation was made to the third metacarpal before the second.

The plate that was used is characterized by a widened center with a cluster of locking screw holes to facilitate fixation of fractures near the articular surface, as its primary design was meant to treat complex distal radius fractures.

Second iteration: Comparison of two described fixation techniques

Based on the results of the pilot study, a second study iteration was designed to more accurately reflect and evaluate the techniques as they were originally described. Two fixation techniques were studied: Distal fixation to the third metacarpal with the plate passed proximally through the floor of the fourth dorsal compartment (3M)[8] and distal fixation to the second metacarpal with the plate passed proximally through the second dorsal compartment (2M)[16]. Because the large cluster of screw holes in the previously used plate (the wide plate, WP) would not permit passage through the second dorsal compartment, a narrow plate (NP) design was used to facilitate passage through the second dorsal compartment.



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Figure 1 Lateral fluoroscopic view demonstrating complete radiocarpal instability following transection of dorsal and volar radiocarpal ligaments.

Twelve fresh frozen cadaveric arms were obtained. The age of the specimens ranged from 37 to 85 (average 65.7 years old) and half of the specimens were male. Each was examined grossly and radiographically to confirm the absence of anatomic deformity. Each cadaver radiocarpal dislocation model was prepared in the manner described above.

For the 3M method, the WP is fixed to the third metacarpal distally and proximally to the radial shaft through the fourth dorsal compartment[17]. Our previous incision used to render the wrist unstable was used to expose the third and fourth dorsal compartments. The extensor pollicis longus was transposed, and the floor of the fourth dorsal compartment was elevated. A third incision over the dorsal shaft of the radius was made, and the WP was passed in retrograde fashion. While holding the radiocarpal joint reduced, the plate was secured under fluoroscopic guidance to the radius midshaft with 3.5 locking screws, and to the center of the third metacarpal with 2.7 locking screws. Fixation was obtained first with a single screw proximally and distally. Once reduction of the radiocarpal joint was confirmed by C-arm, a second screw was placed proximally and distally.

For the 2M method, the NP is fixed to the second metacarpal distally and proximally to the radial shaft through the second dorsal compartment[16]. The plate typically sits more radial on the proximal shaft than is seen with the 3M method. An incision was made over the second metacarpal, and the interval between the extensor carpi radialis longus (ECRL) and extensor carpi radialis brevis (ECRB) tendon insertions was developed. A second incision was made proximal to the muscle bellies of the abductor pollicis longus and extensor pollicis brevis. The interval between the ECRL and ECRB was developed and the radial diaphysis exposed. The NP was passed from distal to proximal. While holding the radiocarpal joint reduced, the plate was secured to the second metacarpal with 2.7 mm screws and then to the radial diaphysis with 3.2 mm screws. Fixation was obtained first with a single screw proximally and distally. Once reduction of the radiocarpal joint was confirmed by C-arm, a second screw was placed proximally and distally.

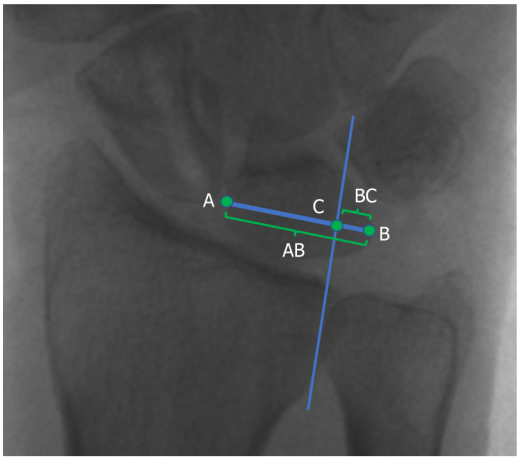
The cadavers and the WP were provided through a research grant awarded by Acumed (Hillsborough, Oregon). The NP was provided on loan by TriMed (Valencia, California). Plates and screws were returned at the conclusion of the study. Surgical indications for bridge plating in the setting of radiocarpal dislocations were not included in the 510k for Acumed or TriMed at the time of this writing.

Radiographic imaging

Radiographic imaging with standardized posterior-anterior (PA) and lateral radiographs were obtained prior to the dislocation procedure and after application of the plates. A true PA view of the distal radioulnar joint was obtained with the beam perpendicular to the distal radioulnar joint (DRUJ) and was defined by clear visualization of the ulnar head and sigmoid notch. Lateral views of the radiocarpal joint were standardized by using a 10 degree lateral tilt to optimize the lunate fossa and defined by overlap of the distal pole of the scaphoid over the pisiform[22].

Specimens in the pilot study were measured before and after each intervention using two indices: Gilula's lunate uncovering technique to measure the quality of radiocarpal reduction in the coronal plane (*i.e.*, the amount of radio-ulnar translation) and the best-fit circle technique for sagittal alignment (*i.e.*, volar-dorsal translation).

Gilula's lunate uncovering has been proposed as the most sensitive method to measure ulnar translation of the carpus[23-25]. It measures the relationship between the total width of the lunate and the portion that is not covered by the radius lunate fossa. This calculation is demonstrated in Figure 2.



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Figure 2 Gilula's technique for measuring ulnar translocation through lunate uncovering. A line is drawn along the transverse axis of the lunate, from the farthest radial point at the mid-portion of the lunate (point A) to its ulnar-most corner (point B). The long axis of the radius is found and a parallel line at the ulnar corner of the radius is drawn until the A-B line is transected (point C). The distance between B and C is divided by the distance between A and B (G = BC/AC) [23].

Lateral views were evaluated to assess radiocarpal reduction. Fitting a circle to the contour of the distal radius and next to the proximal pole of the lunate should result in concentric articular contours. If that relationship was altered, we considered the radiolunate joint noncongruent[26] and defined each state as either reduced or subluxated (Figure 3). Based on what was learned in the Pilot Study, two additional measurements (Chamay and Bouman) were made in the second iteration to further evaluate coronal alignment[23-25]. They are demonstrated and described in Figure 4.

Respective measurements were made before and after plate placement using OsiriX Lite (Pixmeo SARL, Switzerland).

Statistical analysis

Wollstein *et al*[23] found that the average physiologic lunate overhang with the wrist in neutral deviation ranged from 36% to 44% (radial shaft aligned with the third metacarpal). Lunate overhang greater than 50% was defined as pathologic. A power analysis showed that five patients in each group were needed to find a 6% difference between values with an 80% power and a 95% confidence level.

Pilot study

Comparison of lunate overhang was calculated for the Group A method and Group B method using the nonparametric Mann-Whitney U test, independent sample *t*-test, and parametric paired samples *t*-test. All analyses were done using SPSS (Chicago, IL) and significance assigned as $P < 0.05$.

Comparison of 2M and 3M techniques

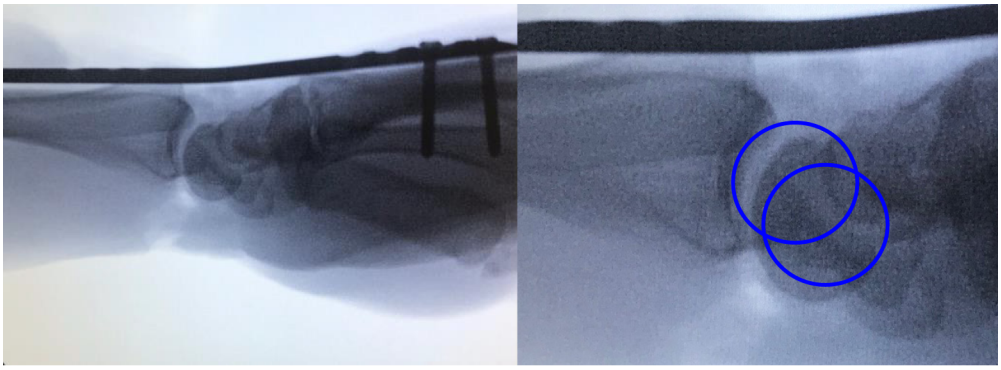
The mean, median, range, minimum and maximum were calculated for each of the three scores (Chamay, Gilula, and Bouman) preoperatively and postoperatively for the 2M and 3M plating techniques. The Shapiro Wilk test was used to examine normality of distribution and all scores were found to have a normal distribution. Next, the paired sample *t*-test was used to compare the means of the preoperative and postoperatively scores for all subjects. Similarly, paired sample *t*-tests were used to compare the means of the postoperative scores of the 2M and 3M plating techniques. Lateral views were evaluated and described as either reduced or subluxated.

RESULTS

Pilot study

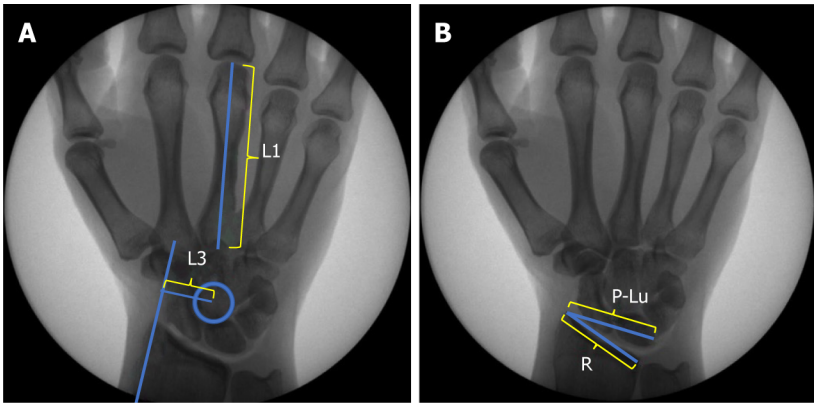
Lunate overhang (Gilula) was 0.29 ± 0.12 mm preoperatively, 0.78 ± 0.20 mm when fixed distally to the second metacarpal, and 0.44 ± 0.19 mm, when fixed distally to the third metacarpal. Paired samples t-test analysis demonstrated a significant difference ($P = 0.001$) between second and third metacarpal fixation for lunate overhang, with more anatomic alignment associated with third metacarpal plating (Figure 5A).

In addition, we found volar subluxation of the radiocarpal joint in 5 out of 10 specimens (Figure 5B). Each of those cases had the plate applied from the floor of the fourth dorsal compartment to the second metacarpal. None of the specimens that had been plated from the floor of the fourth dorsal



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Figure 3 Concentric circle technique for assessing radiolunate joint alignment on the lateral view. Subluxation or inadequate reduction is demonstrated by the lack of concentricity.



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Figure 4 Chamay and Bouman techniques for measuring ulnar translocation. A: Chamay's index is calculated by dividing the distance between a line parallel to the axis of the radius passing through the radial styloid process and the center of rotation of the capitate (L3) and the length of the long finger metacarpal (L1)[25]; B: Bouman's index is calculated by dividing the length of the distal articular surface of the radius (R) by the distance between the radius styloid process and the proximal ulnar corner of the lunate (P-Lu)[25].

compartment to the third metacarpal had volar subluxation of the lunate.

Comparison of 2M and 3M techniques

The pre-operative Gilula lunate overhang measurement was 0.32 ± 0.33 mm with a postoperative measurement of 0.4 ± 0.51 mm and 0.33 ± 0.49 mm for the 2M and 3M techniques, respectively. The preoperative Chamay measurement was 0.27 ± 0.11 mm. The postoperative Chamay measurement was 0.25 ± 0.07 mm and 0.27 ± 0.15 mm for the 2M and 3M techniques, respectively. The Bouman measurements were 0.98 ± 0.37 mm preoperatively and for the postoperative measurements for the 2M and 3M techniques, they were 1.02 ± 0.75 and 1.00 ± 0.44, respectively (Table 1).

Bridge plating from the second dorsal compartment to the second metacarpal (2M) and from the fourth dorsal compartment to the third metacarpal (3M), resulted in no statistically significant differences in radiocarpal alignment compared to pre-dislocation status, according to the indices of Gilula, Chamay and Bouman, suggesting that each technique could achieve anatomic coronal alignment (Table 2 and Figure 6).

In all specimens (2M and 3M), lateral alignment was found to be anatomic using the best-fit circle technique.

DISCUSSION

While there is no consensus for the best fixation strategy for radiocarpal dislocations, it is generally understood that poorer outcomes are associated with inadequate or lost reduction, such as ulnar translocation. It stands to reason, then that anatomic reduction and stable fixation are essential, though not always sufficient, to obtaining a satisfactory clinical outcome. Bridge plating for distal radius fractures has been well-established through multiple biomechanical and clinical studies[26], but its use

Table 1 Differences in coronal alignment between distal fixation to the second and to the third metacarpal, measured in millimeters

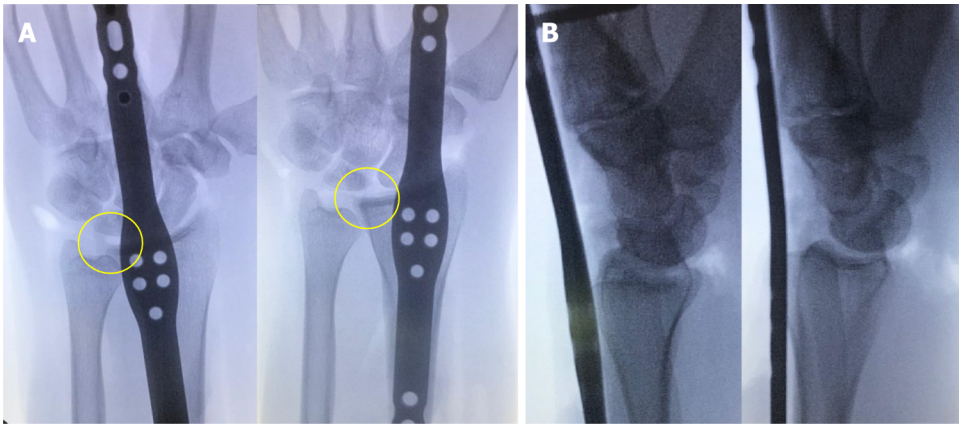
Variable	Mean	Median	Maximum	Minimum	Range
Preoperative Gilula score	0.32	0.34	0.48	0.15	0.33
2M Gilula score	0.4	0.38	0.68	0.17	0.51
3M Gilula score	0.33	0.32	0.59	0.1	0.49
Preoperative Chamay score	0.27	0.28	0.32	0.21	0.11
2M Chamay score	0.28	0.28	0.33	0.26	0.07
3M Chamay score	0.27	0.27	0.34	0.19	0.15
Preoperative Bouman score	0.98	0.95	1.2	0.83	0.37
2M Bouman score	1.02	1.04	1.39	0.64	0.75
3M Bouman score	1.00	0.98	1.23	0.79	0.44

2M: Second metacarpal fixation technique; 3M: Third metacarpal fixation technique.

Table 2 Differences in coronal alignment before and after fixation to the second and third metacarpals (*P* values)

	Chamay	Gilula	Bouman
2M technique	0.199	0.065	0.462
3M technique	0.408	0.846	0.578

2M: Second metacarpal fixation technique; 3M: Third metacarpal fixation technique.



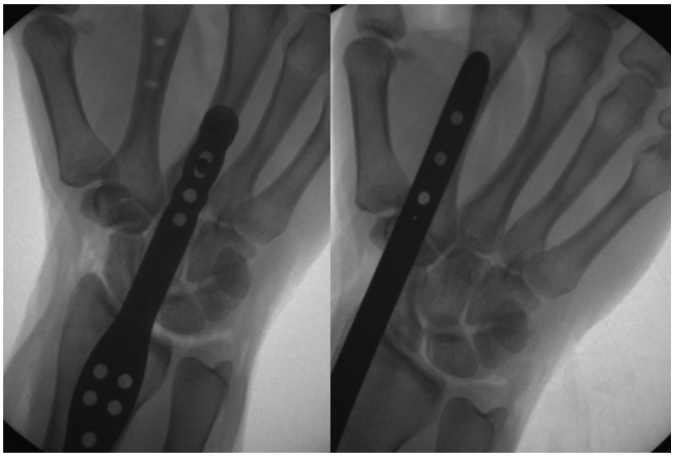
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Figure 5 The effect of focusing on distal fixation alone with proximal bridge plate placement through the fourth dorsal compartment. A: Posterior-anterior view of third metacarpal fixation (left) and second metacarpal fixation (right) demonstrates ulnar translocation of the carpus (even radial translation within the fourth dorsal compartment is insufficient to align the radiocarpal joint); B: Lateral view demonstrates volar subluxation of the radiocarpal joint, which was observed in half of the pilot study specimens with second metacarpal distal fixation (third metacarpal left, second metacarpal right).

in radiocarpal dislocations is less understood.

The present study demonstrates that anatomic alignment is achievable with the two most commonly cited techniques for bridge plate fixation–distal fixation to the second metacarpal through the second dorsal compartment and distal fixation to the third metacarpal through the floor of the fourth dorsal compartment–if the techniques are followed carefully.

In addition to those findings, we believe that the Pilot Study results and subsequent analysis are just as relevant. The initial study exclusively used a plate that includes a cluster of screw holes designed to allow for supplemental periarticular fixation without compromising resistance to fatigability across the wrist joint. This design feature, however, results in a wider section of the plate that does not easily facilitate passage through the second dorsal compartment. In testing the concept of distal fixation to the second metacarpal, proximal fixation was essentially set at a single point, leading to mal-reduction of



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Figure 6 Anatomic radiocarpal alignment was achieved with each the second metacarpal fixation technique (2M) and third metacarpal fixation technique (3M).

the radiocarpal joint when fixed to the second metacarpal *vs* the third metacarpal, which included ulnar translocation in nearly every specimen and volar subluxation at least 50 percent of the time. This is consistent with the results found by Azad *et al*[21] and may at least in part explain their findings. Another design feature, six degrees of dorsal bend, may have contributed to the volar subluxation, but this was found in only 50 percent of the Pilot Study specimens, so its significance is unclear.

The results of the pilot study were carefully studied and led the authors to realize that the second metacarpal fixation model did not accurately reflect the technique as it was originally described[16]. The 2M technique is known for its fixation to the second metacarpal, but it requires passage through the second dorsal compartment and more radial placement proximally on the radial shaft between the ECRB and ECRL tendons in order to maintain alignment. Fixation to the third metacarpal generally assumes passage through the floor of the fourth dorsal compartment and proximal fixation to the more central aspect of the radial shaft[8,17].

Comparing our methods to those of Azad *et al*[21] reveals that our models and techniques may have differed in significant ways and may explain the different results. Their model appears to have removed the extensor retinaculum in addition to the "dorsal radiocarpal capsuloligamentous structures." Though they do not specify that the retinaculum was removed, the clinical photo in their article seems to suggest that this structure (and landmark) has been removed, which might obscure proper proximal placement of the plate when performing the 2M technique to the second extensor compartment. In addition, the authors do not specify the nuances of proximal positioning of the plate on the radius, which may introduce the opportunity for coronal and even sagittal malreduction, as we found in our pilot study.

There are advantages and disadvantages to each approach, and advocates have several studies to cite in support of their preferred technique, such as a potential protective advantage against tendon entrapment for the 2M technique[19] or a potential biomechanical advantage for the 3M technique[18].

Based on their collective experience and the results of this study, however, the senior authors encourage surgeons to be comfortable with both techniques, as each may offer different advantages and disadvantages in different scenarios. A larger patient with a heavier arm, for example, may fare better with a larger plate placed along the central axis of the radiocarpal joint and fixed to the third metacarpal. Similarly, in the setting of an unstable fracture pattern that requires multiple fragment-specific implants and supplemental bridge plate fixation, the surgeon may find it easier to pass the plate through the second dorsal compartment to the second metacarpal. And finally, anatomic variations among patients may at times require small changes in technique and bridge plate application.

Modification of the 3M technique in which we attempted to fix the wider plate to the second metacarpal from the floor of the fourth dorsal compartment consistently resulted in less anatomic reduction of the radiocarpal joint in our cadaveric model with observed ulnar translocation, relative supination of the carpus and volar subluxation, even when trying to translate the plate radially within the fourth dorsal compartment (Figure 5A). Such a finding may not be readily observed in the setting of a distal radius fracture in which the ligaments are intact, but our cadaveric model suggests that this modification of the 3M technique may result in non-anatomic alignment and would not be advised.

When choosing to bridge plate a distal radius fracture or radiocarpal dislocation, the treating surgeon is encouraged to carefully follow the technique as it is described by its proponents and understand the design features of their implant and the implications they may have for their chosen technique. Likewise, the surgeon must recognize that anatomic reduction is ultimately the surgeon's responsibility and should maintain a critical eye for coronal and sagittal alignment, making adjustments as needed to match their patients' normal anatomy. We suggest that obtaining preoperative contralateral images may

help with this assessment, in addition to the various parameters that were used in this study (*i.e.*, Gilula's lunate uncovering and best-fit circles).

Limitations of this study include the use of an unvalidated cadaveric model of radiocarpal instability. Our model represents a completely unstable joint where the radiocarpal joint capsule and the ligaments have been transected completely. Though this may or may not accurately reflect the true nature of a radiocarpal dislocation *in vivo*, our model represents an extreme version of instability and demonstrates that in the setting of complete instability, both the 2M and 3M techniques appear to permit anatomic reduction. However, it is possible that *in vivo*, one technique may more easily facilitate anatomic reduction than the other, perhaps lending some credence to the findings of Azad *et al*[21], but without a consistent validated radiocarpal dislocation model or clinical studies, we cannot answer that question at this time.

Another potential limitation of this study is that the biomechanical strength of each technique was not tested. Therefore, we cannot comment on whether one technique is better than the other with regards to the stability of the construct; however, the aim of this study was to determine whether anatomic alignment could be achieved regardless of distal fixation, not biomechanical advantage. Compared to intramedullary wires and external fixator placement, bridge plating offers the advantage of maintaining an anatomic reduction throughout the postoperative course given that fixation is more robust and closer to the joint axis. While it has been well studied in biomechanical models of distal radius fractures[26], there is not enough data exploring its use in the setting of radiocarpal dislocations[20,21]. Biomechanical strength may either be extrapolated from the study by Alluri *et al*[18] or may represent an area of future research.

Further studies will be needed to advance in the understanding of the intricacies of these rare but devastating injuries. The creation of a validated cadaveric model would indeed enable us to compare the biomechanical advantages of one technique over another, as well as to test dorsal spanning plating *vs* other options such as external fixation or the use of Kirschner wires. Ultimately, *in vivo* studies will be necessary to evaluate the outcome in a real scenario.

CONCLUSION

In our cadaveric radiocarpal dislocation model, we found that bridge plating with distal fixation to the third metacarpal may facilitate more anatomic alignment if fixation to the radius through the fourth dorsal compartment is required. However, anatomic alignment and stable fixation can also be achieved with distal fixation to the second metacarpal through the floor of the second dorsal compartment if the technique is followed appropriately. When considering dorsal bridge plate fixation for radiocarpal dislocations, the surgeon is encouraged to understand the nuances of different fixation techniques and how implant design features may influence placement.

ARTICLE HIGHLIGHTS

Research background

Dorsal bridge plate fixation has been described for various settings in the treatment of complex distal radius fractures and can be fixed distally to the second or third metacarpal, but its application for radiocarpal dislocations has not been established.

Research motivation

To determine whether distal fixation to the second or third metacarpal matters.

Research objectives

Using a cadaveric radiocarpal dislocation model, the effect of distal fixation was studied.

Research methods

Two stages were considered: (1) a pilot study that investigated the effect of distal fixation alone; and (2) a more refined study that investigated the effect of described techniques for distal and proximal fixation. Radiographs were measured in various parameters to determine the quality of the reduction achieved.

Research results

The pilot study found that focusing on distal fixation alone without changing proximal fixation results in ulnar translocation and volar subluxation when fixing distally to the second metacarpal compared with the third. The second iteration demonstrated that anatomic alignment in coronal and sagittal planes could be achieved with each technique.

Research conclusions

Anatomic alignment can be maintained with bridge plate fixation to the second metacarpal or the third metacarpal if the described technique is followed. When considering dorsal bridge plate fixation for radiocarpal dislocations, the surgeon is encouraged to understand the nuances of different fixation techniques and how implant design features may influence proximal placement.

Research perspectives

Further studies will be needed to advance in the understanding of the intricacies of these rare but devastating injuries. The creation of a validated cadaveric model would indeed enable us to compare the biomechanical advantages of one technique over another, as well as to test dorsal spanning plating *vs* other options such as external fixation or the use of Kirschner wires. Ultimately, *in vivo* studies will be necessary to evaluate the outcome in a real scenario.

FOOTNOTES

Author contributions: Tabeayo E, Rodriguez-Merchan EC, and Srinivasan RC designed the research; Tabeayo E, Saucedo JM and Rockwood J performed the research; Karamanos E analyzed the data; Tabeayo E, Shah AR and Karamanos E wrote the paper.

Conflict-of-interest statement: Tabeayo E, Saucedo JM and Rockwood J performed the research. The cadavers and the wide plate were provided to them through a research grant awarded by Acumed (Hillsborough, Oregon). The narrow plate was provided to them on loan by TriMed (Valencia, California). Plates and screws were returned at the conclusion of the study. Karamanos E, Rodriguez-Merchan EC, Shah AR, and Srinivasan RC have no conflict of interest.

Data sharing statement: No data sharing statement.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical outcomes of cemented distal femur replacements with all-polyethylene tibial components for oncologic indications

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Abstract

BACKGROUND

Endoprosthetic distal femoral replacement (DFR) is a well-established salvage procedure following resection of malignant tumors within the distal femur. Use of an all-polyethylene tibial (APT) component is cost-effective and avoids failure due to locking-mechanism issues and backside wear, but limits modularity and the option for late liner exchange. Due to a paucity of literature we sought to answer three questions: (1) What are the most common modes of implant failure for patients undergoing cemented DFR with APT for oncologic indications? (2) What is the survivorship, rate of all-cause reoperation, and rate of revision for aseptic loosening of these implants? And (3) Is there a difference in implant survivorship or patient demographics between cemented DFRs with APT performed as a primary reconstruction *vs* those performed as a revision procedure?

AIM

To assess outcomes of cemented DFRs with APT components used for oncologic indications.

METHODS

After Institutional Review Board approval, a retrospective review of consecutive patients who underwent DFR between December 2000 to September 2020 was performed using a single-institutional database. Inclusion criteria consisted of all patients who underwent DFR with a GMRS® (Global Modular Replacement System, Stryker, Kalamazoo, MI, United States) cemented distal femoral endoprosthesis and APT component for an oncologic indication. Patients

undergoing DFR for non-oncologic indications and patients with metal-backed tibial components were excluded. Implant failure was recorded using Henderson's classification and survivorship was reported using a competing risks analysis.

RESULTS

55 DFRs (55 patients) with an average age of 50.9 ± 20.7 years and average body mass index of 29.7 ± 8.3 kg/m^2 were followed for 38.8 ± 54.9 mo (range 0.2-208.4). Of these, 60.0% were female and 52.7% were white. The majority of DFRs with APT in this cohort were indicated for oncologic diagnoses of osteogenic sarcoma (n = 22, 40.0%), giant cell tumor (n = 9, 16.4%), and metastatic carcinoma (n = 8, 14.6%). DFR with APT implantation was performed as a primary procedure in 29 patients (52.7%) and a revision procedure in 26 patients (47.3%). Overall, twenty patients (36.4%) experienced a postoperative complication requiring reoperation. The primary modes of implant failure included Henderson Type 1 (soft tissue failure, n = 6, 10.9%), Type 2 (aseptic loosening, n = 5, 9.1%), and Type 4 (infection, n = 6, 10.9%). There were no significant differences in patient demographics or rates of postoperative complications between the primary procedure and revision procedure subgroups. In total, 12 patients (21.8%) required a revision while 20 patients (36.4%) required a reoperation, resulting in three-year cumulative incidences of 24.0% (95%CI 9.9%-41.4%) and 47.2% (95%CI 27.5%-64.5%), respectively.

CONCLUSION

This study demonstrates modest short-term survivorship following cemented DFR with APT components for oncologic indications. Soft tissue failure and endoprosthetic infection were the most common postoperative complications in our cohort.

Key Words: Distal femoral replacement; Modular; Revision; Dislocation; Oncologic

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Core Tip: The current study demonstrates modest short-term survivorship following cemented distal femoral replacement with all-polyethylene tibial components for oncologic indications. Approximately one third of patients experienced a postoperative complication. The most common modes of implant failure were soft tissue failure and endoprosthetic infection.

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INTRODUCTION

Background

Endoprosthetic reconstruction of the distal femur has been used as a limb-salvage procedure to treat oncologic processes of the distal femur for nearly five decades[1], and is currently considered standard of practice for this indication. Improvements in design, such as a rotating hinge mechanism and ongrowth collars adjacent to the femoral cut surface, have improved survivorship with regards to aseptic loosening, and are now included in most modern systems[2-4]. However, implant design and research regarding fixation has focused primarily on the femoral side[5-7].

Rationale

Metal-backed and all-polyethylene tibial components are available, both of which can be fixed to the bone with fully cemented, hybrid, or in some cases cementless fashion. However, there is a paucity of literature examining the survivorship of distal femoral replacements (DFRs) with respect to the type of tibial component or fixation used[8,9]. Furthermore, the majority of available studies fail to describe the type of tibial component or fixation used[10,11]. Therefore, the purpose of this study is to assess outcomes of cemented DFRs with all-polyethylene tibia (APT) components used for oncologic indications.

Specifically, we sought to answer the following research questions: (1) What are the most common modes of implant failure for patients undergoing cemented DFR with APT for oncologic indications? (2) What is the survivorship, rate of all-cause reoperation, and rate of revision for aseptic loosening of these implants? and (3) Is there a difference in implant survivorship or patient demographics between cemented DFRs with APT performed as a primary reconstruction *vs* those performed as a revision procedure?

MATERIALS AND METHODS

Study design and participants

After Institutional Review Board approval (IRB HS-20-00396), a retrospective review of consecutive patients who underwent DFR between December 2000 to September 2020 was performed using a single-institutional database. The DFR was performed either as the primary treatment for the disease in question, or as a revision of a previous failed surgery (indications included recurrence, fracture, *etc*.). We then defined reoperation as any subsequent procedure, including manipulation under anesthesia, that was performed after placement of the DFR. Revision of the DFR was defined as a subsequent procedure which specifically required exchange or removal of femoral or tibial components. Inclusion criteria consisted of all patients who underwent DFR with a GMRS® (Global Modular Replacement System, Stryker, Kalamazoo, MI, United States) cemented distal femoral endoprosthesis and APT component for an oncologic indication. Patients were excluded if undergoing DFR for non-oncologic indications or if a different implant design was used. Patients were then stratified into two groups based on whether the index procedure was a primary reconstruction or a revision of a previous DFR. Patients who had undergone previous incisional biopsies or arthroscopic procedures without reconstruction on the operative limb prior to DFR implantation were classified in the primary reconstruction cohort.

Thorough review of patient medical records and operative reports was performed to obtain patient demographic information including comorbidities, age at the time of surgery, sex, race/ethnicity, body mass index (BMI), and American Society of Anesthesiologists score. Operative reports were reviewed to obtain surgical variables including the indication for surgery, a comprehensive surgical history of the operative limb, surgical approach, implants utilized, and operative time. The primary outcome was implant survivorship, with all-cause reoperation and revision total knee arthroplasty as endpoints. Given the primary purpose of the present study was to characterize early complications and implant longevity in the setting of limb-salvage, functional and patient-reported outcome measures were not collected.

Implant design

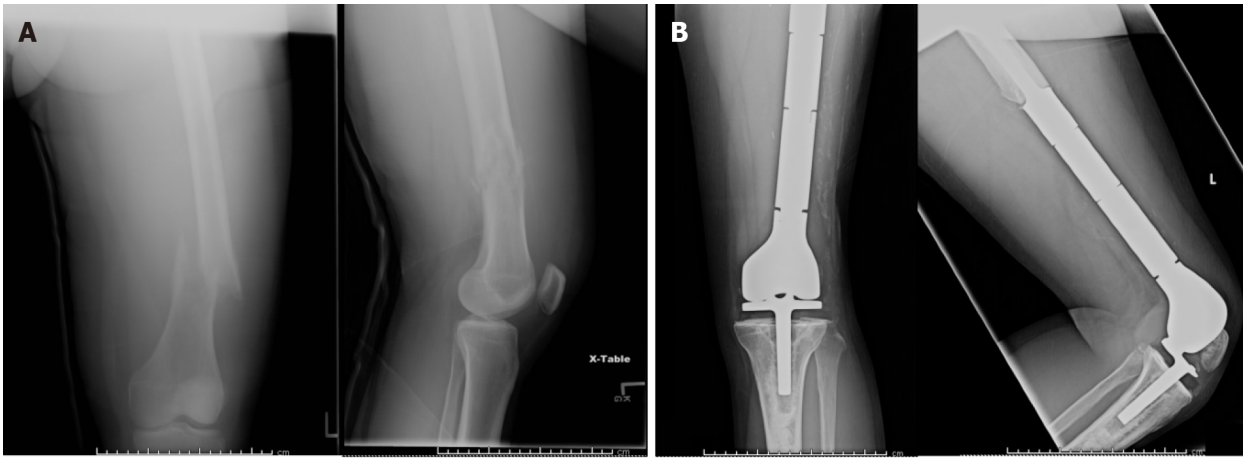
The Stryker GMRS® (Global Modular Replacement System, Stryker, Kalamazoo, MI, United States) was utilized for all cases in this series. This system is designed to assist in the reconstruction of large segmental and osteoarticular defects about the knee joint, particularly in the setting of tumors, previously failed arthroplasty, and traumatic injury. In this system, the standard distal femoral components can be paired with either a modular rotating-hinge tibial baseplate or APT component, the latter of which was used selectively in the present cohort (Figure 1). Multiple cemented stem options are available, including straight, curved, and long curved geometries, both with and without extra-cortical porous-coated intercalated body sections. This construct can be further customized with the use of extension pieces, available in over a dozen sizes, for the optimization of leg length.

Surgical technique

Medial and lateral parapatellar approaches were utilized based upon previous biopsy incisions and location of the neoplasm. Following oncologic resection, the femur and tibia were prepared using conventional jigs and reamers, and the femur was reamed in a sequential manner to accommodate the appropriate stem diameter and length. Trial implants were inserted to assess appropriate range of motion, limb length, and patellar tracking prior to insertion of the final implant. Polymethylmethacrylate cement was used for fixation in all cases.

Clinical follow-up

Each patient's clinical course was followed in detail to characterize postoperative complications and the need for reoperations or revision surgery. Given the complex patient demographics, we decided to not have a minimum follow-up in order to capture all patients who underwent this reconstruction. No follow-up was chosen over the conventional two-year minimum to capture early postoperative complications in this high-risk cohort of patients undergoing limb-salvage procedures, especially those with metastatic disease or prior failed reconstruction. Following the index procedure, any procedure on the affected limb that did not involve removal or alteration of the endoprosthesis was classified as a reoperation. Revision procedures were defined as any surgery involving removal or replacement of any prosthetic component. Implant failure was categorized based on the Henderson classification of failure



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Figure 1 Radiographs of a 28-year-old male patient demonstrating a pathologic fracture of the distal third of the left femoral diaphysis. A: Preoperative anteroposterior and lateral radiographs prior to reconstruction; B: Following left distal femoral replacement with use of an all-polyethylene tibial component.

of limb salvage after reconstructive surgery for bone tumors[12].

Patient demographics and operative variables

In total, 92 patients were identified during the study period and screened for inclusion. Eleven patients (12.0%) with a metal-backed tibial baseplate and 26 patients (28.3%) who underwent DFR for a non-oncologic indication were excluded, leaving 55 patients (59.8%) who were included in the final analysis. The mean age of the cohort was 50.9 ± 20.7 years (range, 16-88 years) and mean BMI was 29.7 ± 8.3 kg/m^2 (range, 16.4-52.9). The average follow-up of the study cohort was 38.8 ± 54.9 mo (range 0.2-208.4 mo), with a total of 21 patients (38.2%) possessing a minimum follow-up of 2 years (Table 1).

DFR with APT implantation was performed as a primary procedure in 29 patients (52.7%) and a revision procedure in 26 patients (47.3%), with a median operative time of 178 minutes across the entire cohort. For the 26 patients who underwent DFR with APT implantation as a revision procedure, the average number of previous surgeries on the affected limb was 2.0 ± 1.3 (range 1-5) (Table 2). The primary procedures for the revision were as follows: distal femoral replacement[12], open reduction internal fixation for pathologic fracture[6], Cryoablation +/- curettage[6], and soft tissue resection[2] (Table 3). The majority of DFRs with APT in this cohort were indicated for oncologic diagnoses of osteogenic sarcoma (n = 22, 40.0%), giant cell tumor (n = 9, 16.4%), and metastatic carcinoma (n = 8, 14.6%) (Table 2).

Statistical analysis

Statistical analyses were performed using SPSS version 26 (IBM, Armonk, New York, United States). Patient demographics, operative variables, and postoperative complications are presented as means or percentages with standard deviations or ranges where appropriate. Univariate analyses were performed to compare differences between groups using the Mann-Whitney-*U* test for continuous variables and Chi-square test for categorical variables or Fisher's exact test where appropriate. Competing risk analyses were performed to evaluate the cumulative incidence of all-cause reoperation, need for revision surgery, and patient death. Competing risk analysis was conducted using the survival[13,14] and cmprsk[15] function within R (R Core Team, 2021 packages)[16]. Figure 2 and Figure 3 were produced using the package ggplot2[17,18].

RESULTS

Modes of implant failure (Henderson classification)

In total, 20 patients (36.4%) experienced a postoperative complication requiring reoperation (Figure 4). The indications for the 26 reoperations were the following: Mechanical failure[11], non-union of prior pathological fracture[7], tumor progression[3], definitive management of a prior open reduction internal fixation for a pathologic fracture[2], local recurrence[1], infection[1], and soft tissue failure[1] (Table 4). Of these 20 cases requiring reoperation, 7 patients (12.7%) required only one reoperation, 2 patients (3.6%) required 2 reoperations, 4 patients (7.3%) required 3 reoperations, and 7 patients (12.7%) required 4+ reoperations. The primary modes of implant failure in this cohort according to Henderson's classification included Type 1 (soft tissue failure, n = 6, 10.9%), Type 2 (aseptic loosening, n = 5, 9.1%), and

Table 1 Patient demographics of the study cohort, including age, gender, race/ethnicity, American Society of Anesthesiologists score, body mass index, and length of follow-up, *n* (%)

Demographic variable	Value
Age (mean ± SD)	50.9 ± 20.7 yr
Gender	
Male	22 (40.0)
Female	33 (60.0)
Race/Ethnicity	
White	29 (52.7)
Hispanic or Latino	9 (16.4)
Black	4 (7.3)
Asian	5 (9.1)
Other	8 (14.5)
ASA score	
1	10 (18.2)
2	21 (38.2)
3	21 (38.2)
4	3 (5.5)
Body mass index (mean ± SD)	29.7 ± 8.3 kg/m^2
Follow-up (mean ± SD)	38.8 ± 54.9 mo

ASA: American Society of Anesthesiologists.

Type 4 (infection, n = 6, 10.9%) (Table 2). Of the 6 patients with a soft tissue failure, 3 were due to arthrofibrosis, 2 due to extensor mechanism failures, and one was due to wound dehiscence. Regarding the patients who failed due to infection, none of the individuals were on chemotherapy when infection was identified. Finally, local recurrence of the primary bone tumor occurred in one patient who was diagnosed with a "neoplasm of unspecified behavior" and was managed with radical resection at 13.2 mo (Henderson Type 5).

Of the five patients who required reoperation for soft tissue failure (Henderson Type 1), two patients experienced arthrofibrosis requiring manipulation under anesthesia with lysis of adhesions at 3.3 and 4.0 mo postoperatively, two patients required extensor mechanism repair for postoperative falls at 14.5 and 19.7 mo postoperatively, and one patient required multiple flaps for soft tissue reconstruction at 6.8 mo postoperatively. All six patients who underwent reoperation for infection (Henderson Type 4) were managed with serial irrigation and debridement procedures (mean 2.2 procedures, range 1-5), with two patients requiring antibiotic spacer placement and three patients undergoing soft tissue reconstruction at the time of reoperation. None of these patients required amputation.

Additionally, two patients required revision surgery for corrosion and metal wear debris at 32.5 mo and 99.5 mo postoperatively (Type 3). Two cases were complicated by deep peroneal nerve palsy, which were managed nonoperatively with ankle-foot orthoses. There were no identified cases for which periprosthetic fracture was the primary indication for revision surgery with the use of these constructs.

Competing risks analysis

Competing risks analysis depicting the need for any revision operation (requiring exchange of either the femoral or tibial component), any reoperation, and patient death were plotted (Figure 3). In total, 12 patients (21.8%) required a revision, resulting in one- and three-year cumulative incidence of 14.6% (95%CI 5.7%-27.4%) and 24.0% (95%CI 9.9%-41.4%), respectively, with all-cause revision as the endpoint. Additionally, 20 patients (36.4%) required reoperation, resulting in one- and three-year cumulative incidences of 26.1% (95%CI 14.2%-39.7%) and 47.2% (95%CI 27.5%-64.5%), respectively, with all-cause reoperation as the endpoint. At final follow-up, one patient (1.8%) had died, with cause of death unrelated to the DFR procedure. No information regarding the date of death was available for this patient.

In total, 10 of the 12 patients (83.3%) who underwent revision surgery required revision of the APT component. Of these 10 patients, three (30.0%) were revised due to aseptic loosening at an average of

Table 2 Operative variables of the study cohort, including procedure type (primary *vs* revision), surgical indications, mode of failure according to the Henderson Classification, and number of previous knee surgeries on the operative knee, *n* (%)

Operative variable	Value
Procedure type	
Primary	29 (52.7)
Revision	26 (47.3)
Surgical indications	
Osteogenic sarcoma	22 (40.0)
Giant cell tumor	9 (16.4)
Metastatic carcinoma	8 (14.6)
Soft-tissue sarcoma[a]	4 (7.3)
Chondrosarcoma	
High-grade	3 (5.5)
Low-grade	2 (3.6)
Synovial chondromatosis	2 (3.6)
Multiple myeloma	2 (3.6)
Non-Hodgkin's lymphoma	1 (1.8)
Pigmented villonodular synovitis	1 (1.8)
Neoplasm of unspecified behavior	1 (1.8)
Primary mode of failure, henderson classification	
Type 1 (soft-tissue failure)	6 (10.9)
Type 2 (aseptic loosening)	5 (9.1)
Type 3 (structural failure)[b]	2 (3.6)
Type 4 (periprosthetic infection)	6 (10.9)
Type 5 (tumor progression)	1 (1.8)
Number of previous surgeries (mean ± SD)	1.1 ± 1.3 surgeries

[a]Soft-tissue sarcomas included malignant fibrous histiocytoma, pleomorphic fibrosarcoma, and myxofibrosarcoma.
[b]Both cases of henderson type 3 failure were due to trunnionosis; there were no periprosthetic fractures observed in this cohort.

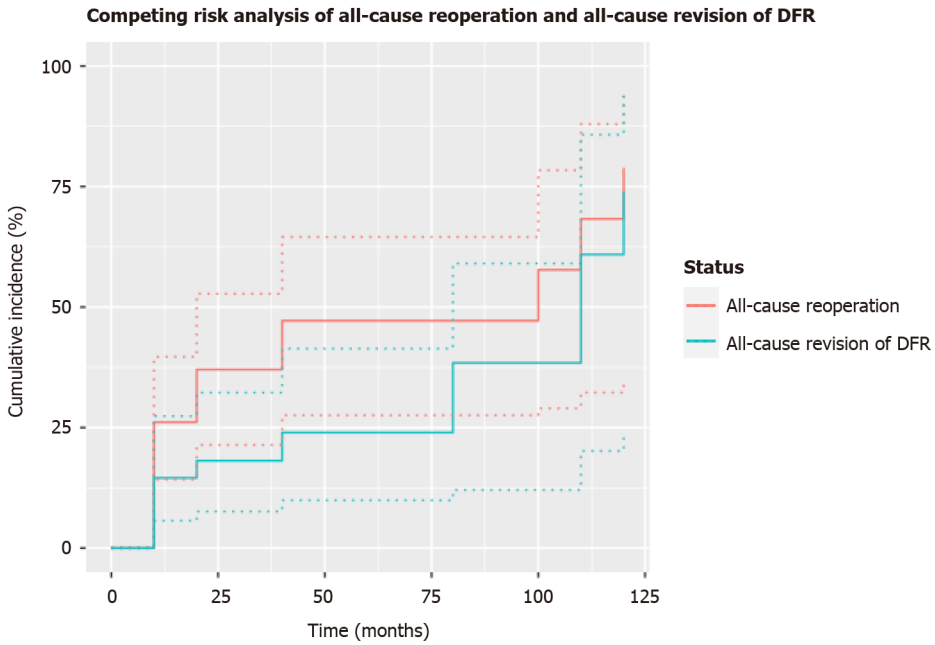
Table 3 Primary procedures for individuals requiring a revision distal femoral replacement

Primary procedure in the revision cohort (N = 26)	
Category	Number of patients
Distal femoral replacement	12
Open reduction internal fixation for pathologic fracture	6
Curettage +/- cryoablation	6
Soft tissue resection	2

80.4 mo postoperatively, six (60.0%) were revised due to periprosthetic joint infection at an average of 44.8 mo, and one (10.0%) was revised due to periprosthetic fracture requiring placement of medial and lateral titanium plates at 9.6 mo. A second competing risks analysis depicting the incidence of all-cause revision of the APT component and APT component failure secondary to periprosthetic joint infection (PJI) was plotted (Figure 3). This analysis demonstrated one- and three-year cumulative incidences of 18.2% (95%CI 2.5%-45.5%) and 47.0% (95%CI 15.1%-74.0%), respectively, with all-cause revision of the APT component as the endpoint. When failure of the APT secondary to PJI was used as the endpoint, the one- and three-year cumulative incidences were 10.0% (95%CI 0.5%-37.4%) and 44.0% (95%CI 6.3%-59.3%), respectively.

Table 4 Indication groupings for individuals requiring revision distal femoral replacement

Reason for revision	
Category	Number of patients
Mechanical failure	11
Nonunion of prior pathological fracture	7
Tumor Progression	3
Definitive management of a prior open reduction internal fixation for a pathological fracture	2
Local recurrence	1
Infection	1
Soft tissue failure	1



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Figure 2 Competing risk analysis for cemented distal femoral replacement with all-polyethylene tibial component constructs for oncologic indications with all-cause revision (femoral or tibial component) and all-cause reoperation as the primary endpoints. One- and three-year cumulative incidences were 14.6% (95%CI 5.7%-27.4%) and 24.0% (95%CI 9.9%-41.4%), respectively, with all-cause revision as the endpoint. One- and three-year cumulative incidences were 26.1% (95%CI 14.2%-39.7%) and 47.2% (95%CI 27.5%-64.5%), respectively, with all-cause reoperation as the endpoint. DFR: Distal femoral replacement.

Univariate analysis

No significant differences in patient demographics or reoperation rates were identified between patients for whom the index procedure was a primary reconstruction ("primary DFR") and patients for whom DFR was performed as a revision procedure ("revision DFR"). Both cohorts had similar lengths of clinical follow-up (42.7 ± 61.4 *vs* 34.5 ± 47.5 mo, $P = 0.946$) (Table 5).

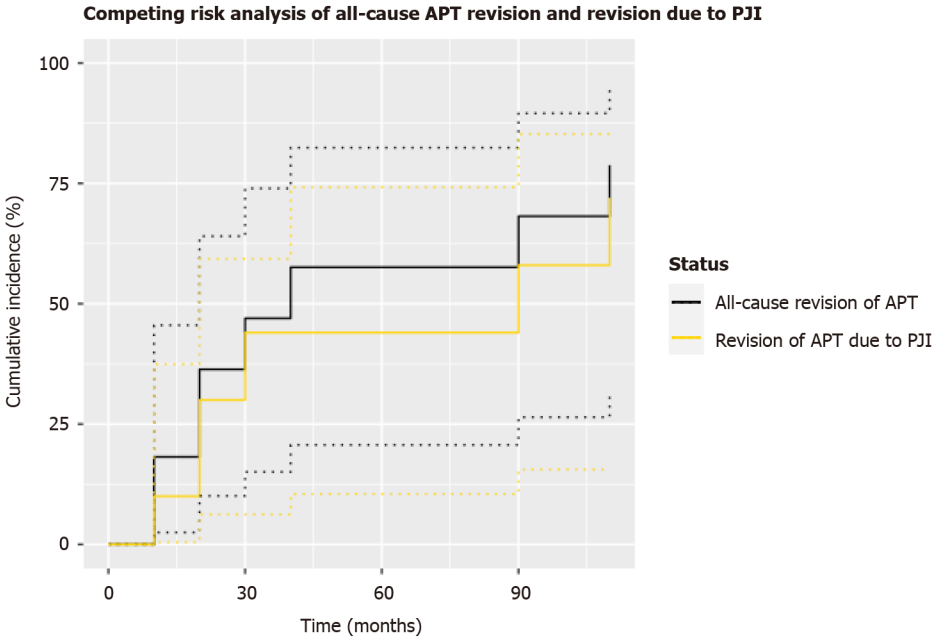
DISCUSSION

Endoprosthetic reconstruction is standard-of-care for oncologic processes of the distal femur, as greater than 90% of patients can be treated with limb salvage. While this procedure is effective in restoring mobility and salvaging the limb, it has a well-known complication and survival profile[19]. Aside from septic failure, aseptic loosening has been the leading cause of failure historically, and improvements have been focused on fixation of the femoral component[5,10]. However, relatively little attention has been paid to the tibial component. Unlike the femoral component, tibial components are available in both metal and all-polyethylene, and fixation of the tibial component can be achieved in a variety of ways, including cemented, cementless, and hybrid fixation. Despite the increased utilization of DFR

Table 5 Univariate analysis comparing demographic characteristics and reoperation rates between the primary distal femoral replacement and revision distal femoral replacement subgroups, *n* (%)

	Primary DFR (*n* = 29)	Revision DFR (*n* = 26)	*P* value
Age (mean ± SD)	49.7 ± 20.6 yr	52.2 ± 21.1 yr	0.649
Gender			0.44
Male	13 (44.8)	9 (34.6)	
Female	16 (55.2)	17 (65.4)	
Body mass index (mean ± SD)	29.5 ± 8.5 kg/m^2	30.0 ± 8.4 kg/m^2	0.567
Follow-up (mean ± SD)	42.7 ± 61.4 mo	34.5 ± 47.5 mo	0.946
Complication requiring reoperation?	11 (37.9)	9 (34.6)	0.799
Total reoperations required (mean ± SD)	1.4 ± 2.6	1.0 ± 1.8	0.624

DFR: Distal femoral replacement.

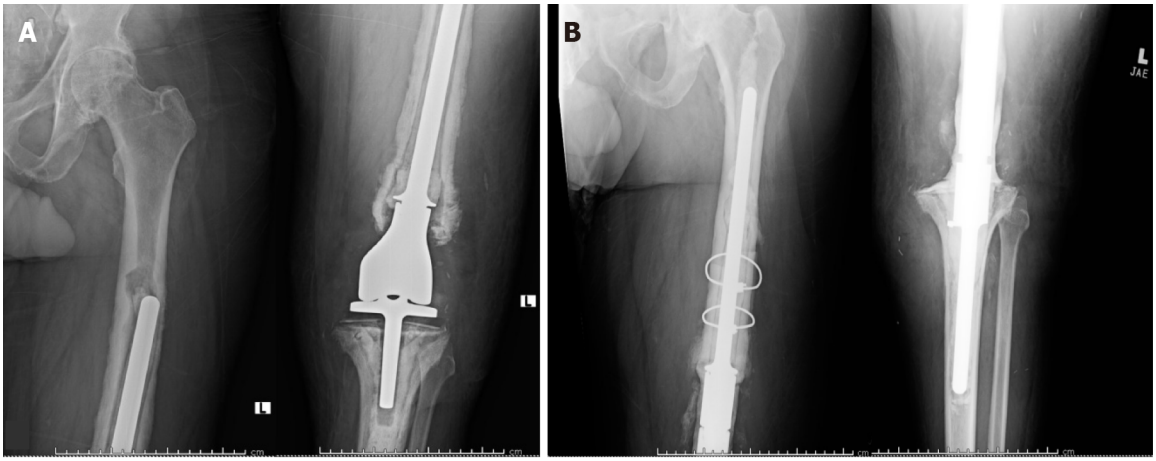


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Figure 3 Competing risk analysis for cemented distal femoral replacement with all-polyethylene tibial components for oncologic indications with all-cause revision of the all-polyethylene tibial component (APT) and revision of the APT due to periprosthetic joint infection as the primary endpoints. One- and three-year cumulative incidences were 18.2% (95%CI 2.5%-45.5%) and 47.0% (95%CI 15.1%-74.0%), respectively, with all-cause revision of the APT as the endpoint. One- and three-year cumulative incidences were 10.0% (95%CI 0.5%-37.4%) and 44.0% (95%CI 6.3%-59.3%), respectively, with revision of APT due to periprosthetic joint infection as the endpoint. APT: All-polyethylene tibial; PJI: Periprosthetic joint infection.

with APTs over time, previous studies have paid little attention to the outcomes of tibial components until recently[6,9,20]. Bukowski *et al*[20] showed that DFRs with APT have a significantly lower incidence of tibial revision at 10 years (1.1% *vs* 12.5%, HR = 0.18, *P* = 0.03) and no difference in infection-free survival (*P* = 0.72) when compared to the traditional DFR with a metal backed tibia.

APTs are monoblock cemented components that offer cost-effectiveness and surgical efficiency when compared to metal-backed tibial components[21,22]. They avoid failure due to locking-mechanism issues and backside wear, but limit modularity and the option for late liner exchange. While we theorized that APTs would suffer from some of the same failure mechanisms as metal backed tibial components, such as periprosthetic joint infection and late polyethylene wear, it is unclear whether they exhibit novel modes of failure, or whether they are more resistant to certain types of failure, such as aseptic loosening, than metal-backed components. The purpose of this study was to examine a large cohort of DFR with APT performed for oncologic indications, with specific focus on failure rate and mechanisms of the APT.



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Figure 4 Radiographs of a 58-year-old male patient showing increased lucency surrounding the proximal femoral stem with abutment of the lateral cortex. A: Anteroposterior radiographs of the loosened distal femoral replacement; B: Interval explantation of the prior distal femoral replacement and placement of an intercalary cemented modular antibiotic spacer.

The most common modes of implant failure in this cohort were soft tissue (Type I) (10.9%) and deep infection (Type IV) (10.9%), followed by aseptic loosening (Type II) (9.1%). Aseptic loosening was evenly split between the femoral and tibial components. There were two revisions for corrosion and metal debris (Type III), and one case of tumor recurrence (Type V). The rate of infection is comparable to previous large series. Sharma demonstrated a 7.8% infection rate (Type IV), 6.5% local recurrence rate (Type V), and no aseptic loosening with line-to-line cemented femoral stems using the same implant system[23]. Henderson demonstrated 1.3% soft tissue failure (Type I), 6.4% aseptic loosening (Type II), 6.3% structural failure (Type III), and 8.3% infection (Type IV) in their cohort's subset of distal femur replacements[12]. Our soft tissue failure rate was significantly higher, for unclear reasons. Given the referral nature of our practice, the present cohort may be inherently at greater risk for soft tissue failure due to a higher proportion of ethnic minorities from underserved areas with greater comorbid burden, many of whom require prior insurance authorization resulting in delayed time to definitive treatment. However, rates of infection, aseptic loosening, and structural failure were similar. Pala demonstrated a 26.6% overall failure rate for DFRs in their study, including 6% soft tissue failure (Type I), 5% aseptic loosening (Type II), and 9% infection (Type IV)[24]. Our series of DFR with APT for oncologic indications appears to have similar modes and rates of failure as previously published studies. We demonstrated a higher rate of soft tissue failure, the reason for which is unclear. However, it is unlikely to be due to the APT, as the rotating tibial component and axel for the APT is approximately 2.5 cm longer for the APT than the metal-backed tibia, conferring a much larger jump distance prior to dislocation, i.e. soft tissue failure leading to instability[25].

Our study demonstrated a 24% revision rate and 47% all-cause reoperation rate at 3 years. This is consistent with large reports of modern distal femoral replacements[9]. The rate of aseptic loosening was 9.1%, which was seen on both the femoral and tibial side. This appears to be consistent with previous reports for femoral-sided aseptic loosening[12,24]. However, few reports have specifically examined the tibial component, so it is unclear how this rate of aseptic loosening of the tibial component (3/55) compares with other historical groups. One recent study suggests that these components achieve durable fixation, with no cases of aseptic loosening and a small number (6) sustaining mechanical failure of the tibial component out of 125 patients[8]. This speaks to the advantage of line-to-line cement technique on the femur, and durable fixation of the APT, with predictable long-term failure like our study. They also observed one patient with polyethylene granuloma over the APT. Finally, they noted an infection rate (Type IV failure) of 10%, nearly identical to our study, and reported a 15% reoperation rate at 1 year and 30% reoperation rate at 5 years.

Finally, we found no significant differences in terms of preoperative demographics or post-operative complications in patients who received DFR with APT as a primary or revision procedure for their oncologic process. The revision cohort had 2.0 ± 1.3 (range 1-5) previous operations prior to DFR. It is surprising that the group performed as a revision procedure did not have a higher complication or reoperation rate, despite having been operated on previously. However, this finding is supported by several previous investigations. The reoperation rate of 38% in the revision DFR cohort is similar to published reports of DFR used for non-oncologic revision total knee arthroplasty, as the Mayo clinic series demonstrated a 46.3% percent all-cause reoperation rate at 10 years for non-oncologic DFR[26]. A similar reoperation rate was found by Staats and colleagues in a cohort of both oncologic and non-oncologic DFRs (36.4% at 2 years), and they were unable to detect a difference in the cumulative incidence of revision surgery in patients with oncologic *vs* non-oncologic disease[27]. Other studies have

found no difference between primary and revision DFRs as well[28,29], indicating that previous oncologic procedures in the same field do not significantly affect outcomes after DFR.

This study has several limitations. It is a single institution, retrospective study in which statistical power is limited due to sample size. Also, given the heterogeneity of oncologic disease, specific indications, treatments, and surgical techniques could not be standardized. However, the risk of unintentional selection bias in the present study is mitigated by the composition of the current cohort, which represents a consecutive series of DFR with APT performed for oncologic indications by a single surgeon at our institution. The APT was used consistently as the primary construct of the treating surgeon in this consecutive series of patients - therefore, we can only make historical comparisons to other studies, and cannot directly compare these patients with a cohort of metal-backed tibial components performed in the same patient population. These types of studies are difficult to accomplish in orthopaedic oncology due to the heterogeneous patient population and rare diseases treated. Nevertheless, the present study provides valuable insight into the survivorship and common modes of implant failure for the DFR with APT construct utilized this high-risk patient population, and there is value in reporting these case series so that they may be analyzed in aggregate with other published reports.

CONCLUSION

Despite the inherent risk of complications and reoperations associated with oncologic surgery, DFR with APT is a reliable reconstructive option for oncologic defects of the distal femur. APTs are efficient, cost-effective, and more likely to avoid failure mechanisms related to modularity. Failures of DFR with APT, like other DFRs, are mostly related to infection, soft tissue failures, and late aseptic loosening. While we observed several cases of aseptic loosening of the tibial component, we did not observe fractures of the APT, which has been reported previously. In concordance with previous studies, we did not observe a difference in complication rates or failures between DFR with APT performed for primary and revision indications. Further studies, including cohort or randomized trials, are needed to determine the optimal tibial component for oncologic DFR.

ARTICLE HIGHLIGHTS

Research background

Future prospective studies with larger sample sizes and longer term followup are necessary to determine the optimal construct for oncologic distal femoral replacement (DFR). Comparative studies investigating the differences in clinical, functional, and patient-reported outcomes between the use of metal-backed *vs* all-polyethylene tibial components and cemented *vs* cementless fixation will provide further insight into the specific failure mechanisms associated with each construct.

Research motivation

This study proposes that DFR with all-polyethylene tibial (APT) is a reliable reconstruction option for oncologic defects of the distal femur.

Research objectives

DFR with APT implantation was performed as a primary procedure in 29 patients (52.7%) and a revision procedure in 26 patients (47.3%). Overall, twenty patients (36.4%) experienced a postoperative complication requiring reoperation. In total, 12 patients (21.8%) required a revision while 20 patients (36.4%) required a reoperation, resulting in three-year cumulative incidences of 24.0% (95%CI 9.9%-41.4%) and 47.2% (95%CI 27.5%-64.5%), respectively.

Research methods

A retrospective review of consecutive patients who underwent DFR with a GMRS® (Global Modular Replacement System, Stryker, Kalamazoo, MI, United States) cemented distal femoral endoprosthesis and APT component for an oncologic indication was performed using a single-institutional database. Univariate analyses were performed to compare differences between those who had a DFR performed either as the primary treatment for the disease in question *vs* those who had a DFR as a revision of a previous failed surgery (indications included recurrence, fracture, *etc*.). Competing risk analyses were performed to evaluate the cumulative incidence of all-cause reoperation, need for revision surgery, and patient death.

Research results

This study was designed to answer the following research questions: (1) What are the most common

modes of implant failure for patients undergoing cemented DFR with APT for oncologic indications? (2) What is the survivorship, rate of all-cause reoperation, and rate of revision for aseptic loosening of these implants? and (3) Is there a difference in implant survivorship or patient demographics between cemented DFRs with APT performed as a primary reconstruction *vs* those performed as a revision procedure?

Research conclusions

Prior studies investigating the outcomes of endoprosthetic distal femoral replacement have largely failed to describe the type of tibial component or fixation used. Unlike the femoral component, tibial components are available in both metal-backed and all-polyethylene designs, and fixation may be achieved *via* cemented, cementless, or hybrid fixation. Future research investigating the effect of tibial component design and fixation on clinical outcomes is critical to determining the optimal construct for oncologic DFR.

Research perspectives

Endoprosthetic reconstruction of the distal femur has been used as a limb-salvage procedure to treat oncologic processes of the distal femur for nearly five decades, and is currently considered standard of practice for this indication. However, there is a paucity of literature examining the survivorship of DFRs with respect to the type of tibial component utilized. The purpose of this study was to report on the clinical outcomes of patients undergoing cemented DFR with all-polyethylene tibial components for oncologic indications.

FOOTNOTES

Author contributions: Christ AB, Menendez LR, and Heckmann ND generated the idea, provided guidance throughout, were heavily involved in copy-editing, and oversaw execution of the project; Chung BC, Urness M, Mayer L, and Gettleman BS were responsible for data collection, literature review, statistical analysis, and drafting the manuscript; All authors listed read and approved the final manuscript.

Institutional review board statement: Proposal #HS-20-00396 indicates that this study is determined to be IRB exempt.

Informed consent statement: The study is IRB-exempt at our institution because we did not employ the use of humans and the use of their protected health information for this study was deemed minimal risk. Thus, an Informed Consent form is not applicable for this study.

Conflict-of-interest statement: One of the authors (N.D.H.) is a paid consultant for Intellijoint Surgical and MicroPort Orthopedics, has stock options from Intellijoint Surgical, and is a committee member of AAOS and AJRR. One of the authors (L.R.M.) is a paid consultant for Onkos Surgical and receives IP royalties from TeDan Surgical. Each author certifies that he has no commercial associations that might pose a conflict of interest in connection with the submitted article. One of the authors (A.B.C) is a board member for AAOS, Musculoskeletal Tumor Society, Orthopaedic Society. (A.B.C) is also a paid consultant for Smith and Nephew, Intellijoint Surgical, and Enovis.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Acute hospital-community hospital care bundle for elderly orthopedic surgery patients: A propensity score-matched economic analysis

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Abstract

BACKGROUND

While Singapore attains good health outcomes, Singapore's healthcare system is confronted with bed shortages and prolonged stays for elderly people recovering from surgery in acute hospitals. An Acute Hospital-Community Hospital (AH-CH) care bundle has been developed to assist patients in postoperative rehabilitation. The core concept is to transfer patients out of AHs when clinically recommended and into CHs, where they can receive more beneficial dedicated care to aid in their recovery, while freeing up bed capacities in AHs.

AIM

To analyze the AH length of stay (LOS), costs, and savings associated with the AH-CH care bundle intervention initiated and implemented in elderly patients aged 75 years and above undergoing elective orthopedic surgery.

METHODS
A total of 862 1:1 propensity score-matched patients aged 75 years and above who underwent elective orthopedic surgery in Singapore General Hospital (SGH) before (2017-2018) and after (2019-2021) the care bundle intervention period was analyzed. Outcome measures were AH LOS, CH LOS, hospitalization metrics, postoperative 30-d mortality, and modified Barthel Index (MBI) scores. The costs of AH inpatient hospital stay in the matched cohorts were compared using cost data in Singapore dollars.

RESULTS
Of the 862 matched elderly patients undergoing elective orthopedic surgery before and after the care bundle intervention, the age distribution, sex, American Society of Anesthesiologists classification, Charlson Comorbidity Index, and surgical approach were comparable between both groups. Patients transferred to CHs after the surgery had a shorter median AH LOS (7 d *vs* 9 d, $P < 0.001$). The mean total AH inpatient cost per patient was 14.9% less for the elderly group transferred to CHs (S$24497.3 *vs* S$28772.8, $P < 0.001$). The overall AH U-turn rates for elderly patients within the care bundle were low, with a 0% mortality rate following orthopedic surgery. When elderly patients were discharged from CHs, their MBI scores increased significantly (50.9 *vs* 71.9, $P < 0.001$).

CONCLUSION
The AH-CH care bundle initiated and implemented in the Department of Orthopedic Surgery appears to be effective and cost-saving for SGH. Our results indicate that transitioning care between acute and community hospitals using this care bundle effectively reduces AH LOS in elderly patients receiving orthopedic surgery. Collaboration between acute and community care providers can assist in closing the care delivery gap and enhancing service quality.

Key Words: Care bundle; Community hospital; Orthopedic surgery; Cost-effectiveness; Care transition; Intervention

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Core Tip: This study evaluated the cost-effectiveness of an intervention that bundled Acute Hospital-Community Hospital (AH-CH) care. The AH-CH care bundle intervention effectively reduced AH length of stay (LOS) and costs for elderly patients aged 75 and above undergoing elective orthopedic surgery in Singapore General Hospital. Our findings indicate that systematically transitioning care between AH and CH using this care bundle reduces AH LOS and achieves cost savings. This intervention increases public hospital bed capacity and reduces inpatient hospitalization costs.

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INTRODUCTION

Singapore is one of the world's fastest-aging countries, with a total population of 5.7 million people[1]. According to the forecasts of demographic statistics[1], the proportion of people aged 65 and beyond is anticipated to quadruple from 8% in 2005 to 20% in 2030 and 38% by 2050[2]. This demographic transition puts Singapore's healthcare system under strain, as an aging population presents a mix of issues. For instance, an aging population increases the demand for joint replacement surgery, particularly among those aged 65 years and above[3]. Orthopedic surgery is sometimes associated with increased mortality and morbidity in the elderly patient population compared to the general population [4-7].

Additionally, the risk of hospitalization for those aged 65 years and above is higher and is associated with a longer length of stay (LOS) in acute hospitals (AHs)[8], resulting in an increased socioeconomic burden. In Singapore, age-adjusted per capita bed days in AHs have been gradually increasing since 2006, primarily due to an increase in admissions[9]. The proportion of patients aged 65 years and older admitted to public healthcare institutions has climbed from 28.6% in 2006 to 39.0% in 2020[9]. The

requirement for postoperative rehabilitation and continuing care following discharge from AHs is also projected to increase as the elderly require a more extended recovery period. Therefore, any interventions that may be utilized to lower inpatient stay costs and shorten LOS in AHs benefit Singapore's public healthcare providers.

Several care bundles or interventions have been adopted to improve patient care and decrease AH LOS in a general population undergoing surgery[10-12]. Most of them are interdisciplinary in nature and focus on optimizing all aspects of the patient's perioperative management while also encouraging the patient to participate actively in their own recovery and rehabilitation. Similarly, Singapore's Ministry of Health (MOH) has developed an AH-CH care bundle to improve the quality of care and provide ongoing postoperative care to assist patients in rehabilitating and reintegrating into their communities[13]. The core concept of this care bundle is to transfer patients out of AHs at the point when clinically necessary and into CHs, where they can receive more beneficial dedicated postoperative care to aid in their recovery while freeing up scarcer capacity in AHs. The AH-CH care bundle aims to recognize CH as an integral aspect of inpatient care by treating the AH and CH stay as a single episode. The workstream of this care bundle collaborates closely with inpatient teams at AHs to facilitate discharge planning and a smooth transfer to CHs.

This study aimed to evaluate the potential benefits and analyze the AH inpatient hospitalization costs and savings associated with this AH-CH care bundle in elderly patients undergoing orthopedic surgery in Singapore General Hospital (SGH).

MATERIALS AND METHODS

This study was approved by our institutional review board (IRB No. 2022/2178) and reported following Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) guidelines[14]. It was a retrospective single-center analysis of outcomes for elderly patients ≥ 75 years admitted to the orthopedic surgery department in SGH between two study periods: 2017-2018 (before the bundled-care period) *vs* 2019-2021 (after the bundled-care period). The inclusion criteria were all elderly patients aged 75 and above undergoing elective major orthopedic surgery between 2017 and 2021. Data was collected from our electronic health intelligence system and finance database. Patients who underwent emergency surgery were excluded from the evaluation.

Propensity score matching was performed to balance the comparison of elderly patients receiving orthopedic surgery in a 1:1 ratio before and after the care bundle periods based on age, sex, American Society of Anesthesiologists classification, Charlson Comorbidity Index (CCI), and surgical approach. The matched cohorts were examined for discharge deposition, AH LOS, and postoperative 30-d mortality. The CCI was calculated based on a patient's diagnosis using the 10th revision of the International Statistical Classification of Disease and Related Health Problems (ICD-10) codes. Patients within the care bundle were further analyzed for CH LOS, total AH-CH LOS, referral waiting time from AH to CH, U-turn rates, and Modified Barthel Index (MBI) scores, which employs a 100-point rating scale that evaluates a patient's capacity to execute ten distinct activities of daily living[15].

Costs were derived from inpatient billing data and indicated the total cost of the inpatient stay per case prior to the subsidy. Cost data were adjusted to 2021 Singapore dollars to account for healthcare inflation (approximately 1.02%-1.08% over the study period; Monetary Authority of Singapore, https://www.mas.gov.sg/). Cost breakdown was calculated and compared between the two matched cohorts.

Statistical analyses were performed in R Statistical Software (version 4.2.1). Continuous variables were reported as median (range) or mean ± SD. Categorical variables were reported as frequency (percentage). The Wilcoxon-Mann-Whitney test was used to analyze continuous variables, and χ^2 or Fisher's exact tests were used to analyze categorical variables. Cost data were presented as mean ± SD following CHEERS guidelines[14]. Statistical significance was set at a P value < 0.05.

RESULTS

Following the AH-CH care bundle intervention, we have developed a rapid transfer pathway from AH to CH for elderly patients undergoing orthopedic surgery (Figure 1). Briefly, once patients have completed surgery at the AH site, they are screened for fast-track transfer to CH sites by nursing professionals from the orthopedic surgery department. Patients who consent to be treated in CH facilities are entitled to financial counseling for an estimated cost of their entire AH-CH stay. Afterward, surgeons initiate CH referral letters, and patients are transported and admitted to CH sites. We analyzed 862 elderly patients in total who underwent elective orthopedic surgery before and after the AH-CH care bundle intervention.

Patient demographics, clinical and surgical characteristics, and hospitalization metrics between the two matched cohorts are shown in Table 1. There was no significant difference in patient demographics, baseline characteristics, and discharge deposition. Elderly patients within the care bundle transferred to CHs after the surgery had a shorter median AH LOS of 7 d (range: 1-44; mean 8.83) compared to 9 d

Table 1 Comparison of patient demographics, clinical characteristics, and hospitalization metrics between elderly patients who underwent elective orthopedic surgery before and after the care bundle intervention

Variable	Before care bundle period (2017-2018)	After care bundle period (2019-2021)	*P* value
	n (%)	*n* (%)	
Matched patients	431	431	
Age (yr), median (range)	79 (75-97)	80 (75-99)	0.184
Gender			
Male	111 (25.8)	123 (28.5)	0.400
Female	320 (74.2)	308 (71.5)	
ASA classification			
1	3 (0.7)	8 (1.9)	0.074
2	336 (78.0)	311 (72.2)	
3	92 (21.3)	112 (26.0)	
4	0	0	
CCI			
0	3 (0.7)	8 (1.9)	0.200
1	12 (2.8)	21 (4.9)	
2	316 (73.3)	292 (67.7)	
3	16 (3.7)	18 (4.2)	
≥ 4	84 (19.5)	92 (21.3)	
Surgical approach			
Open	346 (80.3)	337 (78.2)	0.502
MIS	85 (19.7)	94 (21.8)	
AH LOS (d)			
Median (range)	9 (7-73)	7 (1-44)	< 0.001
Mean (SD)	12.5 (13.8)	8.83 (7.02)	< 0.001
Discharged home	431 (100)	431 (100)	-
Postoperative mortality	0	0	-

Continuous variables were presented as median (range) or mean ± SD; categorical variables were presented as *n* (%). ASA: American Society of Anesthesiologists classification; CCI: Charlson Comorbidity Index; MIS: Minimally Invasive Surgery; AH: Acute hospital; LOS: Length of stay.

(range: 7-73; mean 12.5) in patients before the care bundle period ($P < 0.001$). The mortality rate for all included patients was 0% following orthopedic surgery.

The AH inpatient stay of both groups is shown in Table 2. Elderly patients within the care bundle group had a significantly lower mean total AH inpatient hospitalization cost of S$24497.3 per patient, 14.9% lower than patients before the care bundle period of S$28772.8 per patient ($P < 0.001$). The detailed cost breakdown analysis revealed that the care bundle group had much lower costs for ward accommodation (S$5924.4 *vs* S$8748.8, $P < 0.001$), daily medical treatment (S$2932.4 *vs* S$3980.9, $P < 0.001$), nursing care (S$1379.9 *vs* S$1574.3, $P = 0.040$), investigation (S$1847.1 *vs* S$2173.2, $P = 0.003$), and rehabilitation (S$634.0 *vs* S$905.0, $P < 0.001$) services. There was no significant difference in the costs of surgery procedure, pharmacy, and consumables between the two groups.

The CH hospitalization metrics are shown in Table 3. Our first CH was officially opened in August 2018, followed by the second in January 2019. There was no CH data available prior to the implementation of the AH-CH care bundle. The median CH LOS was 23 d, 24 d, and 22 d within the care bundle group from 2019 to 2021. The median total AH-CH LOS was reduced from 35 d in 2019 to 33 d in 2021. The overall referral time from AH to CH after surgery was around 3 d to 5 d. A U-turn occurs when a patient is readmitted to AH within 8 h of being transferred to CH. The overall U-turn was almost 0, with only one case in 2021 readmitted to AH. MBI scores of elderly patients were significantly increased at the time of being discharged from CHs. The average MBI score for all elderly

Table 2 Comparison of inpatient hospitalization costs between elderly patients receiving elective orthopedic surgery before and after the care bundle intervention

AH hospitalization cost (S$)	Before care bundle period (*n* = 431)	After care bundle period (*n* = 431)	% Difference	*P* value
Total inpatient cost per case	28772.8 (28581.6)	24497.3 (15281.8)	14.9% decrease	< 0.001
Cost breakdown				
Surgery procedure	4861.8 (2076.2)	4594.6 (1847.1)	5.5% decrease	0.561
Ward accommodation	8748.8 (15164.3)	5924.4 (6277.9)	32.3% decrease	< 0.001
Daily medical treatment	3980.9 (4875.8)	2932.4 (2371.8)	26.3% decrease	< 0.001
Nursing	1574.3 (1715.5)	1379.9 (959.5)	12.4% decrease	0.040
Investigation	2173.2 (2086.3)	1847.1 (1828.1)	15.0% decrease	0.003
Rehabilitation	905.0 (1474.5)	634.0 (490.7)	29.9% decrease	< 0.001
Pharmacy	479.6 (1149.3)	414.8 (988.2)	13.5% decrease	0.369
Consumables	2231.4 (1883.8)	2412.2 (1631.4)	8.1% increase	0.132

Cost data were presented as mean ± SD in 2021 Singapore dollars (S$), adjusted for inflation. 1 Singapore dollar (S$) = 0.722 United States dollar (US$).

Table 3 Community hospitalization metrics in elderly patients undergoing elective orthopedic surgery within the care bundle intervention

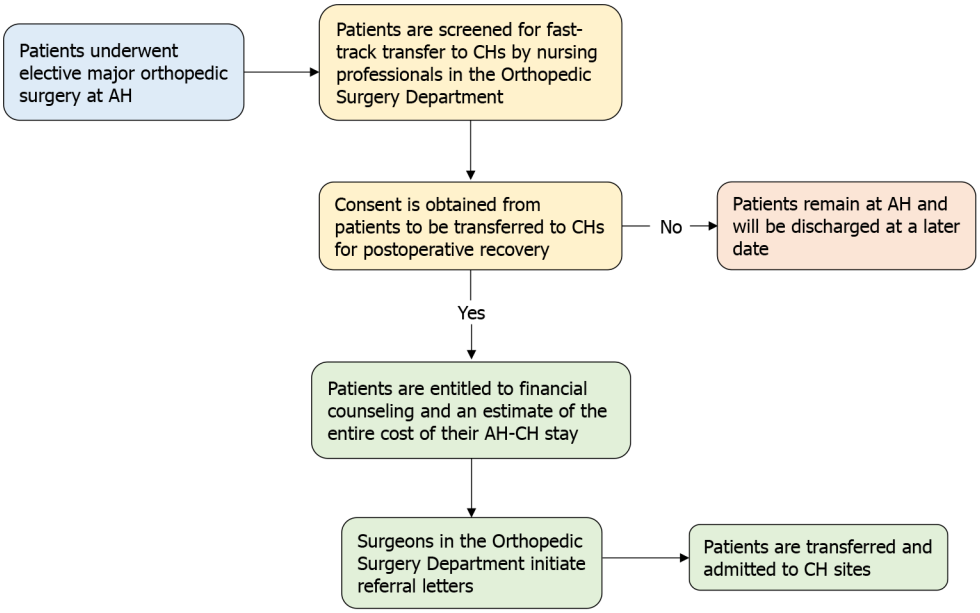
Item	2019	2020	2021
Total case	135	170	126
CH LOS (d) (median, range)	23 (4-98)	24 (2-175)	22 (2-87)
Total AH-CH LOS (d) (median, range)	35 (8-122)	33 (5-184)	33 (9-114)
Referral time from AH to CH (d) (median, range)	4 (1-20)	5 (1-14)	3 (1-12)
U-turn from CH to AH within 8 h (%)	0	0	1 (0.79)
MBI score (median, range)			
Admission	58 (11-98)	47 (5-94)	37 (10-97)
Discharge	74 (14-100)	65 (12-100)	68 (13-99)

Continuous variables were presented as median (range); categorical variables were presented as *n* (%). CH: Community hospital; LOS: Length of stay; AH: Acute hospital; MBI: Modified Barthel Index.

patients within the care bundle group improved significantly from 50.9 (SD: 23.9) at admission to 71.9 (SD: 23.4) at discharge ($P < 0.001$).

DISCUSSION

This study demonstrates that the AH-CH care bundle intervention can directly reduce AH LOS in elderly patients undergoing orthopedic surgery. Regaining movement and strength cannot occur quickly enough for an elderly patient recovering after orthopedic surgery. Physical and occupational therapy are the most effective strategies for resuming normal activities as quickly as possible[16]. Postoperative rehabilitation assists elderly patients in learning to perform their exercise appropriately, monitor their performance, and identify potential problems that the clinician should be aware of. However, rehabilitation and physiotherapy are typically time-consuming, and AH LOS is a quality indicator used by healthcare systems to assess the efficiency of their hospital operation. Reduced AH LOS increases bed turnover, enabling AHs to meet the demand for acute admission and interhospital transfers with an available capacity[17,18]. In Singapore, it has been observed a growth in AH admissions that was disproportionate to the growth of the general population. The mean AH LOS for elderly patients increased from 7.8 d in 2010 to 8.2 d in 2013[19]. As a result, Singapore is implementing system-level strategies to provide excellent care and a safe discharge while preventing prolonged AH



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Figure 1 Fast transfer pathway from acute hospital to community hospitals for elective elderly orthopedic patients. Once patients have completed surgery at the acute hospital (AH) site, they are screened for fast-track transfer to community hospital (CH) sites by nursing professionals from the orthopedic surgery department. Patients who agree to be treated in CH facilities are entitled to financial counseling and an estimate of the total cost of their AH-CH stay. Afterward, surgeons initiate CH referral letters, and patients are transported and admitted to CH sites. AH: Acute hospital; CH: Community hospital.

stays. Our results identified potential benefits of this care bundle in shortening median AH LOS by two days in elderly patients undergoing orthopedic surgery, without sacrificing postoperative complications, readmissions, and mortality.

The total costs of AH inpatient stay were consequently reduced. Cost savings were achieved from cost buckets associated with prolonged AH LOS. Applying the observed decrease in AH LOS to our elderly patient cohort would have resulted in an estimated bed day savings of S$184440.0 between 2019 and 2021 (200 beds reserved for the orthopedic surgery department with an estimated bed day cost of S$461.1). Furthermore, the reduced LOS would improve AH's capacity due to cost savings. As a result, there would be substantial advantages for both patients and the hospital because the increased capacity may boost utilization and cut down on waiting lists.

Compared to AH LOS, a CH stay might last from a few days to a few weeks, depending on the patient's condition. CH services are designed to enhance patient functional impairment statuses and maximize their physical capacities in preparation for discharge home or continuation of treatment at other community-based step-down care facilities. The benefits of admission to CHs for rehabilitation care include the following: (1) A good chance for patients, particularly elderly patients, to improve physical functions; (2) patients can participate in at least two hours of therapy daily; and (3) patients and caregiver can participate in rehabilitation and discharge planning. Patients undergoing orthopedic surgery in this care bundle had a median CH LOS of 22-24 d. One constraint of this study was the limited bed capacity of our two newly-constructed CHs, which resulted in a slower bed turnover rate. The median duration between AH site referral and CH site acceptance was observed to be approximately 3-5 d. To fulfill the demand for intermediate residential care, Singapore's MOH is expanding its network of CHs that will be co-located with their cluster-run AHs to complement acute care services and assist patient care continuums.

Our results demonstrated that CH is critical in providing rehabilitation and continuing care to assist elderly patients in rehabilitation. When elderly patients were discharged from CHs, their MBI scores increased significantly. The second constraint was that we were unable to get MBI scores for the matched cohort before the care bundle period. As such, we were unable to compare MBI scores between matched elderly patients discharged directly from AH and those transferred to CHs for further rehabilitation. Even if patients are discharged immediately from AH following orthopedic surgery, many of them will most likely require weekly postoperative rehabilitation at AH. In comparison, support from CH care professionals is another factor related to positive results for patients referred to CHs for postoperative rehabilitation. CH care teams will work with patients, particularly the elderly, to establish daily, achievable goals for participating in a function-specific exercise to regain strength. This is of great benefit to both patients and healthcare providers.

This study has a few limitations. First, the AH-CH care bundle is designed for a specific patient population and may not be applicable to other populations or healthcare settings. Second, the exclusion of emergency surgery patients may limit the generalizability of the study's findings to a broader patient

population. Third, this care bundle may not capture the unique characteristics and complexities of each specific orthopedic surgery procedure. However, there are a few perspectives on our findings. The AH-CH care bundle is a promising approach to improving the quality and efficiency of care for elderly patients undergoing elective orthopedic surgery. It provides a standardized and evidence-based practice, which may lead to enhanced patient outcomes and reduced costs, as well as promote a multidisciplinary approach to improve communication and collaboration between healthcare providers.

CONCLUSION

Our results show that transitioning care between acute and community hospitals *via* the AH-CH care bundle effectively reduces AH LOS in elderly patients undergoing orthopedic surgery. A well-designed postoperative rehabilitation program at CH sites can help prevent complications that may have a lasting effect on the quality of life.

ARTICLE HIGHLIGHTS

Research background

Singapore's healthcare system has faced bed shortages and extended stays for elderly patients recovering from surgery in acute hospitals.

Research motivation

An Acute Hospital-Community Hospital (AH-CH) care bundle was created to transfer patients to CHs where they can receive specialized care and free up beds in AHs.

Research objectives

To evaluate the impact of the AH-CH care bundle on AH length of stay (LOS), costs, and savings for elderly patients aged 75 years and above who underwent elective orthopedic surgery.

Research methods

The study examined a cohort of 862 patients aged 75 years and above undergoing elective orthopedic surgery at Singapore General Hospital before (2017-2018) and after (2019-2021) the implementation of the AH-CH care bundle intervention. Patients were matched 1:1 based on their propensity scores and compared for AH LOS, CH LOS, hospitalization metrics, postoperative 30-d mortality, modified Barthel Index (MBI) scores, and costs.

Research results

Elderly patients transferred to CHs had a significantly shorter median AH LOS (7 d *vs* 9 d, $P < 0.001$), and the mean total AH inpatient cost per patient was 14.9% less for the elderly group transferred to CHs (S$24497.3 *vs* S$28772.8, $P < 0.001$). The overall AH U-turn rates for patients within the care bundle were low, with no mortality rate following orthopedic surgery. When elderly patients were discharged from CHs, their MBI scores improved significantly.

Research conclusions

The AH-CH care bundle was found to be effective and cost-saving for elderly patients undergoing elective orthopedic surgery.

Research perspectives

Collaboration between acute and community care providers can help to improve clinical service quality and achieve cost savings.

FOOTNOTES

Author contributions: Au MKH, Ang KA, Tan AHC, and Tan EJKW conceived and planned the study; Tan IEH and Chok AY supervised the study and wrote the manuscript; Chok AY and Zhao Y performed the analysis and interpreted the results; Chen YH, Soh MHT, and Foo CH collected and verified data; Koo CH and Aw JJ participated in the review of the manuscript; Chok AY, Tan EJKW, and Au MKH provided critical revisions for final approval; all authors have read and approved the final version of the manuscript.

Institutional review board statement: This study was approved by Singapore Health Services (SingHealth) Institutional Review Board (approval No. 2022/2178).

Informed consent statement: Due to the study's retrospective design using de-identified data, written informed consent collection was waived by SingHealth Centralised Institutional Review Board.

Conflict-of-interest statement: All authors declare that they have no relevant or material financial interests related to the research described in this paper.

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STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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ORIGINAL ARTICLE

Retrospective Study

Knowledge and attitudes of orthopedic surgeons regarding prosthesis joint infection

Mahmut Nedim Aytekin, Imran Hasanoglu, Recep Öztürk, Nihat Tosun

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Abstract

BACKGROUND

Periprosthetic joint infection (PJI) is a critical complication after joint arthroplasty and is accompanied by increasing rates of morbidity and mortality. Several studies have aimed at preventing PJI.

AIM

To research the knowledge level and attitudes of orthopedic surgeons, who play a key role in both preventing and managing PJI.

METHODS

We conducted a web-based survey to evaluate orthopedic surgeons' knowledge level and attitudes regarding PJI. The Likert scale survey utilized consisted of 30 questions which were prepared based on the "Proceedings of the International Consensus on Periprosthetic Joint Infection".

RESULTS

A total of 264 surgeons participated in the survey. Their average age was 44.8, and 173 participants (65.5%) had more than 10 years of experience. No statistically significant relationship was found between the PJI knowledge of the surgeons and their years of experience. However, participants who worked in training and research hospitals demonstrated higher levels of knowledge than the ones in the state hospitals. It was also noticed that surgeons' knowledge concerning the duration of antibiotic therapy and urinary infections was not consistent with their

attitudes.

CONCLUSION
Even though orthopedic surgeons have adequate knowledge about preventing and managing PJI, their attitudes might contradict their knowledge. Future studies are required to examine the causes and solutions of the contradictions between orthopedic surgeons' knowledge and attitudes.

Key Words: Antibiotic prophylaxis; Periprosthetic joint infection; Prevention; Total joint replacement; Turkey

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Core Tip: In this study, researching the knowledge level and attitudes of orthopedic surgeons, who play a key role in both preventing and managing prosthesis joint infections, has been aimed.

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INTRODUCTION

Total joint replacement is the most frequently applied procedure in orthopedic surgery, and the prevalence of this surgery is increasing gradually. However, the number of periprosthetic joint infection (PJI) cases is also increasing in parallel with arthroplasties[1]. PJI is a critical complication after joint arthroplasty operations and is accompanied by higher rates of morbidity and mortality. Apart from increasing the cost of health services, the treatment of PJI is complicated, and patients generally need to undergo more than one major operation and receive antibiotic treatment to annihilate the infection. There have been several studies aimed at preventing PJI[2,3].

Gram-positive bacteria are the most seen pathogens in infected orthopedic prostheses, and 75% of the infections are caused by *Staphylococcus aureus* (*S. aureus*). The most frequently used antibiotics in total joint replacement (TJR) are cephalosporins and semi-synthetic penicillins. Routine prophylaxis is applied as a multi-cefazolin dose by many authors in clean surgical procedures including elective orthopedic surgeries. Most early postoperative infections are the result of intraoperative contamination of the surgical site[3-5].

Guidelines about preventing PJI are published by the International Consensus Meeting, World Health Organization (WHO), and the Center for Disease Control and Prevention, and these guidelines are updated regularly in parallel with the current practices and progression[6]. However, orthopedic surgeons' compliance with these principles might differ depending on their knowledge level, experience, and working conditions. In this research, the examination of the knowledge and attitudes of orthopedic surgeons in Turkey about preventing PJI has been aimed by means of a survey study.

MATERIALS AND METHODS

This study was performed between January and March 2019. An online survey was conducted with orthopedic surgeons who were registered in the Turkish Society of Orthopedics and Traumatology in 2019 and who still performed hip arthroplasty. For this purpose, a total of 30 questions were prepared with the intent of providing an evaluation regarding orthopedic surgeons' knowledge about and attitudes towards PJI after joint prostheses. The questions were prepared based on the "Proceedings of the International Consensus on Periprosthetic Joint Infection"[7].

The survey consisted of questions that inquired about surgeons' demographical data, work experiences, features of the institution where they worked at the time of the study, annual arthroplasty numbers, and pre-surgical, intra-surgical, and post-surgical knowledge levels as well as attitudes regarding PJI. The demographic data and questions regarding surgeons' operations (attitudes of surgeons) were presented in the first section of the survey. The second section was allocated for the questions concerning how the operations should be done (knowledge). In the survey, the Likert scale was used. The study has been carried out in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The data collected were analyzed using the software IBM SPSS version 22.0 (IBM Corp., Armonk, NY, United States). In order to statistically evaluate the data, descriptive statistics and analysis of variance (ANOVA) were utilized. The significance level was defined as $P < 0.05$.

RESULTS

The total number of surgeons who participated in the survey was 264. Their average age was 44.8 ± 8.7, 173 participants (65.5%) had more than 10 years of experience, and 162 participants (61.4%) performed more than 50 TJR operations in a year (Tables 1 and 2). Whereas most of the participants were working in private hospitals (37.5%) at the time of the study, the number of participants who were working in a state hospital was smaller (24.6%) (Table 3).

Participants' answers to the questions that examined their attitudes towards PJI are presented in Table 4. Of the participants, 48.5% stated that they gave 2 g of cefazolin to every patient for surgical prophylaxis in arthroplasty operations. While 28.4% of them stated that they gave 1 g to every patient, 20.8% of them adjusted the dosage according to the patient's weight (Table 5).

Only one out of the total 264 participants stated that he/she did not change gloves during operation (0.4%). Whereas 20.5% of the participants said that they changed gloves once during an arthroplasty operation, 53% of them changed gloves twice, and 26.5% of them changed gloves three or more than three times. Of the participants, 54.9% noted that they changed their gloves when they were disintegrated, yet the rest reported that they did not change gloves. While 54.2% of the participants stated that they changed their gloves after contact with cement, the rest said that they did not change. Regarding the frequency, 38.6% of the participants stated that they changed their gloves every 1 h, while 9.5% changed their gloves every 90 min. More than half (59.5%) of the participants noted that they performed irrigation and debridement to the persistent drainage that continues more than 1 wk after the prosthesis operation, while the rest stated that they did not perform these. Just over a half (51.5%) of the participants pointed out that they administered antibiotic treatment, whereas the rest did not. Of the participants, 50.8% remarked that they discontinued anticoagulants, whereas the rest continued to administer anticoagulants.

While all participants finished the first section of the survey, 192 of them (73%) completed the second section. Participants' answers to the questions that examined their knowledge level in the second section are demonstrated in Table 6.

As a result of the ANOVA, it was determined that the knowledge levels of the participants did not differ in terms of their working period as an orthopedics and traumatology specialist ($P = 0.483$) (Table 7).

In addition, the results of the ANOVA revealed that the knowledge levels of participants did not differ in terms of the number of performed operations per year ($P = 0.675$).

When the average knowledge levels of the participants were examined according to the hospital types, it was seen that the knowledge level of those who worked in training and research hospitals (4.0403) was higher than the ones who worked in state hospitals (3.6580). The ANOVA also revealed that the knowledge levels of participants differed in terms of the type of hospital they currently worked in ($P = 0.030$). In the post-hoc multi comparison test that was done to discriminate between which hospital types this difference occurred, it was determined that there was a significant difference in the knowledge levels between those who worked in training and research hospitals and the ones who worked in state hospitals (Table 8).

DISCUSSION

The most important outcome of this study is the finding that the knowledge levels of the doctors who participated in the study are not congruent with their operations. While the most popular answer is that antibiotic therapy should not be continued longer than 24 h in mega-prosthesis operations, those who have stated that they give antibiotic treatment longer than 24 h construct the most crowded group. In recent survey studies, it has been reported that most orthopedic surgeons in Turkey do not follow antibiotic prophylaxis for TJR and administer antibiotic treatment longer than 24 h. This recent study has shown that orthopedic surgeons in Turkey have a good level of PJI knowledge, and antibiotics are used longer than 24 h in operations, which is in line with literature findings[6,8]. In addition, it has been reported in studies that 58% of the surgeons in Canada and 30% of the surgeons in Italy prefer antibiotic treatment that lasts longer than 24 h[9,10]. However, there is proof that antibiotic prophylaxis that is longer than 24 h is unnecessary and probably increases bacteria resistance[11]. We think that further studies are needed to determine why orthopedic surgeons in Turkey prefer antibiotic treatment that lasts longer than 24 h and to search for solutions to this issue. Another example of knowledge and attitude contradiction in this study is about urinary tract infections. While the most popular answer is 'urine tests should be ordered,' the majority of the participants have stated that they never order urine

Table 1 Number of years as an orthopedic and traumatology specialist

	Frequency	%
< 5	37	14.0
5-10 yr	54	20.5
10-20 yr	104	39.4
> 20 yr	69	26.1
Total	264	100.0

Table 2 Average number of arthroplasty operations per year

	Frequency	%
< 50	102	38.6
50-100	85	32.2
100-200	50	18.9
> 200	27	10.2
Total	264	100.0

Table 3 Hospital type

	Frequency	%
State hospital	65	24.6
University hospital	53	20.1
Training and research hospital	47	17.8
Private hospital	99	37.5
Total	264	100.0

tests in clinical practice. With that being stated, according to up-to-date literature, while symptomatic urinary tract infection should be diagnosed and treated before PJI, routine tests and treatment are not suggested for asymptomatic bacteriuria since it has been reported that asymptomatic bacteriuria is not a risk factor for PJI. Routine tests and following treatment operations lead to unnecessary treatments[12]. In the survey study by Çimen *et al*[6], 59% of the participants perform a routine test prior to arthroplasty while 12% of them never perform it. Azboy *et al*[8] have found in their survey study that almost every surgeon who performs an arthroplasty operation more than 20 times a month orders routine urinary tests. These contradictory findings about urinary tract infections in our country might indicate that well-attended studies are required and that we do not have standardization in our country.

S. aureus is the agent that mostly causes surgical site infections besides many other infections[13]. The nasal colonization of *S. aureus* is around 25%, and the risk of surgical site infection increases in nasal methicillin-resistant *S. aureus* (MRSA) carriers. In addition to this, no consensus has been arrived at on the issue whether an MRSA scan should be done or not before TJR[10,14]. In this study, it has been noted that the majority of the orthopedic surgeons in Turkey have not performed routine tests.

It has been shown that skin cleaning before TJR surgery decreases the rate of PJI, and guidelines highly recommend skin cleaning before surgery. Chlorhexidine is reported as the most effective agent in this matter[15]. Çimen *et al*[6] have reported that half of the orthopedic surgeons in Turkey do not follow the recommendations related to skin cleansing before surgery. In the current study, while 44% of the participants stated that they never do chlorhexidine bathing, 35% of them maintained that they do it occasionally, and 30% of them always do it.

In a survey study conducted in Canada, it has been reported that most of the participants use 1 g of first-generation cephalosporin before TJR[9]. The literature promotes 2 g of first-generation intravenous cephalosporin dosage, which is higher, regarding antibiotic prophylaxis[16]. Besides, the American National Surgical Infection Prevention Project guideline group has determined that the dosage should be adjusted according to the weight of the patient[11]. Almost half of the participants (48.5%) in this study have stated that they administer 2 g of cefazolin.

Table 4 Participants' answers to the questions that examine attitudes towards periprosthetic joint infection

	Never		Rarely		Occasionally		Frequently		Always	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Do you consult your patients to the dentist before total knee or hip arthroplasty?	94	35.6	61	23.1	61	23.1	21	8	27	10.2
Do you perform urine screening prior to elective arthroplasty of a patient with no symptoms of urinary tract infection?	119	45.1	25	9.5	22	8.3	21	8	77	29.2
Do you delay elective arthroplasty of asymptomatic patients with bacteriuria?	186	70.5	14	5.3	29	11	14	5.3	21	8
Do you screen your patients for nasal MRSA carriage prior to elective arthroplasty?	179	67	28	10.6	20	7.6	9	3.4	28	10.6
Do you recommend chlorhexidine bathing to your patients before elective arthroplasty?	117	44.3	15	5.7	35	13.3	19	7.2	78	29.5
Do you administer surgical prophylaxis in the second stage of the two-stage revision surgery?	10	3.8	0	0	13	4.9	10	3.8	231	87.5
Do you pay attention to the fact that the prophylaxis agent covers the patient's previously isolated prosthetic infection agent?	11	4.2	2	0.8	9	3.4	16	6.1	226	85.6
Do you administer surgical prophylaxis for a mega prosthesis (TM prosthesis) longer than 24 h?	40	15.2	8	3	27	10.2	26	9.8	163	61.7
Do you have your patients wear a mask during arthroplasty surgery?	214	81.1	15	5.7	14	5.3	5	1.9	16	6.1

MRSA: Methicillin-resistant *Staphylococcus aureus*.

Table 5 Prophylaxis agent and dosage used in arthroplasty operations

	Frequency	%
1 g of cefazolin	75	28.4
2 g of cefazolin	128	48.5
I adjust cefazolin according to the patient's weight.	55	20.8
Gentamicin	1	0.4
Other	5	1.9
Total	264	100.0

The knowledge and attitudes of the participants regarding the subject of performing prophylaxis surgery in the second stage of the two-stage revision surgery and the subject of paying attention to the fact that the patient's agent of prophylaxis covers the patient's previously isolated prosthetic infection agent been consistent.

New algorithms are being presented to orthopedists related to complication protection, diagnosis, and treatment in TJR practices at regular intervals[17]. However, different attitudes emerge in applying these algorithms due to factors such as the experiences of orthopedists and the opportunities provided by the hospital they work in, which results in the discussion of these differences in studies[6,8-10]. In the present study, it has been determined that there is a significant knowledge level difference between participants who work in training and research hospitals and those who work in state hospitals, and surgeons who work in training and research hospital have higher knowledge levels. Discussing the guidelines that are created to prevent PJI and the standardized protocols in courses and congresses in detail might be beneficial in raising awareness as well as in generating documents for this field.

There have been some restrictions in this study. Even though the types of institutions are questioned, there has not been data concerning the geographical distribution and the location of the hospitals in Turkey. In addition, although our survey was composed of two sections, 27% of the participants did not complete the second section.

Table 6 Participants' answers to the questions that examine their knowledge

Participants' answers	Never		Rarely		Occasionally		Frequently		Always	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
The patient should consult the dentist before total knee or hip arthroplasty	20	7.6	37	14	63	23.9	15	5.7	57	21.6
A urinary test should be ordered for the patient with dysuria complaint during the preoperative stage of an arthroplasty operation	33	12.5	22	8.3	29	11	13	4.9	95	36
Surgical prophylaxis should be administered in the second stage of a two-stage revision surgery	16	6.1	2	0.8	5	1.9	11	4.2	158	59.8
Prophylaxis agents should involve the factor of previously isolated prosthesis infection	9	3.4	2	0.8	4	1.5	6	2.3	171	64.8
Gloves should be definitely changed after contact with cement	14	5.3	10	3.8	26	9.8	25	9.5	117	44.3
For the diagnosis of prosthesis infection, 3–5 culture samples should be obtained	11	4.2	5	1.9	19	7.2	20	7.6	137	51.9
Irrigation and debridement should be applied to the patient in case of persistent drainage that continues more than 1 week after the total hip and knee arthroplasty operation	19	7.2	21	8.0	51	19.3	16	6.1	85	32.2
Surgical prophylaxis should not be longer than 24 hours for a mega prosthesis	52	19.7	18	6.8	43	16.3	11	4.2	68	25.8
The risk of infection increases as the duration of surgery gets longer	4	1.5	3	1.1	4	1.5	3	1.1	178	67.4

Table 7 Comparison of participants' knowledge level and work experience

	n	Mean	Standard deviation	Standard error
< 5	21	3.7143	0.71277	0.15554
5-10 yr	42	3.8829	0.52707	0.08133
10-20 yr	74	3.9032	0.54305	0.06313
> 20 yr	55	3.7924	0.60175	0.08114
Total	192	3.8464	0.57638	0.04160

Table 8 Comparison of participants' knowledge level and type of hospital they work in

Hospital type (I)	Hospital type (J)	Mean difference (I-J)	Standard error	Significance
State hospital	University hospital	-0.21482	0.12318	0.304
	Training and research hospital	-0.38234[1]	0.13071	0.020
	Private hospital	-0.21535	0.10486	0.172
University hospital	State hospital	0.21482	0.12318	0.304
	Training and research hospital	-0.16752	0.13730	0.615
	Private hospital	-0.00053	0.11296	1.000
Training and research hospital	State hospital	0.38234[1]	0.13071	0.020
	University hospital	0.16752	0.13730	0.615
	Private hospital	0.16699	0.12113	0.514
Private hospital	State hospital	0.21535	0.10486	0.172
	University hospital	0.00053	0.11296	1.000
	Training and research hospital	-0.16699	0.12113	0.514

[1]The mean difference is significant at the 0.05 level.

CONCLUSION

Even though orthopedic surgeons have enough knowledge about preventing and managing PJI, their attitudes might contradict their knowledge. Future studies that examine the causes and solutions of contradictions between orthopedic surgeons' knowledge and attitudes are required.

ARTICLE HIGHLIGHTS

Research background

Periprosthetic joint infection (PJI) is a critical complication after joint arthroplasty and increases morbidity and mortality. There have been several studies aimed at preventing PJI.

Research motivation

The treatment of PJI is difficult, and patients generally need to undergo more than one major operation and receive antibiotic treatment to annihilate the infection. Therefore, PJI also increases the cost of health services.

Research objectives

In this study the examination of knowledge about and attitudes toward preventing PJI of the orthopedic surgeons who work in Turkey has been aimed by means of a survey study. A good understanding of orthopedic surgeons' knowledge and attitudes about preventing PJI may guide new interventions to prevent PJI.

Research methods

A web-based 30-question survey was conducted in order to evaluate orthopedic surgeons' knowledge level about PJI and their attitudes towards it.

Research results

The knowledge and practices of surgeons regarding the duration of antibiotic treatment and urinary tract infections in prosthesis operations are different in Turkey.

Research conclusions

This study has shown that even though orthopedic surgeons have got enough knowledge about preventing and managing PJI, their attitudes might contradict their knowledge.

Research perspectives

The knowledge and attitudes of orthopedic surgeons may be different in practice. Future research that examines the causes and solutions concerning the contradictions between orthopedic surgeons' knowledge and attitudes are needed.

FOOTNOTES

Author contributions: Aytekin MN and Hasanoglu I designed the manuscript and collected the data; Öztürk R performed the data analysis and wrote the manuscript; Tosun N contributed by critically reviewing the manuscript; and all authors have read and approved the manuscript.

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Conflict-of-interest statement: The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Observational Study

Perceived barriers and facilitators of day-case surgery for major foot and ankle procedures? A cross-sectional survey of United Kingdom surgeons

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Abstract

BACKGROUND

Advances in minimally invasive surgery and improved post-operative pain management make it possible to consider performing even major foot/ankle operations as day-case. This could have significant benefits for patients and the health service. However there are theoretical concerns about post-operative complications and patient satisfaction due to pain.

AIM

To scope the current practice of foot and ankle surgeons on day-case surgery for major foot and ankle procedures in the United Kingdom (UK).

METHODS

An online survey (19 questions) was sent to UK foot and ankle surgeons *via* the British Orthopaedic Foot & Ankle Society membership list in August 2021. Major foot and ankle procedures were defined as surgery that is usually performed as an inpatient in majority of centres and day-case as same day discharge, with day

surgery as the intended treatment pathway.

RESULTS

132 people responded to the survey invitation with 80% working in Acute NHS Trusts. Currently 45% of respondents perform less than 100 day-case surgeries per year for these procedures. 78% felt that there was scope to perform more procedures as day-case at their centre. Post-operative pain (34%) and patient satisfaction (10%) was not highly measured within their centres. Lack of adequate physiotherapy input pre/post-operatively (23%) and lack of out of hours support (21%) were the top perceived barriers to performing more major foot and ankle procedures as day-case.

CONCLUSION

There is consensus among UK surgeons to do more major foot/ankle procedures as day-case. Out of hours support and physiotherapy input pre/ post-op were perceived as the main barriers. Despite theoretical concerns about post-operative pain and satisfaction this was only measured by a third of those surveyed. There is a need for nationally agreed protocols to optimise the delivery of and measurement of outcomes in this type of surgery. At a local level, the provision of physiotherapy and out of hours support should be explored at sites where this is a perceived barrier.

Key Words: Day-case; Foot; Ankle; Physiotherapy; Survey

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Core Tip: We have identified an appetite to increase the number of major foot and ankle procedures within United Kingdom foot and ankle surgeons who completed our survey. Despite theoretical concerns about post-operative pain and satisfaction this was only measured by a third of those surveyed. Out of hours support and physiotherapy input pre/post-op were perceived as the main barriers to doing day-case surgery in foot and ankle surgery.

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INTRODUCTION

Day-case surgery is defined as surgery performed where the patient is undergoing a planned procedure, where day surgery is the intended management plan and the patient is admitted, operated upon and discharged on the same day[1]. Day-case surgery brings recognised benefits for both patients and the healthcare system in relation to patient quality and experience, reduced bed days and significant financial savings[2]. The British Association of Day Surgery (BADS) is a multidisciplinary professional organisation which promotes day surgery by setting standards for day surgery and has developed national benchmarking for day surgery performance[1]. The Academy of Medical Royal colleges also strongly recommended that patients be given the option of day surgery wherever possible and guidelines have been produced to this effect[3]. This guideline has helped to increase the number of day-case surgeries performed. Their recommendations are aimed at surgeons and anaesthetists to offer updated guidance on changes within day surgery and how they may implement these within their practice. These were to offer guidance on day/short-stay surgery, including: The selection of patients; Social, medical and surgical factors in day-case surgery; Pre-operative preparation; Urgent cases; Management and staffing; Postoperative recovery and discharge.

There are many factors in choosing these surgeries to be inpatient or day-case such as the injury sustained, patient health and social circumstances, hospital bed availability, hospital protocols, surgical team, anaesthesia protocol *etc*[4]. There is disparity across the UK in day-case provision. In terms of orthopaedic procedures, some hip and knee surgeries are commonly performed as day-case and are effective, safe and cost-saving[5-7]. The most recent figures from Model Health System (NHS England) for the proportion of all admissions for trusts that were day-cases for all procedures was 69% (in this quartile July 2022 data based on the latest 3 months of activity with primary total replacements of hips/knees excluded from the total). For orthopaedic surgery this day-case rate was 78% (NHS England Model Health System, July 2022). However there are only 3 procedures listed within the BADS day-case directory of procedures (January 2022[1]) for foot and ankle day-case surgery (bunion operation, open

reduction and fixation of ankle, lengthening/ shortening of tendons). Therefore day-case rates for foot and ankle procedures are low.

Major foot and ankle surgery in the UK is usually carried out as an inpatient due to the complexity of surgery, pain post-surgery requiring opiates and ongoing observations required[8]. Major foot and ankle procedure include ankle and hindfoot fusion, joint replacements and tendon repair[9]. However in many cases, day-case surgery can be highly satisfactory for patients and providers in major foot and ankle cases in adults[9] and children[10]. Day-case foot and ankle surgery is known to be safe for the patient with high satisfaction rates as well as being cost effective for the service[11]. There is recent evidence showing there were little to no differences in complication rates or readmissions following foot/ankle surgeries (total ankle replacements, ankle fractures, total ankle arthroplasty and hindfoot fusions) that were performed as day-case *vs* inpatient[12-17]. However there are no specific guidelines for foot and ankle day-case surgery.

As previously outlined, there is evidence to suggest there are benefits to performing foot and ankle surgeries as day-case over inpatient procedures as well as guidance on performing surgeries as day-case. However there is a gap within the literature around what are the perceived barriers and facilitators to performing major foot and ankle surgeries as day-case and no specific guidelines for foot and ankle day-case surgery. The aim of this survey therefore was to scope the current practice of UK foot and ankle surgeons in terms of perceived barriers and facilitators to performing day-case surgery for major foot/ankle procedures.

MATERIALS AND METHODS

A cross-sectional survey (Table 1) consisting of 19 questions was created using the online platform SurveyMonkey. The questionnaire was designed following a qualitative synthesis of published literature. The questions were broken into 3 separate categories to evaluate: current practices and protocols, pre-operative and post-operative management and what are the perceived barriers and facilitators of performing major foot and ankle surgeries as day-case.

The study was reviewed and approved by the British Orthopaedic Foot and Ankle Society (BOFAS) Scientific Committee who also deemed the proposed statistical methods as appropriate. The questionnaire was sent to the membership of BOFAS *via* an administrator. It was sent to 605 recipients of whom 482 were full BOFAS members. A total of 365 recipients opened the email and 152 started the survey. For the purpose of this survey a major foot and ankle procedure was defined as surgery that is usually performed as an inpatient (*e.g.* ankle fusion, reconstruction). Day-case surgery was defined as patients that were discharged on the same day, with day surgery as the intended treatment pathway. There were two rounds of communication *via* email, the survey was then closed and data extracted into Microsoft Excel. The available data was analysed (as proportions/percentages) and free-text responses were tabulated for word clouds to be generated.

RESULTS

The survey design allowed multiple responses to some of the questions and this was taken into account in the final analysis.

Population

Out of 132 respondents, 120 were foot and ankle surgeons and 12 were trauma and orthopaedic consultants. The majority (80%) worked in acute NHS care trusts and a proportion (28%) had additional work within private or district healthcare. 20% worked in just private or district general hospitals. 11% of those working in private practice only, 29% work in district general hospitals and 7% work in both private practice and district general hospitals.

Current practices and protocols

Table 2 outlines the responses for current practices and protocols. The most responses when asked approximately how many major foot and ankle surgeries are performed in their centre in 1 calendar year was less than 100 (45%) and 200-500 (22%) with an average of 31.5% being performed as day-case. 78% of all respondents think there is a potential for more major foot and ankle surgeries to be performed as day-case in their centres. From the total respondents 48% said they did follow a protocol, 90% following their local protocol and 10% following generic national guidance.

The most common type of anaesthetic used was a combination of general and regional anaesthetic (81%) the second highest was specific blocks *e.g.* popliteal, ankle *etc.* (76%). 64% of respondents put both a combination of regional and general as well as specific blocks. 64% of respondents do not routinely discharge patients with opiate/controlled drugs post-surgery.

Table 1 Survey sent to British Orthopaedic Foot and Ankle Society membership list in August 2021

Question 1
What is your occupation?
Open-response
Question 2
In what setting do you work? Select all that apply
Acute NHS Trust -specialist foot and ankle unit
Acute NHS Trust – non specialist foot and ankle unit
District General Hospital
Community care
Private practice
Question 3
Please estimate the number of major foot and ankle procedures that your primary centre performs in 1 calendar year
Less than 20
20-50
50-75
75-100
100-200
200-500
500-1000
Over 1000
Don't know
Question 4
Please estimate what percentage of these major ankle and hindfoot procedures are performed as day case procedures
Open response
Question 5
Do you think there is potential for more of these cases to be done as day case in your own unit?
Yes
No
Question 6
Do you follow a protocol for day case procedures?
Yes- national
Yes- local
No
Unsure
Question 7
If you follow a national protocol for day case surgery, please state which one
Open-response
Question 8
Which type of anaesthesia do you offer for day case procedures? Tick all that apply
Don't know
Regional
General

Combination of GA and regional

Specific blocks

Question 9

If you use blocks, please state which

Open-response

Question 10

Do you routinely discharge day case patients with opiate/controlled drugs such as oxycodone/oromorph?

Yes

No

Unsure

Question 11

What post-op analgesia do you offer for day case procedures? Tick all that apply

Don't know

Amitriptyline

Gabapentin

Ibuprofen

Paracetamol

Codeine

Other: Please state

Question 12

Are all patients seen by physiotherapy pre-op for walking aid/ weight bearing instruction and education?

Yes

No

Unsure

Question 13

Are all patients seen by physiotherapist post-op (before discharge) for walking aid instruction and education?

Yes

No

Unsure

Question 14

Is a post-op phone call/email/text message made to the patient?

Yes

No

Unsure

Question 15

If yes who provides this contact?

Open-Response

Question 16

Which outcome measures are recorded for day-case patients? Tick all that apply

pain levels using Visual Analogue Score (VAS)

patient satisfaction, please state which measure

complication rate and type

MOX-FQ

EQ-5D
Other (please specify)
Question 17
What are the barriers for day case surgery for major foot and ankle procedures in your unit?
No provision of physiotherapist out of hours
No anaesthetist to perform peripheral nerve blocks
Lack of managerial support
Out of hours support/ point of contact for patients not available
Never done it before
No physiotherapy input at pre-assessment
Other: Please state
Question 18
Which complications have you witnessed or heard about in major foot and ankle procedures done as a day case? Tick all that apply
Wound healing problems
Wound infection
Breakthrough pain
Patient dissatisfaction
Unplanned readmission
Need for further surgery
Delayed/non-union
Other, please state
Question 19
When and how are patients first re-evaluated after discharge? Tick all that apply for
24 h face to face
24 h telephone call
1 wk face to face
1 wk telephone call
2 wk face to face
2 wk telephone call
6 wk face to face
6 wk telephone call
Other: Please state

GA: General Anaesthetic.

Pre and post-operative management

Table 3 shows all responses for pre-operative and post-operative management. Physiotherapy assessment was performed pre-operatively (61%) and post-operatively (70%). The most common post-operative analgesic drugs used are paracetamol (86%) and codeine (84%) or a combination of the two (80%). 42% offer ibuprofen, paracetamol and codeine. The majority of surgeons responded that they did not routinely discharge patients with opiates/controlled drugs such as; oramorph or oxycodone (64%).

Barriers to increasing day-case surgery in major foot and ankle procedures

The top two perceived barriers to performing day-case surgery were lack of physiotherapy input pre/post operatively (23%) and no of out of hours support (21%). Free text responses from respondents were tabulated and created into a word cloud diagram (Figure 1). The main complications respondents have witnessed/heard about in major foot and ankle surgery done as day-case were breakthrough pain (64%) and unplanned readmission (45%). Respondents most commonly reported re-evaluating patients 2

Table 2 Survey results showing current practices of major foot and ankle surgeries within their centre, *n* (%)

Factor	Result
Estimated number of major foot and ankle surgeries performed in 1 calendar year	Less than 100 (*n* = 60) (45)
	100-200 (*n* = 25) (19)
	200-500 (*n* = 29) (22)
	500-1000 (*n* = 9) (7)
	Over 1000 (*n* = 2) (2)
	Unsure (*n* = 7) (5)
Estimated procedures performed as day-case	0-50 (*n* = 99) (75)
	50-100 (*n* = 30) (23)
	Unsure (*n* = 3) (2)
Is there a potential for more to be done as day-case	Yes (*n* = 103) (78)
	No (*n* = 29) (22)
Follow a protocol for day-case	Yes Local (*n* = 57) (43)
	Yes national (*n* = 6) (5)
	No (*n* = 50) (38)
	Unsure (*n* = 19) (14)
Types of Anaesthesia offered for day-case[a]	Regional (*n* = 63) (48)
	General (*n* = 69) (52)
	Combination of regional & general (*n* = 107) (81)
	Specific blocks (*n* = 100) (76)
	Unsure (*n* = 3)
Routinely discharge with controlled drugs	Yes (*n* = 34) (26)
	No (*n* = 85) (64)
	Unsure (*n* = 13) (10)

[a]Percentage is more than 100 as respondents can select more than 1 option.

weeks post operatively, and this being face to face (90%) (Table 4).

DISCUSSION

Main findings

This survey found that there are a small number of major foot and ankle surgeries taking place as day-case within the centres of respondents. The majority of those who responded believed that there was scope to perform more major foot and ankle procedures as day-case. The main perceived barriers for performing more major foot and ankle procedures as day-case were lack of adequate physiotherapy input before or after surgery and lack of out of hours support for patients to contact in an emergency following their surgery. Although lack of physiotherapy input was one of the top perceived barriers, the majority of respondents selected yes to whether patients were seen by physiotherapy pre and post-operatively. This response was in relation to surgeon's current management with no specificity to whether this was inpatient or day-case surgery management.

Previous evidence has suggested that a concern for patients' pain and satisfaction levels post-surgery is a reason for major foot and ankle surgeries to be performed as inpatient over outpatient[8]. This survey found that majority of respondents have heard or witnessed breakthrough pain and unplanned readmissions as the top two complications to day-case surgery, however patients' pain and satisfaction levels was only measured by a third of respondents. The top two highest complications heard/witnessed by respondents agrees with previous evidence however the low response rate to measuring post-operative pain/satisfaction means it is not possible to determine whether these are a barrier to major foot and ankle surgeries being performed as day-case.

Table 3 Survey results showing pre/post-operative management of major foot and ankle surgeries within their centre, *n* (%)

Factor	Result
All patients seen pre-operatively by physiotherapy	Yes (*n* = 80) (61)
	No (*n* = 45) (34)
	Unsure (*n* = 7) (5)
All patients seen post-operatively by physiotherapy	Yes (*n* = 92) (70)
	No (*n* = 28) (21)
	Unsure (*n* = 12) (9)
Post-operative contact made to the patient	Yes (*n* = 20) (15)
	No (*n* = 92) (70)
	Unsure (*n* = 20) (15)
Outcome measures recorded for day-case[a]	VAS (*n* = 45) (34)
	Complication rate & type (*n* = 41) (31)
	Patient satisfaction (*n* = 13) (10)
	MOX-FQ (*n* = 42) (32)
	EQ-5D (*n* = 31) (23)
	Other (*n* = 7) (5)
Types of post-op analgesia offered for day-case[a]	Amitriptyline (*n* = 1) (1)
	Gabapentin (*n* = 5) (4)
	Paracetamol (*n* = 114) (86)
	Ibuprofen (*n* = 64) (48)
	Codeine (*n* = 111) (84)
	Unsure (*n* = 9) (7)
	Other (*n* = 18) (14)
	Paracetamol & codeine (*n* = 105) (80)
	Ibuprofen, codeine & paracetamol (*n* = 55) (42)
	Ibuprofen & paracetamol (*n* = 6) (5)

[a]Percentage is more than 100 as respondents can select more than 1 option.

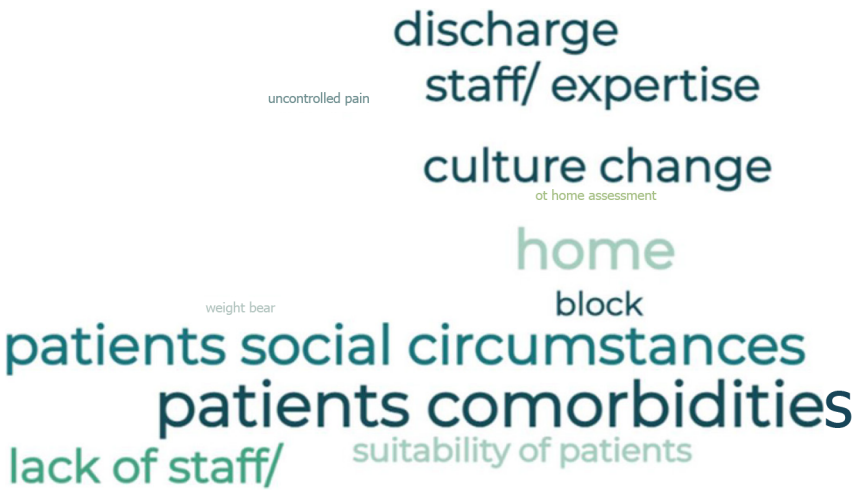
When observing the outcomes following outpatient total ankle replacements Sadoun and colleagues found that re-admission for acute care did not occur for any patient for haematoma or uncontrolled pain; only 1 patient had delayed wound healing but this did not require any implant revision[18]. The evidence for foot and ankle surgeries such as total ankle replacement and other hind foot procedures is promising and shows that they can be performed safely as day-case. There is, howevera lack of evidence around other major procedures such as ankle fusions being performed as day-case. The safety of outpatient compared with inpatient ankle surgery is comparable and therefore they suggest that outpatient ankle surgeries should be considered for patients that are suitable[19].

Recently, the Get It Right First Time (GIRFT) initiative has been working with British Association of Day Surgery (BADS) to 'address common misconceptions and making the case for expanding and increasing day case surgery, especially at a time when the NHS needs to re-start and catch up with demand for elective surgery following the Covid-19 pandemic'[2]. Part of the work of the GIRFT initiative is to develop a generic day case pathway which can be applied to specific surgical areas. Alongside this, specific best practice pathways, templates and checklists will be produced[2]. Nearly half of the respondents reported that they do follow a protocol for day-case surgeries and this was predominately a local protocol. To our knowledge there are no known national protocols for day-case foot and ankle surgery which could account for the lack of day surgeries taking place within this patient population. This is in contrast to other lower-limb orthopaedics procedures. Therefore by achieving consensus on guidelines and making them more specific for foot and ankle procedures, this may increase the amount of day-case surgeries for foot and ankle. Thereby extending the list of day-case procedures in the BADS directory [1].

Table 4 Results from the survey showing potential barriers to performing major foot and ankle surgeries as day-case within their centre, *n* (%)

Factor	Result
Barriers to performing day-case	No out of hours support (*n* = 28) (21)
	No Physio pre/post-op (*n* = 31) (23)
	No Anaesthetist (*n* = 12) (9)
	Lack of managerial support (*n* = 10) (8)
	Never been done before (*n* = 9) (7)
	Non-response (*n* = 15) (11)
	Unsure (*n* = 23) (17)
	Other (*n* = 7) (5)
Complications heard/witnessed from day-case[a]	Wound healing (*n* = 33) (25)
	Wound Infection (*n* = 23) (17)
	Breakthrough pain (*n* = 84) (64)
	Patient dissatisfaction (*n* = 33) (25)
	Unplanned readmission (*n* = 60) (45)
	Further surgery (*n* = 12) (9)
	Delayed non-union (*n* = 12) (9)
How are patients first re-evaluated after discharge[a]	24 h (Face to face, *n* = 3, 2%) (Telephone, *n* = 14, 11%)
	1 wk (Face to face, *n* = 15, 11%) (Telephone, *n* = 3, 2%)
	2 wk (Face to face, *n* = 119, 90%) (Telephone, *n* = 1, 1%)
	6 wk (Face to face, *n* = 54, 41%) (Telephone, *n* = 2, 2%)
	Other (*n* = 9) (7)

[a]Percentage is more than 100 as respondents can select more than 1 option.



DOI: 10.5312/wjo.v14.i4.248 **Copyright** ©The Author(s) 2023.

Figure 1 Word cloud for free text response to barriers to performing major foot and ankle surgeries as day-case.

Limitations

There are limitations within this scoping survey. The survey design in itself relies on accurate self-report by the respondents who may over/underestimate data from their unit. Therefore, the data should be interpreted with caution. The number of responses from the survey was relatively low (37% response rate from those who read the email invitation). This is a fairly typical response rate; however may not be

representative of the BOFAS organisation as a whole. Also the survey was only sent to surgeons; therefore there were no responses from other health professionals who manage this patient group (*e.g.* physiotherapists, plaster technicians). It may be important to capture the views of these professionals in future work. More in depth responses may also be valuable in the form of qualitative interviews/focus groups. For example, it would be useful to know more about in-operative anaesthesia, catherisation and on discharge pain medication.

Future work

Moving forwards to further explore/overcome the facilitators and barriers for performing major foot and ankle surgeries as day-case would include; out of hours support, therapy input pre and post-op, standardising outcome measures, patient education and culture shifts within patient and professionals mind sets. Breakthrough pain and unplanned readmissions were the most prevalent complications heard about/witnessed from day-case surgery in respondents and could therefore influence decisions about performing this type of surgery. Further work to address these risks is warranted. Future work should explore a cost effectiveness analysis of increasing day-case surgery in major foot and ankle procedures.

CONCLUSION

We have identified an appetite to increase the number of major foot and ankle procedures within UK foot and ankle surgeons who completed our survey. Post-operative pain and patient satisfaction was only measured by a third of those surveyed; despite theoretical concerns about these outcomes. Out of hours support and physiotherapy input were perceived as the main barriers to doing day-case surgery in foot and ankle surgery.

ARTICLE HIGHLIGHTS

Research perspectives

There is a need for nationally agreed protocols to optimise the delivery of and measurement of outcomes in this type of surgery. At a local level, the provision of physiotherapy and out of hours support should be explored at sites where this is a perceived barrier.

Research conclusions

There is consensus amongst United Kingdom (UK) surgeons to do more major foot and ankle procedures as day-case. Despite theoretical concerns about post-operative pain and satisfaction this was only measured by a third of those surveyed. Out of hours support and physiotherapy input were perceived as the main barriers.

Research results

A total of 132 respondents completed the survey and 80% worked in Acute NHS Trusts. Currently 45% of respondents perform less than 100 day-case surgeries per year for these procedures. Post-operative pain (34%) and patient satisfaction (10%) was not highly measured within their centres. The top perceived barriers to performing more major foot and ankle procedures as day-case were: Lack of adequate physiotherapy input and lack of out of hours support.

Research methods

Online survey sent to British orthopaedic foot and ankle society members. Quantitative and qualitative data collected.

Research objectives

To scope the current practices of UK foot and ankle surgeons on day-case surgery for major foot and ankle procedures.

Research motivation

Day-case is used in other orthopaedic procedures with benefits of patients and providers.

Research background

There are currently no specific guidelines for day-case surgery in major foot and ankle procedures.

FOOTNOTES

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CASE REPORT

Subclinical ankle joint tuberculous arthritis - The role of scintigraphy: A case series

Raden Andri Primadhi, Achmad Hussein Sundawa Kartamihardja

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Abstract

BACKGROUND

Tuberculosis remains a complicated problem. A lack of awareness accompanied by difficulty in diagnosis hinders the management of tuberculosis. Delayed management, particularly in osteoarticular regions, results in unnecessary procedures, including joint-sacrificing surgery.

CASE SUMMARY

Three cases of subclinical ankle joint tuberculosis without clear signs of tuberculosis were presented. The efficacy of technetium-99m-ethambutol scintigraphy in diagnosing early-stage tuberculous arthritis is reported.

CONCLUSION

The reports suggested that scintigraphy is recommended to diagnose subclinical tuberculous arthritis, especially in tuberculosis endemic regions.

Key Words: Ankle; Infectious arthritis; Ethambutol; Scintigraphy; Tuberculosis; Case report

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Core Tip: Tuberculosis may present in a subclinical state that hindered the diagnosis and subsequent management. Technetium-99m-ethambutol scintigraphy is a useful noninvasive method to detect early stage of joint tuberculosis in which morphological and laboratory changes are still unclear. By using this method, earlier diagnosis and prompt intervention can be made especially in tuberculosis endemic regions, to avoid unnecessary procedures resulting from disease advancement.

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INTRODUCTION

Tuberculosis remains a currently public health problem worldwide, especially in developing countries. The resurgence of this disease, which began in the mid-1980s after a period of decreasing incidence, has been influenced by poverty, failures in the treatment system, immigration, and, unsurprisingly, the human immunodeficiency virus (HIV) epidemic[1,2]. Tuberculosis affects not only the lungs but also any other organs in the body, which is known as extrapulmonary tuberculosis, including osteoarticular sites. Tuberculosis of the foot and ankle is exceedingly rare, accounting for approximately one percent of all cases of osteoarticular tuberculosis[3-5].

The relative infrequency of foot and ankle tuberculosis may result in a lack of awareness among health care providers, and when combined with the similarity of tuberculosis symptoms with those of other diseases, diagnostic delays often occur[5]. The clinical features of this condition at early stages are nonspecific and may result in inadequate treatment and subsequent damage[4]. Subclinical tuberculosis occurs in asymptomatic, immunocompromised hosts, with loss of effective containment. Therefore, subclinical tuberculosis rapidly progresses if left untreated[6].

The final diagnosis of tuberculosis can be made by histopathological testing and/or microorganism culture. However, these methods are hindered by their long processing time and the difficulty of obtaining adequate specimen tissues. Nuclear medicine modalities, particularly Technetium-99m-Ethambutol scintigraphy, are quick and effective methods to diagnose tuberculosis even at an early stage of the disease[3,7].

This report describes three cases of subclinical ankle joint tuberculosis with diagnostic difficulty that were subsequently diagnosed by scintigraphy. All scintigraphy procedures were carried out in the Department of Nuclear Medicine and Molecular Imaging, Hasan Sadikin Hospital, Bandung, Indonesia. Informed consent for publications was obtained from all patients or family. This case series was recognized and approved by Hasan Sadikin Hospital Institutional Review Board No. LB.02.01/X.6.5/250/2022.

CASE PRESENTATION

Chief complaints

All patients presented a slight pain and swelling on their ankle joints for several months.

History of present illness

Case 1: A 17-year-old female presented with slight pain and swelling of the bilateral ankle. The complaint slowly worsened, starting four months prior to the hospital visit. There was no history of injury near the ankle, swelling in any other body regions, fever, chills, or unexpected weight loss. She had taken analgesics for one month, but the pain and swelling remained.

Case 2: A 22-year-old female was referred to our foot and clinic for a chronic ankle sprain resulting from a low-energy trauma. Initial treatment from a previous hospital included immobilization with a semirigid cast for three weeks followed by protective partial weight bearing, along with anti-inflammatory analgesics. After six weeks, she still complained of pain, swelling, and limited motion.

Case 3: A 36-year-old female presented with slight pain and a swollen right ankle that had lasted for two months. There was no history of injury near the ankle, swelling in any other body regions, fever, chills, or unexpected weight loss. She had been given anti-inflammatory analgesics, but the pain and swelling persisted.

History of past illness

No relevant history of past illness was found in Case 1 and 2. However, Case 3 present a pulmonary tuberculosis that might be related to current symptoms.

Personal and family history

No relevant personal and family history was found in all cases.

Physical examination

Case 1: The patient appeared healthy based on general appearance. Upon physical examination, slight swelling was observed by inspection and palpation (Figure 1A). Pain was induced by direct pressure and joint motion, especially ankle dorsiflexion.

Case 2: The patient presented at the clinic using crutches due to difficulty and pain while walking. Swelling was visible on the whole ankle, including the lateral and medial sides (Figure 1C). Pain was induced with palpation and ankle joint movement.

Case 3: She was undergoing pulmonary tuberculosis treatment and had been administered anti-tuberculosis therapy for four months. On physical examination, slight swelling was observed in the ankle region by inspection and palpation (Figure 1E). She was still able to walk normally.

Laboratory examinations

Case 1: Laboratory blood tests showed normal values, including a white blood cell (WBC) count of 8.6 × 10^9/L, erythrocyte sedimentation rate (ESR) of 9 mm/h, and C-reactive protein (CRP) level of 3 mg/L. Other biochemical parameters were within the normal range, and chest radiography was unremarkable.

Case 2: The WBC count was 11.0 × 10^9/L, ESR was 20 mm/h, and the CRP level was 4.9 mg/L. Other laboratory results were within normal reference values.

Case 3: Laboratory blood tests showed a WBC count of 10.4 × 10^9/L, ESR of 25 mm/h, and CRP level of 7.4 mg/L. Other biochemical parameters were within the normal range.

Imaging examinations

Case 1: Plain ankle radiography was inconclusive, showing no localized bony lesion, osteoporosis, or articular changes (Figure 1B).

Case 2: Ankle radiography showed soft tissue swelling without remarkable bony derangement (Figure 1D).

Case 3: Narrowing joint space was observed on plain ankle radiography (Figure 1F).

FINAL DIAGNOSIS

Referring to positive scintigraphy results (Figure 2), all patients were diagnosed as tuberculous arthritis of ankle joint.

TREATMENT

All patients were subsequently given anti-tuberculosis therapy according to extrapulmonary tuberculosis treatment protocol.

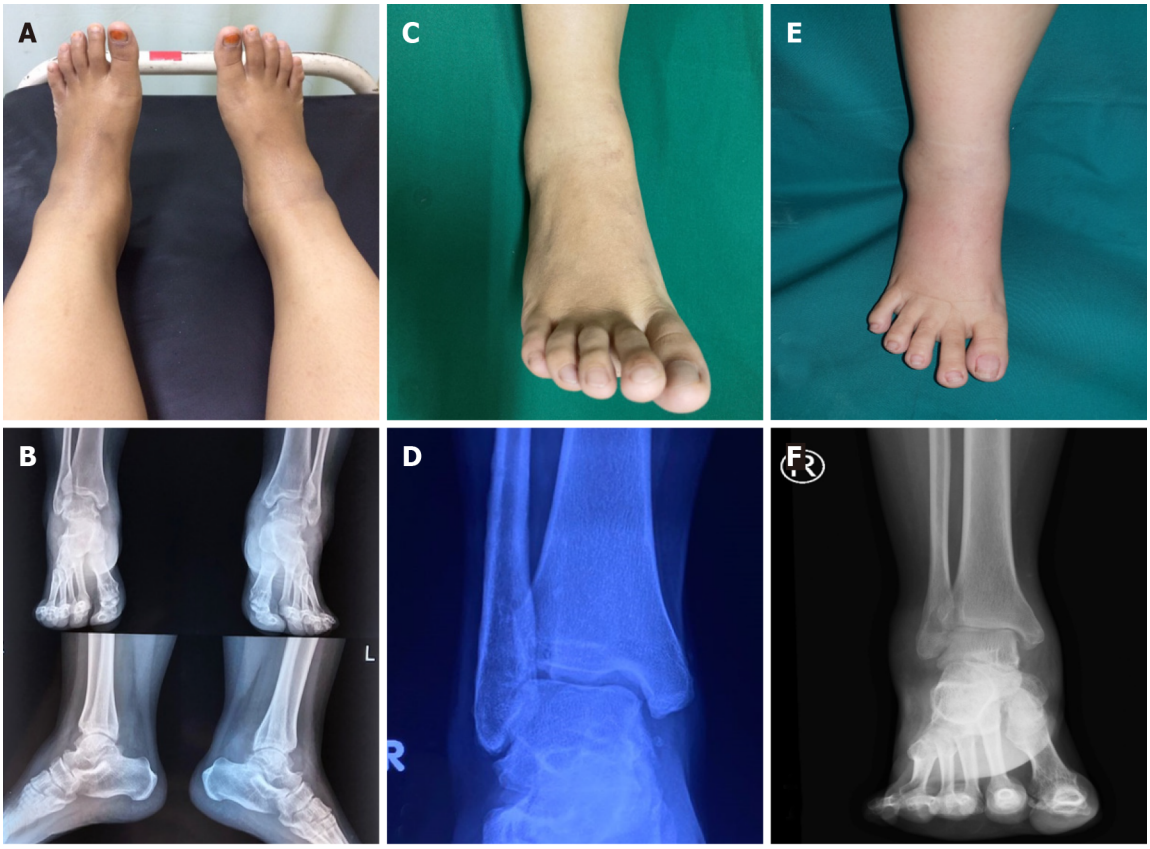
OUTCOME AND FOLLOW-UP

Case 1

After the completion of therapy, the symptoms had improved, and she returned to normal daily activities.

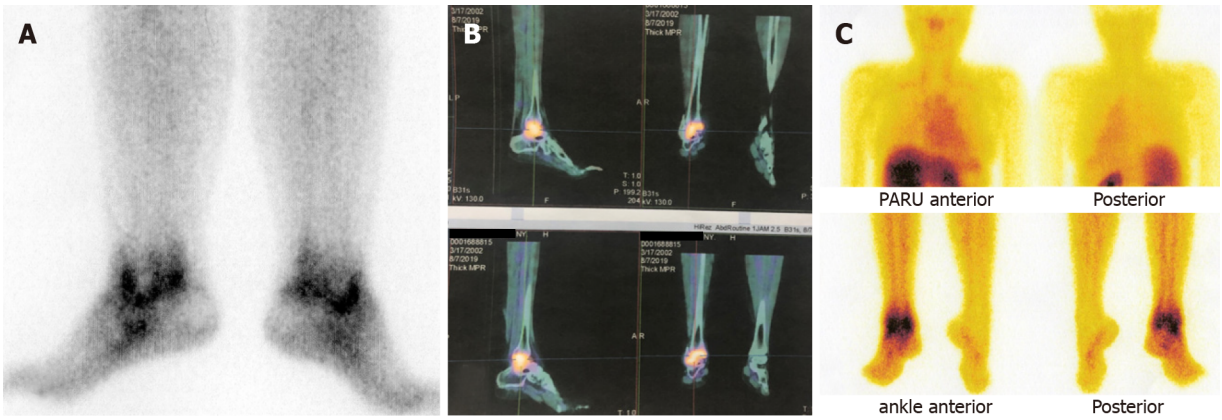
Case 2

The symptoms improved afterward, although the patient still needed physical therapy due to ankle arthrofibrosis.



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Figure 1 Clinical and radiological images of case 1, 2, and 3, respectively. A, B: Case 1; C, D: Case 2; E, F: Case 3.



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Figure 2 Scintigraphy images of case 1, 2, and 3, respectively. A: Case 1; B: Case 2; C: Case 3.

Case 3

After the completion of therapy, the symptoms improved, although the swelling did not completely resolve.

DISCUSSION

Subclinical tuberculosis disease is difficult to identify. It may be entirely asymptomatic or may present subtle symptoms that are underreported according to classic tuberculosis symptom screenings. Tuberculous arthritis shows wide variability in clinical symptoms and imaging appearance, ranging from asymptomatic with normal radiographic examination to severe joint pain along with joint destruction. Its slow progression and chronicity cause patients to present with subtle symptoms and

signs, resulting in delayed diagnosis. The identification of people who have asymptomatic tuberculosis is a diagnostic challenge[8,9]. From a public health perspective, the concern is whether these people are infectious or not[10]. The significance from an osteoarticular problem standpoint is that timely intervention will help avoid the sequelae of joint destruction and disability that require joint-sacrificing surgical procedures, such as ankle fusion or arthroplasty.

Clinical features of tuberculosis are nonspecific and may overlap with other conditions, including pyogenic osteomyelitis or arthritis, bone tumors, pigmented villonodular synovitis, avascular necrosis of the talus, and other inflammatory processes[4,11]. However, the diagnosis of mycobacterial arthritis should be entertained when chronic monoarticular arthritis is encountered. The Phemister triad is an eponym that refers to three classic radiological features seen in tuberculous arthropathy: (1) Juxta-articular osteoporosis; (2) peripheral osseous erosions; and (3) gradual narrowing of joint spaces (Figure 3)[12]. A flaky sequestrum in a cavity and/or dystrophic calcification in soft tissue are suggestive of tuberculous pathologies[5]. Specialized investigations, such as computed tomography (CT) or magnetic resonance imaging, may be helpful to assess signals, synovial proliferation, and bone marrow edema. However, radiological findings are still often inconclusive and lack specific findings, especially at an early stage. By the time bony destruction appears, the tuberculosis disease process is severe and capable of contiguous or hematological spread to the sites[13]. Confirmatory tests included the isolation of acid-fast bacilli on specialized culture media and histopathological findings depicting a chronic granulomatous inflammatory process with multinucleated giant cells (Figure 4). A positive Mantoux tuberculin skin test can be obtained in patients with long-standing tuberculosis but is also considered not specific since it can also be obtained in vaccinated populations and in people in endemic areas[5].

Some inflammatory markers, such as those measured in laboratory blood tests, reflect the activity of tuberculosis. In tuberculosis patients, the serum hemoglobin level, red blood cell count, and platelet count are decreased, whereas ESR, CRP, and WBC are increased compared with controls[14]. ESR is an inflammatory marker and reflects the sedimentation of erythrocytes after a period of 60 min. In the acute inflammatory phase, increased serum proteins neutralize red blood cells, resulting in stacking aggregation and subsequent increased ESR[15]. A prior study reported that although an elevated ESR may be expected in tuberculosis patients, one-third of children had a normal ESR at the time of diagnosis[16]. CRP is considered a favorable tool for active tuberculosis screening[17]. CRP is an acute-phase reactant protein that is primarily induced by IL-6 during the acute phase of an inflammatory/infectious process[18]. There are numerous causes for elevated CRP, including acute or nonacute and infectious or noninfectious. Trauma can also cause CRP elevation. However, it is most often associated with infection. The WBC count is increased during infection due to the body's immune defense mechanism that combats invading bacteria, in which the numbers of polymorphonuclear and macrophage cells increase[14]. In these reported cases, all patients' WBC, ESR, and CRP data were within the normal range. Considering the inconsistency of laboratory results for tuberculosis diagnosis, adjunct examination is still needed to establish the diagnosis.

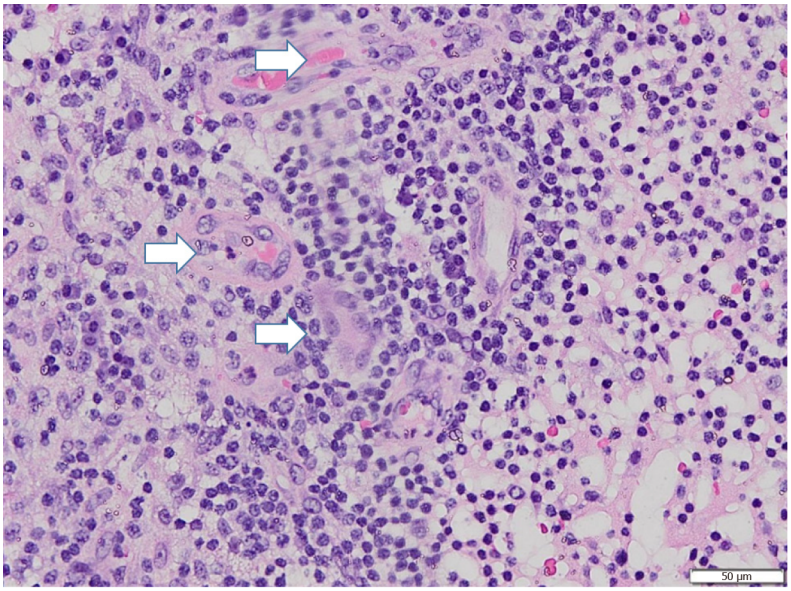
Nuclear medicine scintigraphy is known as a noninvasive diagnostic modality with high sensitivity and specificity for detecting and locating the lesion at an early stage. The metabolic activity of the skeleton can be visualized by bone scan. Nuclear scintigraphy of the bone commonly utilizes the radionuclides technetium-99m or fluoride-18. These molecules are intravenously injected, and then a dual-head SPECT-CT gamma camera is used to capture the decay of photons from the radioisotope at the suspected site[3,19]. Ethambutol is an active specific antibiotic against mycobacterium. Technetium-99m-labeled ethambutol is specifically taken up by *Mycobacterium tuberculosis* and detected under a gamma camera at 1 h and 3 h after the intravenous injection of 370-740 MBq. Technetium-99m-ethambutol remains in tubercular lesions as it is bound to mycolic acid in the cell wall of bacteria but is cleared from nontubercular lesions[7]. The image interpretation was as follows: (1) Normal scan, if there was no pathologically increased uptake other than the normal uptake in the kidney, urinary bladder, liver, and spleen; (2) positive scan, if pathological uptake was observed at the suspected site and gradually increased with time; and (3) negative scan, if pathological uptake was observed at 1 h and gradually decreased (washed out) at the 3-h image[3]. Negative scan implies that the tuberculosis infection is not established, as the strong bond between technetium-99m-ethambuthol and the mycobacteria is not formed. Other radiopharmaceutical agents have also been introduced, such as ciprofloxacin and isoniazid. Technetium-99m-ciprofloxacin can be useful for bacterial infection imaging but cannot differentiate tuberculosis from other bacterial infections, as it acts as a broad-spectrum antibiotic that can be taken up by any living bacteria. Technetium-99m-isoniazid has also been developed but is not widely used clinically[7,20]. This method results in only minimal or no side effects, since the dosage of radiotracer given to the patient is only 2 mg and excreted through the physiological process[3].

The basic principles of tuberculosis control include early detection and well-timed management of the affected patients. There was a clear association between delay of treatment and clinical severity at presentation due to the longer time for disease progression[21]. In general, in septic arthritis, when the infection is not cleared quickly, the potent activation of the immune response with the associated high levels of cytokines and reactive oxygen species leads to joint destruction through glycosaminoglycan loss[22]. The infection process also promotes joint effusion that increases intra-articular pressure,



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Figure 3 Radiological image depicting Phemister Triad.



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Figure 4 Histopathological image showing multinucleated giant cells (arrows).

mechanically hindering blood and nutrient supply to the joint and causing damage to the synovium and cartilage[22]. In tuberculous arthritis, cartilaginous tissue is more resistant to destruction. However, penetration of the epiphyseal cartilage plate occurs more often in tuberculous disease than in pyogenic infection . In these cases, anti-tuberculosis drugs were directly given to the patients after a positive scan. All patients had received systemic antituberculosis drugs under an extrapulmonary tuberculosis treatment protocol consisting of two months of combined rifampin, isoniazid, pyrazinamide, and ethambutol, followed by ten months of rifampin and isoniazide. This treatment approach was in line with a prior report that allowed the anti-tuberculosis regimen to proceed to the histopathological examination first[3]. In our institution, technetium-99m-ethambutol scintigraphy has been chosen for many orthopedic cases with tuberculosis suggestion. Kartamihardja *et al*[7] had reported that as much as 78% subjects with tuberculosis infection were positive on both technetium-99m-ethambutol scintigraphy and microbiological/histopathological findings, and 14.9% subjects presented negative results on both examinations, yielding more than 90% specificity. However, there are still 12 (7.1%) discordant results between examinations[7].

CONCLUSION

This report showed that technetium-99m-ethambutol scintigraphy is simple and effective for detecting subclinical tuberculosis in the ankle joint. Patients with a positive result could be directly treated with anti-tuberculosis drugs. The advantages of this method include the rapid results, noninvasive features,

ability to detect disease in early stages, and avoidance of the risk of inadequate tissue specimens. The use of this method for diagnosing such cases should be advocated, especially in tuberculosis endemic regions, to avoid treatment delays.

FOOTNOTES

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EVIDENCE REVIEW

Unhappy triad of the knee: What are the current concepts and opinions?

Amir Human Hoveidaei, Reza Sattarpour, Haleh Dadgostar, Saeed Razi, Mohammad Razi

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Abstract

The association between injuries to the anterior cruciate ligament, medial collateral ligament, and medial meniscus (MM) has been known to orthopedic surgeons since 1936; O'Donoghue first used the term "unhappy triad" of the knee to describe this condition in 1950. Later studies revealed that involvement of the lateral meniscus is more common than MM in these cases, leading to a change in the definition. Recent studies have revealed that this triad may be primarily linked to knee anterolateral complex injuries. Although there is not a definite management protocol for this triad, we try to mention the most recent concepts about it in addition to expert opinions.

Key Words: Anterior cruciate ligament; Lateral meniscus; Anterolateral complex; Medial collateral ligament; Medial meniscus

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Core Tip: Traditionally, the anterior cruciate ligament (ACL), medial collateral ligament (MCL), and medial meniscus (MM) were thought to be the unhappy triad of the knee; however, lateral meniscus injuries are thought to be more common in association with ACL and MCL tears. Clinicians, radiologists, and orthopedic surgeons should be aware of the unhappy triad of the knee, while performing physical examinations, radiologic assessments, or knee arthroscopy. MCL spontaneous healing is possible in some cases with lower grades of tear; however, consideration of patient knee alignment and accuracy in MCL size for non-operative treatment decision-making is critical.

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INTRODUCTION

Overview: Medial meniscus or lateral meniscus, triad or tetrad?

Campbell first described a "combination" knee injury in 1936[1], which included injury to the anterior cruciate ligament (ACL), medial collateral ligament (MCL), and medial meniscus (MM), but the term "unhappy triad" was not used until O'Donoghue (1950) reported that about a quarter of all acute athletic knee injuries involve damage to the ACL, MCL, and MM. The MM was initially suspected as the main site of injury compared with lateral meniscal (LM) tears, and O'Donoghue found that only 3% of his sample of 33 patients had LM injuries[2,3]. However, arthroscopy studies showing the higher prevalence of LM tears shifted this dominance[4-6]. The definition of "medial meniscus injury" might have been misunderstood. Perhaps what O'Donoghue considered a MM injury was actually a capsular injury[7].

Extreme reflectoric muscle contractions brought on by rotational stress may result in chondromalacic lesions in the femoro-patellar joint, expanding the "unhappy triad" syndrome into the "unhappy tetrad [8]. According to Müller *et al*[9], the fourth component of this tetrad is antero-lateral femoro-tibial ligament lesions. These are the distal posterior portions of the iliotibial tract that pass from the linea aspra to Gerdy's tubercle[10]. The jerk test, a type of pivot-shift test, can be used to assess anterolateral rotatory instability[11], and magnetic resonance imaging (MRI) has been shown to be useful[12]. According to some studies, anterolateral ligament abnormalities can increase the risk of a complete ACL tear and collateral ligament injuries[13,14]. Nonetheless, the MM is intact in these patients[15].

The injury pattern in the lateral compartment is usually stretching and hemorrhage of the antero-lateral capsule; Segond's fracture is less reported[10]. Ferretti *et al*[16] reported anterolateral capsule and ligament injuries in isolated ACL injuries. They also announced a new classification for this type of injury: Type I (stretching and bleeding in the anterolateral capsule alone), type II (stretching and bleeding from the front to the back), type III (complete tear of the anterolateral ligament [ALL]), and type IV (bone avulsion and Segond's fracture).

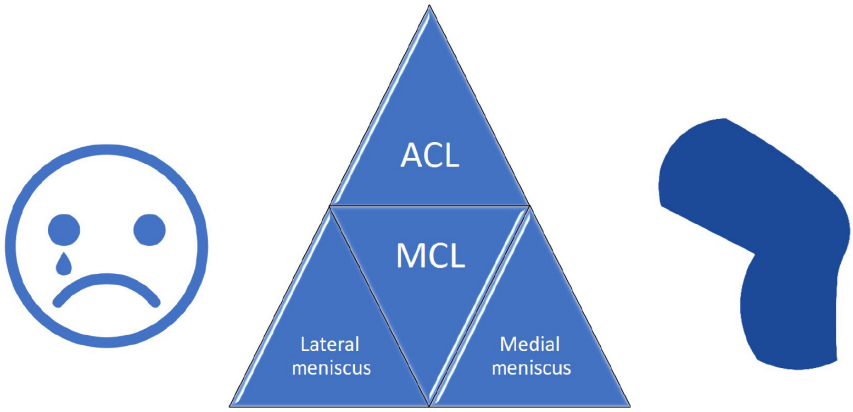
Recent studies have focused on the anterolateral femur-tibial ligament as a stabilizer of the knee's internal rotation and pivotal shift[17-19]. So, repairing these ligament injuries could help people who are getting their ACLs reconstructed.

Grading of MCL injuries is based on joint space widening by applying a valgus force on a 0-30° flexed knee[11,20,21]. Seventy-eight percent of MCL grade III injuries are associated with ACL injuries[22]. Shebourne and Posch proposed that parallel meniscus injuries have a relatively protective effect for higher-grade injuries[20,21].

In general, we can conclude that this triad should be defined as concomitant ACL, MCL, and MM/LM injuries, mostly associated with the anterolateral complex of the knee (Figure 1).

EPIDEMIOLOGY, MECHANISM OF INJURY, AND TYPE OF SPORTS

O'Donoghue reported an incidence as high as 25% of the "unhappy triad" in acute athletic knee injuries, and in a study of 22 patients with combined ACL and MCL injuries, it was found that 17 (or 77%) of them had an associated MM tear. However, later studies showed more dominant LM injuries. Shelbourne *et al*[23] found a 32-71% prevalence of LM injury while finding significantly lower rates of MM injury, even 0% in one of their study groups. The mechanism of injury in the unhappy knee triad is sudden valgus impact with external or internal rotation[16]. However, it is controversial whether the MCL or ACL is injured first[24,25].



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Figure 1 Unhappy triad of the knee. ACL: Anterior cruciate ligament; MCL: Medial collateral ligament.

This triad often occurs in contact and non-contact sports such as netball, basketball, soccer, skiing, and rugby[26,27]. A recent study, for example, discovered that the ACL was involved in all skiers' knee injuries[21], contrary to the popular belief about the MCL's dominance[28].

CLINICAL PRESENTATIONS

Immediately after trauma, the "unhappy triad" is observed. Swelling, hemorrhage, and serous effusion form after hours and accompany the meniscal and ligament injuries. However, in disrupted capsular injuries, effusion can be negated[29]. There is pain, impaired muscle control, edema, and reflex muscle inhibition in the acute phase. Through an accurate history and physical examination, we can determine injured structures. When rotating on a fixed knee, the majority of patients reported hearing a snapping click noise. Physical examinations, usually the Lachman test, pivot shift test, anterior drawer test, and valgus stress test, are positive, and patients have localized tenderness through the MCL[10,30]. Some patients have patellar instability because of a concomitant injury to the medial patellofemoral ligament and a superficial part of the MCL[27].

DIAGNOSTIC IMAGING TOOLS

X-ray images are not used often because of their low input except for insertion site bone avulsions and lower limb alignment. Using valgus stress X-ray, we can classify injuries into complete medial side tears and isolated high-grade MCL injuries by measuring the opening of medial tears[31]. Valgus stress X-ray results depend on patients' pain and muscular relaxation and could not be accurate in patients with higher degrees of immobility[32]. MRI and arthroscopy are considered accurate diagnostic tools for ACL injuries (around 90% sensitivity), but a blind arthroscopic approach could result in inappropriate treatment for 35% of patients[33,34]. We can use MRI to detect medial side and meniscus injuries, as well as cartilage injuries. As said, lateral side bruises and MRI findings can indicate a higher grade of injury in the medial compartment[27].

MANAGEMENT

Most cases require surgery and a recovery period of 6 to 9 mo. Reconstruction and repair of the ALL lesions should be considered to improve the control of rotational stability and future knee kinematics scores provided by ACL reconstruction. For high-risk patients, a combined ACL and ALL reconstruction improves rotational control and reduces the rate of re-rupture without increasing postoperative complication rates compared to an ACL-only reconstruction[35-39]. However, it needs further investigation for different degrees of injury[39,40]. Another important aspect of surgery is determining whether we can choose a conservative approach for MCL injuries in patients with an unhappy triad (tetrad). Treatment of MCL injuries evolved from an aggressive surgical approach[5,41] around 1960 to non-operative MCL treatment and early range of motion regarding the extra-articular healing ability of the MCL[42,43]. This healing potential is because of the enriched blood supply of the medial compartment of the knee. The Hughston grading system can be used to classify MCL injuries: Applying valgus stress opening in MCL tears between 1 and 5 mm is considered grade I; between 5 and

10 mm is considered grade II; and more than 10 mm is considered grade III[44]. In the original Hughston grading system, grades I and II injuries are named after incomplete MCL injuries, which are not present in the unhappy triad (tetrad). Several studies have highlighted that non-operative and operative managements of MCL injuries have similar satisfactory results, but these patients only had ACL injuries parallel to the MCL[27,45-47]. Patients with the unhappy knee triad (tetrad) with grades I and II MCL injuries can be treated conservatively (using injections and physiotherapy) with a delay in ACL reconstruction, allowing the MCL to heal by itself[48]. It is essential to note that early range of motion is recommended because of better collagen organization and healing outcomes[49]. Grade III injuries and competitive athletes are better treated surgically because of the risk of future ACL reconstruction failure, knee osteoarthritis, which has an increasing burden, and valgus knee instability [50,51]. The reason may be the disruption of menisco-tibial and menisco-femoral attachments during injuries involving deeper layers of the medial compartment (deep MCL). Even so, some studies show satisfactory outcomes in the non-operative management of isolated MCL grade III injuries, but confounding factors such as parallel ACL and meniscal injuries are not considered[52,53]. Meniscus repair is the other consideration that surgeons need to address. The MM is usually repaired because of its role in knee stability and protective effect on osteoarthritis[54].

PROGNOSIS

The unhappy triad can cause osteoarthritis in 50% of patients in 10-20 years due to intra-articular processes initiated by injury. Also, MCL injuries can cause long-term knee instability and increase susceptibility to meniscus injuries[26,55]. The osteoarthritis risk is not covered by anyone, with its pain and function impairment playing a major role in these patients, but the most important question is its rate in these patients and treatment outcomes. In Lundberg's study, 13% of patients with MCL injuries treated non-operatively showed radiographic signs of osteoarthritis[56]. Ochiai *et al*[57] found that in patients with injuries to the ACL, MCL, and LM, reconstruction of the ACL with or without the MCL and LM significantly improved the outcome. However, scores were higher in the group with a conservative approach to MCL. Physiotherapy, early range of motion, and limited weight bearing after reconstruction can improve knee mobility[58]. Using knee braces in high-grade injuries can help keep the knee in correct healing alignment, but it needs further study for long-term outcomes[59].

CONCLUSION

Even with recent studies, choosing between the conservative and operative approaches remains controversial among clinicians. In some cases, spontaneous healing of the MCL occurs without a surgical intervention[60]. Using some expert recommendations, we propose that patients with the unhappy triad of the knee who have varus alignment in the physical examination could undergo a conservative approach, meaning MCL non-operative treatment and ACL reconstruction surgery. These patients should be observed for complications like patellofemoral subluxation and pain. Although some previous studies have mentioned that low grade MCL tearing may not require surgical intervention, considering the fact that MCL tear size estimation without performing arthroscopy may not be accurate, we recommend operative treatment in patients with valgus and normal alignments.

FOOTNOTES

Author contributions: Hoveidaei AH and Sattarpour R contributed equally to the work. All authors contributed to the conception and design of the study; Hoveidaei AH, Sattarpour R, and Razi S drafted the article; Dadgostar H and Razi M made critical revisions related to the important intellectual content of the manuscript; all authors approved the final version of the article to be published.

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REVIEW

Tuberculosis of the spine

Wattana Leowattana, Pathomthep Leowattana, Tawithep Leowattana

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Abstract

Pott's spine, commonly known as spinal tuberculosis (TB), is an extrapulmonary form of TB caused by Mycobacterium TB. Pott's paraplegia occurs when the spine is involved. Spinal TB is usually caused by the hematogenous spread of infection from a central focus, which can be in the lungs or another location. Spinal TB is distinguished by intervertebral disc involvement caused by the same segmental arterial supply, which can result in severe morbidity even after years of approved therapy. Neurological impairments and spine deformities are caused by progressive damage to the anterior vertebral body. The clinical, radiographic, microbiological, and histological data are used to make the diagnosis of spinal TB. In Pott's spine, combination multidrug antitubercular therapy is the basis of treatment. The recent appearance of multidrug-resistant/extremely drug-resistant TB and the growth of human immunodeficiency virus infection have presented significant challenges in the battle against TB infection. Patients who come with significant kyphosis or neurological impairments are the only ones who require surgical care. Debride-ment, fusion stabilization, and correction of spinal deformity are the cornerstones of surgical treatment. Clinical results for the treatment of spinal TB are generally quite good with adequate and prompt care.

Key Words: Tuberculosis; Pott's disease; Spinal tuberculosis; Kyphosis; Medical treatment of spinal tuberculosis; Surgical treatment of spinal tuberculosis; Drugs resistance

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Core Tip: Pott's spine is a type of spinal tuberculosis (TB) characterized by hematogenous dissemination of mycobacterium from a primary lesion. It accounts for roughly half of all skeletal TB patients. The most frequent type of spinal TB is para-discal TB. Untreated infections can result in consequences such as a cold abscess, paraplegia, and deformity, all of which may necessitate surgical intervention. Rapid molecular approaches have aided in the detection of spinal TB and drug resistance, but it remains difficult due to sample collection issues and the paucibacillary nature of spinal TB. The presence of human immunodeficiency virus, which is endemic in some areas, increases the burden and complexity of care. Moreover, the emergence of multidrug-resistant TB and extremely drug-resistant TB has posed a big challenge in the management.

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INTRODUCTION

Tuberculosis (TB) is a disease characterized by poverty, economic distress, vulnerability, stigma, and discrimination[1-3]. TB affects roughly one-quarter of the world's population. In 2021, 10.6 million people were infected with TB, equating to 134 cases per 100000 people. Human immunodeficiency virus (HIV)-positive individuals accounted for 6.7% of all TB cases. Geographically, the WHO areas of South-East Asia (45%), Africa (23%), and the Western Pacific (18%) had the highest percentages of TB cases in 2021, while the Eastern Mediterranean (8.1%), the Americas (2.9%), and Europe (2.2%) had the lowest percentages[4]. Despite being a disease that may be prevented and treated, TB is still not completely under control on a worldwide scale. This is caused by a variety of factors, such as rising HIV infection rates, drug misuse, an increase in the population of developing nations, and the migration of people to developed countries. Involvement of the skeletal system has been documented in 1%-2% of all TB patients and 10% of extrapulmonary TB cases[5,6]. More than half of all skeletal TB patients are caused by spinal TB, which commonly affects the productive age group and is costly to the family and the nation. It is more common in developing countries, where many people continue to live in poverty, have poor nutrition, are overcrowded, and lack proper hygiene. There is no difference in susceptibility to TB depending on gender. Because of longer life expectancies, diabetes, cancer therapy, HIV, and greater use of immunosuppressive drugs, spinal TB is becoming more common among the elderly[7,8].

The clinical presentations of spinal TB are often mild. Patients may show up with typical symptoms including weight loss, evening fever, lack of appetite, and back pain that doesn't go away with physiotherapy, or they may show up with no symptoms at all. The importance of taking a detailed history and completing a thorough examination of the spine and other joints cannot be overemphasized. A TB family history, interactions with a patient with active TB, habits, and socioeconomic situations might all be indicators of an early diagnosis. After the clinical examination, one should be able to recognize the pathology and any new issues that may require further testing and treatment.

SIGNS AND SYMPTOMS

According to several retrospective studies, the lower thoracic and upper lumbar vertebrae account for 90% of individuals with spinal TB. Overall, the thoracolumbar junction is most frequently affected, followed by the lumbar, and cervical areas. The biomechanical change from an inflexible thoracic spine to a dynamic lumbar spine makes the thoracolumbar area susceptible to microtrauma, which may facilitate the seeding of TB bacteria. This region is commonly affected. TB bacteria often migrate from a primary location, such as the lungs or genitourinary system, to the vertebral body *via* a hematogenous pathway[9-13]. Each vertebra has a rich vascular plexus in the subchondral region, which makes it easier for TB bacteria to spread to the paradisiacal area. Two neighboring vertebrae are supplied by the same segmental artery, so often both are affected. A valveless system known as Batson's venous plexus connects the spine to the intra-abdominal and intra-thoracic chambers. Whereas TB bacilli propagating through the Batson's plexus generate core lesions in the vertebral body as well as involvement of non-contiguous vertebrae, dissemination through the anterior or posterior longitudinal ligaments leads in the involvement of numerous contiguous vertebrae[14,15]. The proportion of non-contiguous spinal involvement in skeletal TB was 63.6%, according to a published case series using FDG-PET SCAN to assess therapy response[16].

The clinical presentation is generally determined by a number of parameters, such as age, location of the lesions, duration, and so on. Immunological conditions, co-morbidities, and the emergence of issues such as a cold abscess, deformity, secondary infection, and neurological sequelae further complicate the neurological picture. The most common symptom is chronic low back pain, which is subtle at first, gradually worsening, dull and aching in nature, and typically non-radiating. There may be a link between constitutional symptoms such as malaise, lack of appetite, and weight loss. There may have been previously healed cases of pulmonary TB, cases in other places, or contact with a patient who had the disease[17,18]. Nighttime discomfort is a hallmark of this condition. If it's there, it wakes the sufferer. The absence of a protective muscle spasm, which indicates the spine's instability, is associated with the abrupt, excruciating pain. Night discomfort in the supine position is also connected to swelling and venous engorgement. Back pain in skeletal TB is particularly resistant to conservative treatment. When a root is squeezed owing to abscess development or a bone fragment, radicular pain might be a presenting symptom. Radicular discomfort directed to the belly might be mistaken for cholecystitis, pancreatitis, appendicitis, and renal disorders, leading to a delay in diagnosis and, in some cases, inappropriate examinations and operations[19]. There is muscular spasm on examination, which might manifest as prominent paraspinal muscles in the thoracolumbar spine and sciatic pain due to a unilateral spasm. Local sensitivity for the affected area might be evoked. Patients move with extreme caution while supporting the afflicted portion. The "Tripod Sign" with thoracolumbar spine involvement is one of the symptoms of skeletal TB[20,21].

Neurological deficit

Neurology is involved in 23% to 76% of cases of spinal TB. As the spinal cord terminates at L1 and the canal is somewhat large here, paraparesis is more common in the thoracic and cervical spines than below L1. Neurological symptoms might range from minor gait problems to total bladder and bowel incontinence. Patients in impoverished regions typically present after experiencing weakness. Patients first walk awkwardly and slowly as a result of their discomfort and weakness. Weakness in all four limbs is a sign of cervical cord compression. Whereas lumbar spine involvement is defined by lower motor neuron symptoms, thoracic cord compression is characterized by paralysis in both lower limbs, including or excluding bladder and bowel involvement[22]. When a disease is actively spreading or the body is healed slowly, paresis might develop. The active state is produced by either direct compression from an abscess, inflammatory tissue, sequestrum, or instability, or intrinsic causes such inflammation, meningitis, infective thrombi, or vascular damage brought on by endarteritis. Paraplegia is caused by the spinal cord expanding over the internal gibs, bony ridges, scarring, or disease recurrence in cured diseases.

With a spinal cord compression, motor function frequently deteriorates first, followed by sensory and autonomic impairments. Compression frequently starts anteriorly in an anterior lesion and progresses posteriorly. Spasticity may first develop without the patient being aware of it. During a clinical examination, it can be identified by brisk deep tendon reflexes and an extensor plantar response. The anterior columns gradually get implicated as a result of increased compression, which results in a loss of motor function. Further compression results in involvement of the lateral spinothalamic pathways, which results in a loss of pain, warmth, and rough touch. Complete loss of feeling happens when the posterior columns are involved, and by then, bladder and bowel irregularities have developed. When compression is applied for a long time, flaccidity and flexor spasms take the place of spasticity. Lesions at the conus medullaris or cauda equina may present mixed symptoms of upper motor neuron and lower motor neuron lesions with asymmetrical loss of feeling when bladder and bowel function is impaired early. It is possible to categorize neurological abnormalities in spinal TB using the Frankel and ASIA ratings, which were initially developed to identify neurological deficits in acute spinal injuries [23]. The most appropriate categorization of Pott paraplegia with spinal cord involvement is the modified Tuli classification[24]. Pott paraplegia was classified into five stages (Table 1). Despite the fact that the majority of neurologic abnormalities would fit into this category, neurological impairments in intraspinal granulomas, cauda equina syndromes, conus medullaris syndromes, or TB of other uncommon sites may not correlate to any of the phases described above.

Cold abscess

In at least half of cases with spinal TB, paravertebral abscesses are seen. As the name suggests, a cold abscess lacks signs of inflammation, including redness, dolor, and rubor, yet its existence indicates an active infection. Most cold abscesses can evoke a fluctuation, and they typically have a well-defined boundary with smooth, uniform borders. The skin above an abscess is typically swollen and glossy if it is large. Subcutaneous and dermal tissue are steadily destroyed by superficial abscesses, leading to a sinus that discharges. The abscess's pus is often light yellow or white. It contains caseous material with detritus and sequestered bone and has no unpleasant odor indicative of a pyogenic or fungal infection. When the underlying disease process is under control, tubercular sinuses gradually heal with a thin scar after a protracted period of time. Common symptoms of inflammation brought on by secondary infection might heal with an unsightly fibrotic scar that is anchored to the underlying tissue. According to culture, the presence of pyogenic organisms in the pus does not rule out TB. Paravertebral abscesses have a tendency to migrate along the path of least resistance after inflicting damage to the surrounding

Table 1 Classification of paraplegia in tuberculosis of the spine[24]

Stage	Complaints	Motor	Sensory	Autonomic
I	Nil	Plantar extensor/ankle clonus; ASIA motor score−100	Nil	Nil
II	Able to walk with support	ASIA motor score; Tetra paresis (60–100); Paraparesis (80–100)	Lateral column; Involvement	Nil
III	Confined to bed; Can move limbs	ASIA motor score; Tetra paresis (0–30); Paraparesis (50–80)	Lateral column; Involvement	May be present
IV	No limb movement	ASIA motor score; Tetra paresis (0); Paraparesis (50)	Both lateral and posterior column involvement	May be present
V	Flexor spasms	Flaccid paralysis	Complete loss	Complete loss of bladder and bowel control

areolar tissue, including the muscular, subpleural, sub-peritoneal, perivascular, perineural, and fascial planes, and may manifest as a superficial abscess far from the initial focus[25-27].

Swellings in the axilla, subscapular region, or anterior or posterior triangles of the neck might be signs of retropharyngeal abscesses in the cervical spine. The usual pharyngo-vertebral crepitus, which is felt when the larynx is gently pressed from side to side against the vertebral column, is absent in cases with retropharyngeal abscesses. Together with stridor, hoarseness, and dysphagia, it can also present as a potentially lethal condition. An abscess in the arm or forearm might occur if the infection spreads through the brachial plexus. A cold abscess is identified as a fusiform paravertebral swelling in the thoracic area. It may occasionally adhere to the arcuate ligament or the diaphragm aperture. It can also travel *via* the intercostal arteries and cause a protrusion in the chest wall. A lumbar spine cold abscess is generally detected in the Petit's triangle or groin. It has the potential to migrate down the psoas muscle and cause a hip pseudo-flexion deformity. It can occasionally appear as a tumor in the Scarpa's triangle or a gluteal abscess and follow the femoral or gluteal arteries. If the obturator vessels are followed, the abscess will show up in the adductor region. The abscess may develop in the gluteal area, the posterior thigh, or, on rare occasions, even the popliteal fossa if the sciatic nerve is suspected. Understanding the distribution of the pus is crucial since it can take the examiner away from the source of the TB focus. Although involvement of the thoracic spine may diffuse into the lumbar region through the diaphragmatic orifice, the emphasis on the cervical spine may present as an abscess in the mediastinum or elbow. A lumbar spine abscess might appear in the thigh, calf, or even the ankle[28,29].

Spine deformity

Patients may appear to have deformities during either the active or healed stages. After a surgical debridement, deformities may appear right away, or it may take years for older patients whose skeletal architecture has been weakened by osteoporosis to develop. TB first affects the anterior column, and increasing deterioration causes kyphotic deformity and, eventually, instability. If therapy is started at this point, the lesion heals without significant deformity when the intervertebral disc is destroyed and the cancellous bones come into contact with one another. Further degradation occurs if therapy is delayed, resulting in increased deformity. The clinical presentation is determined by the number of vertebrae affected. Further collapse will result in vertebral body retropulsion, resulting in cord compression and neurological impairment. Regular follow-up is critical in the development of children until they reach adulthood. Children who have facet damage during an active illness are more likely to suffer severe deformities later in life. Severe abnormalities can impair quality of life, impede cardiac function, and cause cerebral deficits. Kyphosis is less problematic in the cervical and lumbar spines than it is in the thoracic and thoracolumbar spines because of natural lordosis[30,31].

Pediatric spinal TB

Despite the fact that there may not be any discernible trends today, children are more influenced than adults. Due to their juvenile skeletons, flexibility, and levels of activity, it is crucial to have a high level of suspicion when a child complains of back discomfort at the spine clinic. Children's vertebral bodies contain more cartilage, which is quickly damaged by active diseases and mechanical stress. A neurological sequela can result from asymmetric loading of the ring apophysis, which causes the formation of new deformities or the advancement of previously existing deformities. Even after being pronounced cured, children should continue to get frequent clinical and radiological checks until they reach skeletal maturity, since residual deformity might worsen due to a developing spine and physical activity. More than two of the four spine-at-risk indicators were present in one-third of the kids, which is an undesirable development. Children under the age of seven, people with more than three vertebral bodies sick, and people with conditions affecting the lower thoracic or thoracolumbar junction are more likely to progress[32-34]. There are four symptoms of "spine at risk" in children: (1) Retropulsion of the affected vertebra; (2) Facet subluxation; (3) Lateral translation of vertebrae; and (4) Toppling of one

vertebra over the other.

Children who exhibit two or more of these symptoms may have posterior facet dislocation and necessitate surgical treatment, according to Rajasekaran[35,36]. Additionally, he proposed three categories for how the deformity progresses in children: Type 1 curves (curvature increases until growth stops or skeletal maturity is reached, at which point surgical intervention is necessary); type 2 curves (the deformity lessened as the child grew); and type 3 curves (there was minimal change in the deformity either during the active or healed phases of the disease).

Spinal TB in elderly

As people live longer, more and more older people are being identified as having spinal TB. Compromised health, co-morbidities, and medication interactions are specific issues that older people face. The elderly population has a threefold increased chance of experiencing drug reactions, a sixfold increased risk of mortality, and a twentyfold increased risk of receiving an incorrect diagnosis. Malignancy, diabetes, poor nutrition, immunosuppression, prolonged hospitalization, and other variables are risk factors for an increased incidence of spinal TB. When assessing an elderly person, look for signs of TB meningitis, disseminated TB, or other system involvement. Elderly low back discomfort is frequently disregarded in terms of degenerative conditions[37-39].

Atypical presentations

Intervertebral disc prolapses, isolated abscesses without skeletal involvement, and pure intraspinal granulomas are a few examples of unusual clinical presentations. Atypical radiographic appearances include circumferential vertebral involvement, solitary vertebral involvement, isolated meningeal, neural, or perineural involvement without any vertebral destruction, concentric vertebral collapse, isolated posterior arch involvement, and multifocal osseous lesions[40-43].

LABORATORY DIAGNOSIS

Spinal TB is diagnosed based on clinical and radiographic cues, as well as microbiological and histological markers. Diagnosis is challenging, even when there is a strong clinical suspicion of spinal TB. Clinical symptoms lack specificity, and testing for TB infection may yield conflicting results. Spinal TB is usually paucibacillary, and the sites of infection may be difficult to collect specimens adequate for molecular testing, histology, culture, or microscopy. Despite this, mycobacterium isolation from clinical samples is critical for both diagnostic confirmation and drug susceptibility testing. Diagnostic delays are prevalent due to the subtle clinical features of spinal TB[44,45]. It should be underlined that early identification of TB spine is crucial in minimizing deformity and neurological damage and improving patient outcomes from this illness. If discovered early, TB of the spine may typically be treated with antitubercular medication without the need for surgery. Despite technological developments, the diagnosis is still predicated on a strong clinical index of suspicion based on the history and examination results, which are complemented with biochemical and radiographic evidence[46,47].

Microscopy

Because of the high lipid content in their cell walls, mycobacteria are also known as acid fast bacilli (AFB). When exposed to acid alcohol, this binds to the fuchsin dye, preventing it from escaping from the cells. Early diagnosis is aided by the presence of AFB on microscopy, as well as a history of constitutional TB symptoms and evidence of pulmonary lesions on chest X-rays. Acid fast smears, in addition to supporting diagnosis, can aid in monitoring therapeutic response. The main limitation of smears is that they require a minimum of 10000 AFB per ml of material to be recognized, which is typically not the case with paucibacillary diseases like spinal TB[48,49]. Acid fast staining procedures include:

Carbol fuchsin stains: A fuchsin and phenol (carbolic acid) combination.

Ziehl–Neelsen (ZN, hot stain): Mycobacteria are stained red in this smear, whereas the backgrounds are bright blue. It is called "hot staining" because heat is used to help carbol fuchsin penetrate the bacilli. The smear is then decolored with 20% H_2SO_4 before being counterstained with methylene blue. Tubercular bacilli are acid fast because they resist decolorization by H_2SO_4 due to their high lipid content in the cell wall. Ziehl-Neelsen staining has the benefit of being a dependable, repeatable, and inexpensive process that may also be used to evaluate antitubercular treatment response. The limitations of this technology are that it has poor sensitivity and cannot distinguish between various species of Mycobacteria[17].

Kinyoun (cold stain): When compared to ZN staining, this procedure uses a higher quantity of phenol, removing the requirement for heat to penetrate carbol fuchsin. Mycobacteria look red on a pale blue background, similar to ZN staining.

Fluorochrome stains: rhodamine, a second fluorochrome, with or without auramine O. Compared to ZN staining, fluorochrome staining has the benefit of being able to scan a substantially broader region of the smear. This leads to greater sensitivity to detect bacteria as well as a reduction in the time necessary to scan the smear[50].

Culture

Culture methods identify substantially fewer tubercle bacilli (10-100/mL of specimen) than microscopy. Furthermore, the isolated bacilli can be utilized to identify the species as well as for drug susceptibility tests. As a result, the presence of TB bacilli in culture is regarded as the "gold standard" for TB diagnosis. The limitation of traditional culture procedures is the length of time required to detect noticeable growth, which can range from 4 to 8 wk. The various cultural mediums used to grow Mycobacterium TB are classified as follows:

Solid medias

Egg-based: Whole eggs or egg yolks, potato flour, salts, and glycerol that have been stiffened by inspissation are among the ingredients. They have a long shelf life and promote the growth of the majority of mycobacteria. The Lowenstein-Jensen (LJ) medium is the most often used egg-based medium.

Agar-based: Compared to egg-based media, this medium has a higher chemical definition. Colonies may therefore appear considerably sooner than in egg-based media (10-12 d).

Selective media: Due to the usage of antibacterial medications that prevent contaminating germs, this medium is more selective, allowing the development of Mycobacteria alone. It is therefore frequently used in conjunction with a non-selective egg or agar medium. Both the Gruft modification, which enhances LJ media with nalidixic acid and penicillin, and the Mitchison selective 7H11 medium, which enhances LJ media with carbenicillin, polymyxin B, trimethoprim, and amphotericin B, are examples of selective media.

Liquid medias

Mycobacteria growth indicator tube (MGIT): To help identify tubercle bacilli development in modified Middlebrook 7H9 culture, the MGIT includes a fluorescence-quenching-based oxygen sensor (silicon rubber impregnated with ruthenium pentahydrate).

BACTEC 460 TB system: A method that is semi-automated and uses palmitic acid that has been 14C-labeled as the carbon source for the medium. The apparatus detects $^{14}CO_2$, which is produced as a result of this being digested in the presence of bacteria. Bacilli in a smear-positive specimen for TB often take 9 to 14 d to be found. The drawbacks of this approach are the inability to monitor colony shape, difficulties detecting mixed cultures, contamination overgrowth, expense, and radioactive disposal.

Automated continuous monitoring systems: Similar to the MGIT system, the BACTEC 9000 MB system uses a fluorescence quenching-based oxygen sensor to identify growth. The MB/BacT ALERT 3D system monitors the presence and generation of CO_2 dissolved in growth media using a colorimetric CO_2 sensor in each bottle and reflected light. When the bacilli grow, CO_2 is produced. This gas diffuses to the sensor across the membrane, dissolves in water, and builds up as hydrogen ions. The amount of CO_2 generated is proportional to the development of microorganisms in the medium, leading to the accumulation of hydrogen ions and a decrease in the sensor's pH. As a result, the color shifts from dark to bright green or yellow[51].

Serological tests

IgM levels are known to be a predictor of TB activity and have been proven to decrease during a three-month period after starting medication. IgG levels, on the other hand, show an increasing trend over the same time period and are therefore non-diagnostic but suggestive of chronic or cured disorders. Interferon (IFN) gamma, a cytokine produced by the body as part of its cell-mediated inflammatory response to tubercular antigen, is detected by the Interferon Gamma Release Assay, an ELISA test. One such test is QuantiFERON-TB Gold, which can detect IFN gamma in patients with spinal TB and vertebral body collapse with a sensitivity of 84% and specificity of 95%. While ELISA has improved the detection of these antibodies, it cannot tell the difference between current and latent infections or pulmonary and extrapulmonary TB[52,53].

Molecular testing methods

Nucleic ACID probes: Ribosomal RNA (rRNA), which is abundant in cells and culture, serves as a genetic target in this approach. Stable DNA-RNA complexes are produced when single-stranded radiolabeled (acridine ester) DNA probes hybridize with rRNA. An instrument that is proportional to the amount of probe present measures the light an unhybridized probe produces after it is deactivated.

To assess positivity, a specified threshold is applied. It takes two hours to complete this technique[54].

In situ hybridization: This technique uses an oligonucleotide probe that has been fluorescein-labeled, and interpretation is done by direct fluorescence microscopy viewing. The phrase "fluorescence in situ hybridization" (FISH) is a popular one[54].

Nucleic acid amplification (NAA) methods: Nowadays, the PCR technique is often used in research and diagnostic applications. This technique works by amplifying certain DNA sequences into several copies that may be distinguished using gel electrophoresis separation. Synthetic oligonucleotide primers that are complementary to a certain DNA sequence are used to achieve amplification. The target DNA is amplified a million times as a result of this technique. The most often amplified target is the IS 6110 repetitive element, which is present in many copies in the majority of *M. tuberculosis* strains. The precision and expertise of the technician performing the assay determine the efficacy of PCR for TB. Using real-time PCR, the amount of *M. tuberculosis* in a clinical sample may be quantified while the detection time is sped up. In a closed system, the entire amplification and detection process takes place in a single reaction vessel. The risk of amplicon contamination in the lab is thereby diminished. There is no need for electrophoresis or post-amplification processing because this process is entirely automated.

Xpert MTB/rifampicin (RIF) test: An automated PCR test called the Xpert MTB/RIF Test (Cepheid, Sunnyvale, California) may detect rifampicin resistance and TB in less than two hours. To conduct the test, lysis reagent and tissue samples acquired during a biopsy are combined, and a mixture is then swiftly oscillated between the two. Two mL of the mixture are removed and put through the GeneXpert machine after being allowed to stand. After around 90 minutes, the results will be available[55,56]. Rapid results, a fully automated system, simultaneous detection of rifampicin resistance, the ability to detect very low amounts of TB bacilli, and the ability to differentiate between typical and atypical mycobacteria are all advantages of this system. The Xpert MTB/RIF test has the disadvantage of detecting non-viable pathogens, missing mono drug resistance, and having a single gene target.

Multiplex PCR: Instead of amplifying just one *M. tuberculosis* gene, the multiplex PCR aims to do so. Under these circumstances, it has been demonstrated that multiplex PCR, which amplifies both the IS6110 and MPB 64 genes identified in mycobacterium, has higher sensitivity and specificity. It has been established that both genes may be amplified from a single tissue sample to lower the expense of this inquiry[57,58].

Nanotechnology

Despite improvements in the field of TB diagnosis, there is still no point-of-care test for *M. tuberculosis* that is accurate in detecting children, extrapulmonary TB, or HIV-associated TB. This gap will be filled by nanotechnology, which will provide a point-of-care diagnosis that is rapid, effective, and affordable and uses particles with a size range of 1-100 nm. The possibility of using different physiological fluids, such as blood, sputum, or urine samples from patients, in nano-diagnostic methods to get reliable and quick results using affordable and portable tools, seems to be promising in the detection of infectious diseases like TB[59-61].

Among the nano-diagnostic techniques being explored for TB are:

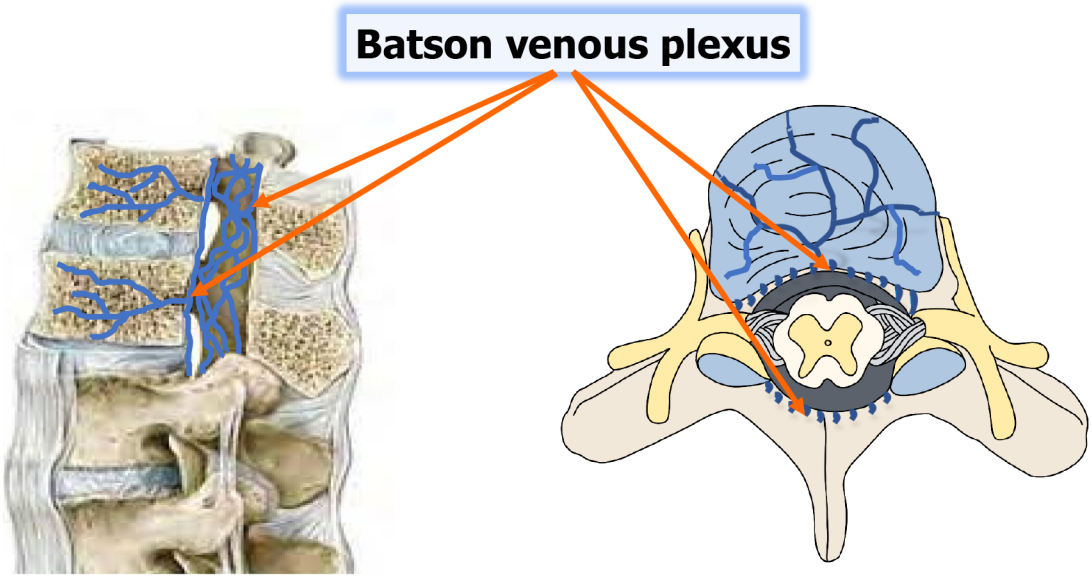
Gold nanoparticle (NP)-based TB diagnostic techniques: For colorimetric detection of *M. tuberculosis*, gold NPs are combined with DNA probes. If complementary DNA is present, the nanoprobe solution remains pink at a wavelength of 526 nm, when complementary DNA is missing from the samples, the solution becomes purple.

Dipstick with gold NPs: Alkanethiol derivatives were used to coat colloidal gold NPs with the *M. tuberculosis* antigen; this coating produced a pronounced red color when mixed with serum containing antibodies.

Detection based on silica NPs: Indirect immunofluorescence microscopy has been created to detect *M. tuberculosis* using NPs linked with fluorescent dye.

Detection system based on quantum dots: In this approach, one probe accurately binds to the mycobacterium's *23S rRNA* gene, and when the mycobacterium is treated with sulfuric acid and chromium quantum dots, a second probe accurately identifies the IS900 conserved sequence. As a consequence of hybridization with target gene sequences of mycobacterium DNA isolated from probable TB patient samples, a sandwich is produced. The conjugates of quantum dots and magnetic beads are then exposed to ultraviolet light, which causes red fluorescence that can be seen with the unaided eye.

Biosensors detection: Based on finding short nucleotide sequences of *M. tuberculosis* DNA, this is done. Sensors are classified as mass/piezoelectric, biological, electrical, or optical.



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Figure 1 The Batson venous plexus is a network of valveless veins that connects the deep pelvic veins and thoracic veins (which drain the inferior end of the urine bladder, breast, and prostate) to the internal vertebral venous plexuses in the human body.

Erythrocyte sedimentation rate and C-reactive protein

In spinal TB, the erythrocyte sedimentation rate (ESR) is often greater than 20 mm/hour (60%-90% sensitivity) and decreases with treatment response. It is, however, not a particularly sensitive test. C-reactive protein (CRP) has a higher specificity (71% sensitivity) than ESR[62,63].

IMAGING MODALITIES

Plain radiographs

In the early stages of illness, plain radiographs may be normal. Before the lesions become radiographically visible, a 30% mineral loss must occur. Various publications have reported an average of 3.4 to 3.8 degrees of vertebral involvement over the years. Immunocompromised patients, diabetics, and people with hemoglobinopathies may have extensive spinal involvement. A "skipped lesion" occurs in 7% of patients when two non-contiguous vertebrae are implicated without the involvement of neighboring vertebral bodies and intervertebral discs; the mechanism is assumed to be infection transmission through the Batson's plexus of veins[64,65] (Figure 1). The thoracic spine is the most commonly involved area, followed by the lumbar region. The posterior arch is more commonly impacted than the vertebral body. There are four radiographic forms of spinal involvement: para-discal, anterior, central, neural arch, or appendiceal (pedicles, laminae, spinous processes, or transverse processes).

Para-discal type

It is the most typical type of vertebral involvement, in which two contiguous vertebrae close to the disc space are involved at the same time. This points to a shared blood supply in this area. On radiographs, it appears as a decrease in intervertebral disc space associated with endplate irregularities in the adjacent vertebrae. Plain radiographs show tuberculous granulation tissue and abscess development in the paravertebral area as soft tissue shadows next to the spine. It is best apparent on a lateral radiograph in the cervical area as an enhanced prevertebral soft tissue shadow. Abscesses below the T4 spinal level have a distinctive fusiform shape (like a bird's nest), but bigger abscesses may have a broad posterior mediastinal shadow. A globular-shaped shadow might form when an abscess is under strain. The psoas shadow in the lumbar region enlarges as an indication of an abscess tracking down the muscle. In cases of long-standing destruction of adjacent para-discal vertebral bodies, the spine may angle, and one or both bodies may show posterior convexity with wedge collapse. The most frequent spinal deformity is kyphotic deformity, which is caused by involvement of the thoracic vertebrae. Multiple involvement of neighboring vertebrae may result in a significant kyphotic deformity[66].

Central type

When the infection starts in the center of the vertebral body and spreads *via* Batson's venous plexus or the branches of the posterior vertebral artery, the pattern of involvement described above occurs. Later,

with axial stress, the diseased vertebral body collapses due to trabecular bone loss. Because the loss of disc space and paravertebral shadow is minor in comparison to the para-discal type, it is sometimes mistaken for having neoplastic origins. However, with a longer follow-up, there may be a reduction in the nearby disc area[45].

Anterior type

When the disease process begins just below the anterior longitudinal ligament and periosteum, this pattern is observed. This results in erosions of the vertebral body's anterior aspect, which may be detected on lateral radiographs as uneven cortical borders. Multiple adjacent vertebrae may be involved if the infection spreads beneath the anterior or posterior longitudinal ligaments. Vertebral body collapse with loss of neighboring disc space is generally minor and appears later[41,42].

Appendiceal type

This involves either isolated or mixed involvement of the neural arch (pedicles and laminae), transverse processes, and spinous processes. When there are indirect symptoms of involvement, such as paravertebral shadows or erosive alterations with an undamaged disc, these lesions may be suspected radiographically. Routine radiography makes it difficult to see the involvement of the posterior spinal joints. Posterior spinal articulations may also be affected, resulting in lateral translation, an uncommon malformation. The fundamental drawback of radiography is that it is insensitive in the early stages of illness. The craniovertebral and cervicodorsal junctions are two spinal locations that are difficult to identify on X-ray. Plain X-rays make it difficult to assess spinal cord alterations, soft tissue involvement, and the exact location and extent of abscesses. So, the appearance of any of the radiographic signs may be a sign that the disease process has progressed to a fair degree[67,68].

COMPUTED TOMOGRAPHY

Computed tomography (CT) reveals findings significantly earlier than normal radiography because it shows more detail of bone irregularity, disruption, sclerosis, and disc collapse. Fragmentary, osteolytic, sclerotic, and subperiosteal bone disintegration patterns have all been documented. Aside from bony detail, paraspinal abscesses are assessed better than plain radiography. It's essential for detecting calcification within an abscess or bone pieces within epidural lesions. It is quite useful for providing direction for percutaneous diagnostic sampling, particularly in inaccessible locations. The main drawback is that magnetic resonance imaging (MRI)scores higher than CT when evaluating the effect of the disease on brain structures. In spinal TB, radiological evidence of healing lags behind clinical and laboratory results. Several months after the start of combination therapy, many patients may not exhibit any signs of improvement on X-rays or CT scans, which should not be construed as a sign that the treatment is failing. Nevertheless, if the pictures are repeated more than 6 months after the commencement of the treatment and do not demonstrate improvement, the possibility of an extra lesion or a condition that is therapeutically resistant should be taken into account[69,70].

MAGNETIC RESONANCE IMAGING

Because of its improved soft tissue contrast and capacity to spot and classify anomalies in the spinal cord, bone marrow, and intervertebral disc, MRI outperforms other imaging modalities. For the entire examination of the tuberculous spine, MRI is the modality of choice. The craniovertebral junction, cervicodorsal junction, neural arch components, vertebral appendages, sacroiliac joint region, sacrum, and coccyx are just a few tough places where it is very helpful in diagnosing disorders. Standard MRI procedures include fat-suppressed T1W, T2W, and short tau inversion recovery sequences in the axial, sagittal, and coronal planes, as well as contrast-enhanced T1W sequences after gadolinium contrast injection. An abnormal marrow signal intensity that appears hypointense on T1W sequences and hyperintense on T2W sequences, showing heterogeneous enhancement and a lack of cortical definition, is indicative of the vertebral body being involved. Contiguous vertebral body disease with disc degeneration is common. Loss of normal internuclear cleft with increased signal on T2W images, as well as post-contrast enhancement, are indications of disc involvement. Because mycobacterium lacks proteolytic enzymes, disc involvement occurs later than in pyogenic spondylitis. The "floating disc sign" may arise infrequently if there is severe spinal damage with disc sparing. In children, the disc is highly hydrated and more susceptible to infection.

The intercostal space, mediastinum, pleural cavity, or even the intercostal arteries themselves may get enclosed by the paraspinal collection as it just barely breaches the anterior longitudinal ligament in the thoracic region. When the psoas muscle is involved in the lumbar area, there is a loss of typical muscle shape, increased muscular size, and uniform signal intensity on T1W imaging. In T2W imaging, the psoas abscess appears as a high-signal fluid with dense peripheral post-contrast enhancement.

Although posterior element involvement is less likely in TB than in a pyogenic infection, it is nonetheless more common. The disease's involvement manifests as an aberrant signal and in the homogeneous amplification of the afflicted spot. The posterior elements can be afflicted alone, although they are most typically encountered in conjunction with anterior element abnormalities. Composite lesions, or panvertebral lesions, are defined as involving both the posterior and anterior components. The epidural/subdural space or the spinal cord may be involved in addition to granulomatous lesions inside the spinal canal. Around 61% of afflicted vertebrae have epidural extension that may be seen on an MRI. When the spinal cord is squeezed from the front or the rear, compression myelopathy can happen[71-73].

MEDICAL MANAGEMENT

Multidrug antitubercular therapy

Unlike other infections, TB needs multidrug treatment for a variety of microbiological reasons, as mentioned below: Mycobacteria exist in four types in the human body: (1) Extracellular fast dividing; (2) Extracellular slowly dividing; (3) Intracellular intermittently dividing; and (4) Dormant bacilli. As a result, it needs the use of many medications that are effective against various bacterial types. Rifampicin destroys slowly growing bacteria, ethambutol kills intracellular bacteria inside macrophages, and streptomycin kills rapidly multiplying bacteria. In contrast, isoniazid, ethambutol, and streptomycin all kill rapidly multiplying bacteria[74].

Mycobacteria's modest growth rate is both a blessing and a curse. While the illness progresses slowly, medications that work on quick multipliers become ineffective, limiting therapy choices. As a result, it is necessary to use medications for a longer period of time.

The drug permeability is minimal due to the restricted permeability of mycobacterial cell walls and intra-macrophage bacilli. As a result, specialized medications that penetrate macrophages and thick bacterial cell walls are required for therapy[75].

Mycobacteria are well-known for rapidly acquiring antibiotic resistance to monotherapy. Isoniazid resistance mutations occur at a rate of 1 in 10^6, while rifampicin resistance mutations occur at a rate of 1 in 10^8. Resistance to both can be found in 1 in 10^{14} people. As a result, a minimum of two medications are administered in combination to prevent the development of resistance[76].

Most anti-tubercular medications, with the exception of thioacetazone, have a protracted period of action known as the "lag-effect." This quality made it possible to take medications on an intermittent schedule, which was essential for the success of directly observed therapy[77].

FIRST-LINE DRUGS

Despite decades of extensive study, only a few medications have been shown to be effective. Since the current anti-tubercular treatments consist of the five first-line drugs isoniazid (INH), RIF, ethambutol (EMB), pyrazinamide (PZA), and streptomycin, which are the most efficient and least toxic, it is advised to use these drugs with caution and a focus on compliance in order to prevent the emergence of resistance. Prolonged use of numerous medicines may increase the risk of a variety of side effects and problems. To achieve a safe and effective therapy, a detailed understanding of pharmacokinetics, medication interactions, and side effect profiles is required, as well as monthly monitoring.

INH

Isoniazid is an important drug in the treatment and prevention of TB. INH is a prodrug that, when activated by the catalase-peroxidase KatG, creates a variety of radicals. The bonding of the radicals with nicotinamide adenine dinucleotide (NAD) causes an INH-NAD adduct, which inhibits the enoyl-ACP reductase *Inh*A of the fatty acid synthase type II (FASII) pathway, ultimately leading to cell death. INH is especially effective against rapidly developing mycobacteria. It can pass the blood-brain barrier and act on both intracellular and extracellular bacteria. Only dividing bacteria are killed when INH penetrates the bacterial cell; mycobacteria in the stationary phase are unaffected. INH is bacteriostatic for the first 1-4 days, thereafter, it becomes bactericidal, which coincides with its lack of acid fastness. Multiple genes in different pathways are involved in INH resistance. A mutation in the *katG* gene is the most prevalent source of resistance, followed by mutations in other genes such as *inhA*, *ahpC*, *kasA*, and *ndh*. Adults should take 5 mg/kg, while children should take 10 mg/kg. Peripheral neuropathy, lethargy, hepatitis, and, in rare cases, convulsions, insanity, and a lupus-like condition are among the side effects. Pyridoxine (10-25 mg/d) is also indicated to help reduce the risk of peripheral neuropathy. INH is a cytochrome P450 inhibitor that has been shown to raise the plasma concentrations of anticonvulsants, benzodiazepines, acetaminophen, and oral anticoagulants[78,79].

RIF

Rifampicin, a rifamycin derivative, inhibits messenger RNA elongation by binding to the β-subunit of the RNA polymerase. Both intracellularly and extracellularly, it is effective against bacteria that quickly proliferate and slowly metabolize. This impact on bacteria with irregular metabolism provides a "sterilizing effect". Adults should take 10 mg/kg, while children should take 15-20 mg/kg. High dosages can cause hepatotoxicity; hence, the maximum daily dose shouldn't exceed 600 mg. Additional adverse effects include hemolytic anemia, gastrointestinal distress, purpura, and orange-red urine stains. Rifampicin is a cytochrome P450 inducer, which necessitates dose changes for other medications that are processed in the liver, such as oral hypoglycemics, anticonvulsants, antifungals, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, cardiac therapies, and so on. Rifampicin resistance is most frequently caused by a mutation in the 81-bp *rpo*B gene (codons 507–533), which codes for the β-subunit of RNA polymerase[80,81].

PZA

An amidase enzyme produced by the *pnc*A gene transforms the prodrug PZA into its active form, pyrazinoic acid. PZA is thought to hinder membrane transport, trans-translation, and coenzyme A production, all of which are required for bacteria to thrive. The primary characteristic of PZA is its ability to combat non-replicating persisters in an inflammatory, acidic environment. The first two months of treatment, when acute inflammatory changes are still apparent, are when it works best. It has a great "sterilizing effect" and is critical in decreasing the length of chemotherapy. Adults should take 25 mg/kg, while children should take 35 mg/kg. The recognized side effects are hepatotoxicity, hyperuricemic arthralgia, exanthema, and pruritis. Cyclosporine and gout patients need dosage adjustments. *Pnc*A mutations in the 561 bp open reading frame or an 82 bp putative promoter region are the main causes of PZA resistance in *M. tuberculosis*[82,83].

EMB

Ethambutol is only effective against growing bacteria (bacteriostatic), where it prevents mycobacterial arabinogalactan biosynthesis by inhibiting the enzyme arabinosyltransferases. Other pathways include glycerol metabolism and RNA synthesis disruption. Adults should take 15 mg/kg, while youngsters should take 15-25 mg/kg. Dose-dependent retrobulbar neuritis is the most significant side effect. The central fibers are frequently compromised, leading to loss of visual acuity, scotomas, and the inability to discern between green and red colors. The effects are reversible if recognized early and the medicine is stopped. Abdominal discomfort, eosinophilia, peripheral neuritis, myocarditis, and hypersensitivity are some of the other side effects. The drug is not recommended for children due to the difficulties in evaluating visual acuity consistently. Dosage adjustments are necessary for patients with low creatinine clearance (30 mL/min). The *emb*B gene, which codes for arabinosyltransferases, has codon 306, which is the most often occurring mutation for EMB resistance[84,85].

Streptomycin

Streptomycin is a *Streptomyces griseus* aminocyclitol glycoside. It is highly effective against actively proliferating bacilli found in cavities when administered intramuscularly. The ribosomal proteins S12 and 16S rRNA, which are encoded by the genes *rps*L and *rrs*, respectively, are not translated as a result of their action. The fact that it is active at an alkaline pH is significant. Adults should take 15 mg/kg of streptomycin, whereas children should take 15-25 mg/kg. Ototoxicity, vestibulotoxicity, nephrotoxicity, rashes, eosinophilia, and fever are among the side effects. The most prevalent mutation giving streptomycin resistance is a lysine to arginine change in codon 43 of *rpsL*. Streptomycin can cross the placenta and cause fetal ototoxicity and nephrotoxicity; hence, it is not recommended for use during pregnancy. All other first-line medications are safe to use while pregnant. Children's pharmacokinetics differ from those of adults. Children metabolize medicines quicker than adults, and their blood concentrations are substantially lower, necessitating a greater body weight dosage[86,87].

The first-line anti-tubercular medications' dose, pharmacological activities, and side effects are summarized in Table 2.

SECOND-LINE DRUGS

The emergence of first-line antibiotic resistance has required the frequent use of second-line treatments. Second-line medications are less effective, have more toxicity, and are more expensive than first-line treatments. The most often used second-line medications include fluoroquinolones, injectable aminoglycosides, ethionamide, and cycloserine.

Fluoroquinolones

Fluoroquinolones (FQs) are antibiotics with broad spectrum action against *M. tuberculosis in vitro* and *in vivo*. They are bactericidal, with the mechanism of action being DNA synthesis inhibition.

Table 2 The first-line anti-tubercular medications' dose, pharmacological activities, and side effects[85]

Anti-tuberculosis drugs	Dose (mg/kg)	Pharmacological activities	Side effects
Isoniazid	5	-Inhibits the enoyl-ACP reductase *Inh*A of the fatty acid synthase type II (FASII) pathway	-Peripheral neuropathy, lethargy, hepatitis, insanity, convulsions, and a lupus-like condition
Rifampicin	10	-Inhibits messenger RNA elongation by binding to the β-subunit of the RNA polymerase	-Hemolytic anemia, gastrointestinal distress, purpura, and orange-red urine stains
Ethambutol	15	-Inhibits enzyme arabinosyltransferases, glycerol metabolism, and RNA synthesis	-Abdominal discomfort, eosinophilia, peripheral neuritis, myocarditis, and hypersensitivity
Pyrazinamide	25	-Disrupts membrane energetics and inhibits membrane transport function	-Hepatotoxicity, pruritis, hyperuricemic arthralgia, and exanthema
Streptomycin	15	-Binds to the small 16S rRNA of the 30S ribosomal subunit irreversibly, interfering with the binding of formyl-methionyl-tRNA to the 30S subunit	-Ototoxicity, rashes, fever, nephrotoxicity, eosinophilia, and vestibulotoxicity

Fluoroquinolones that are routinely utilized include ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin. The suggested daily dose is 400-600 mg. Adverse effects such as headache, gastric discomfort, rashes, and dizziness are uncommon. A mutation in DNA gyrase, the biological target for FQs, is the most prevalent route for drug resistance[88,89].

Aminoglycosides

Amikacin (AMK), kanamycin (KAN), and capreomycin (CAP) are injectable aminoglycosides that are crucial to the treatment of multidrug-resistant (MDR) TB. They are made from Streptomyces and are bactericidal. AMK and KAN work by inhibiting protein translation, but capreomycin works by inhibiting mRNA-tRNA translocation by attaching to the 70S ribosome. All three drugs are administered in a single dose of 15 mg/kg per day. Due to the adverse effects, which include renal toxicity, ototoxicity, and electrolyte abnormalities, frequent monitoring of hearing and renal function is required. Resistance to AMK and KAN is associated with changes in the 16S rRNA, and cross-resistance between both drugs is frequent. Capreomycin resistance is linked to a *Tly*A mutation and is more likely to result in treatment failure and death[90,91].

Cycloserine

Cycloserine is a bacteriostatic drug derived from *Streptomyces orchidaceus*. It prevents the formation of mycobacterial cell walls. Moreover, cycloserine could successfully permeate bone and reach quantities that were equivalent to those in plasma, which supports its use in the treatment of osteoarticular TB [92]. The recommended daily dosage is 1 g, taken as a single dose. Those with psychiatric disorders and renal insufficiency should avoid using the medication since it might cause seizures, headaches, and psychosis. Because of its high stomach tolerance and low drug-drug interactions, it may be used to treat MDR and extremely drug-resistant (XDR) TB[93].

Ethionamide/prothionamide

Iso-nicotinic acid is used to make the bacteriostatics ethionamide and protionamide. The mechanism of action is similar to that of INH in that it inhibits *Inh*A of mycolic acid production. The medication is administered in a single daily dosage of 1 g. Severe gastrointestinal intolerance, hepatitis, peripheral neuropathy, hypothyroidism, and depression are among the adverse effects. There is a lot of cross-resistance between the two medications[94,95].

Para-aminosalicylic acid

Para-aminosalicylic acid was one of the first anti-tubercular medications to be developed. However, due to quick resistance and gastrointestinal intolerance, it was replaced. Hypothyroidism, hepatic dysfunction, and hypersensitivity are some of the other side effects. A single or two split dosages of 12 g are advised[96].

NOVEL DRUGS

In view of rising treatment failure in *M. tuberculosis*, there is an unmet need for innovative medicines that act on novel targets and have higher effectiveness while requiring fewer drug interactions and having a lower toxicity profile.

Delamanid

Delamanid is a prodrug (dihydro-nitroimidazo-oxazole derivative) that inhibits the formation of mycobacterial cell wall components when activated by the enzyme deazaflavin-dependent nitroreductase (Rv3547). Headache, nausea, dizziness, and QT prolongation are all side effects. The safety profile is good, with the least amount of toxicity and no major drug interactions with other anti-TB drugs. Given the inconsistent findings of effectiveness trials, WHO recommends using the medicine only in a more protracted MDR regimen if no viable alternative can be discovered[97,98].

Bedaquiline

Bedaquiline is a new anti-tubercular drug that was released in 2012. It targets the mycobacterial ATP synthase and binds to one of its components to prevent it from functioning. Like other second-line medications, it is advised for use in MDR and XDR-TB patients. Its distinct mode of action makes it less likely than other anti-TB medications to produce cross-resistance. Among the side effects that have been seen are nausea, arthralgia, headaches, hemoptysis, chest pain, anorexia, rashes, and an increase in hepatic transaminases[99]. The most significant side effect is QT prolongation; hence, it should not be used with other QT-prolonging medications. Mutations in the *rv0678* gene, which encodes the MmpL5 efflux pump repressor, have been linked to low-level bedaquline resistance and cross-resistance to clofazimine.

SURGICAL MANAGEMENT

Chemotherapy is the primary treatment for spinal TB. Long-term antitubercular chemotherapy is a crucial component of the treatment of spinal TB. Surgery for TB of the spine is a contentious subject, with no clear consensus on the indications for surgical therapy. To prevent and cure complications of spinal TB, such as cold abscess, deformity, and neurological deficiency, surgical intervention may be necessary. Excisional treatment and antitubercular therapy were shown to be equivalent in studies. In fact, excisional treatment alone causes anterior column deficiency, deformity, and delayed neurological damage[100].

According to Mak *et al*[100] the following circumstances warrant surgical intervention:

Progressive neurological deficit: Early surgical decompression contributes to the resolution of the deficiency, which lowers morbidity and improves quality of life.

Progressive spinal deformity: More kyphosis in the thoracic spine may be tolerated if the lumbar spine compensates, but an excessive loss of lordosis in the lumbar spine is not acceptable. Kyphosis of sixty degrees should be surgically corrected since it can cause paraplegia and cardiovascular impairment.

Failure of conservative treatment: Following 3-4 wk of chemotherapy with or without a brace or bed rest, any increase in discomfort or neurological deficit should be treated surgically as a therapeutic failure.

Uncertain diagnosis: Making a diagnosis or determining medication sensitivity might be challenging when there isn't a surface abscess or when percutaneous biopsy samples are either insufficient or impossible to acquire. In these circumstances, surgery should be done to collect enough tissue samples.

END POINT OF CHEMOTHERAPY

The major issue with spinal TB is that there are no clear standards for determining "healed status." Therefore, it is difficult to determine when to discontinue using anti-tubercular medications. In order to determine the end point of treatment for spinal TB, the "gold standard" in pulmonary TB—repeated tissue biopsy and culture conversion—is not used because, the paucibacillary nature of the TB spine makes it an invasive, time-consuming, and consequently impractical method with a very poor yield. Additionally, there is no established method for estimating the total body burden of *M. tuberculosis* or forecasting clinical results. Therefore, the trifecta of clinical improvement, laboratory markers, and radiographic evaluation continues to be used as corroborated indicators of healing status.

Clinical improvement

Pain: Although the majority of spinal TB patients who are recovering report lessening of their pain, this cannot be taken as an absolute criterion because there can be several different causes of back pain, and more importantly, healing can take place without a strong bony fusion, which can result in persistent pain from spinal instability despite the disease's recovery. In addition, there is currently no accurate metric for measuring the degree of pain.

Deformity: The same is true for spinal deformity, which in most individuals either worsens or remains as the illness progresses and collapses.

Neurology: Although the patient's neurology improves when the diseased soft tissue crushing the neural components is reduced, in a small number of cases, neurologic dysfunction may continue despite the illness healing due to chronic bony compression.

Laboratory improvement

ESR: In most situations, ESR is increased. It is used to track how well patients respond to therapy. Failure to normalize following therapy should raise concerns about primary drug resistance or alternate causation.

CRP: CRP levels have been shown to be up to 75% higher in patients with spinal TB. It is more targeted toward viral and inflammatory lesions. It takes around 2 wk to detect a change, whereas ESR takes about 4 wk and hence has more relevance in monitoring therapy response.

Imging improvement

MRI: There are numerous well-known criteria for determining spinal TB healing.

Even after the infection has been completely eradicated, an MRI may still reveal soft tissues and even sterile abscesses.

MRI often lags behind clinical recovery by up to 3 mo.

MRI may be too sensitive when utilized as a sole source of information to assess the degree of a current infection, inflammatory edema, or active disease pus.

Poor disease management is indicated by the development of new lesions while receiving treatment, the worsening of existing lesions, marrow edema, and new bone damage or abscesses, particularly when these symptoms are coupled with clinical deterioration[101,102].

PROGNOSIS

Younger age and earlier diagnosis have been reported to be favorable prognostic factors. The severity of the disease (number of damaged vertebrae) and the extent of spinal deterioration (instability, deformity, abnormalities) influence the clinical outcome. The existence of paraplegic symptoms at the time of the initial diagnosis is considered a bad prognosis. Immunodeficiency (HIV, drug addiction, and alcoholism), malnutrition, and poverty are additional risk factors[103,104].

CONCLUSION

Early identification and prompt treatment enhance the prognosis for spinal TB. Even in the absence of neurological symptoms and indications, individuals who appear to have persistent back pain must be viewed with a high degree of clinical suspicion. Medical treatment is generally effective. However, MDR/XDR TB is increasing and should be identified early by using molecular methods to diagnose spinal TB and drug resistance. Advanced instances with significant bone involvement, abscess development, or paraplegia require surgical intervention. Young individuals are susceptible to spinal TB; thus, measures should be taken for effective prevention. The only strategy to avoid spinal TB is to stop the spread of the disease.

FOOTNOTES

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MINIREVIEWS

Implications of obesity in patients with foot and ankle pathology

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Abstract

Obesity is a growing problem defined as a body mass index of greater than 30 kg/m^2. It is predicted that by 2030, 48.9% of adults will be classified as obese which expands surgical risk factors to a broad population while increasing healthcare costs at the same time in different socioeconomic groups. This specific population has been widely studied in multiple surgical fields and published studies have shown the implications in each of these fields. The impact of obesity on orthopedic surgical outcomes has been previously reported in several total hip and knee arthroscopy studies, with evidence indicating that obesity is strongly associated with an increased risk of post operative complications together with higher revision rates. In line with increasing interest on the impact of obesity in orthopedics, there has been a similar output of publications in the foot and ankle literature. This review article evaluates several foot and ankle pathologies, their risk factors associated with obesity and subsequent management. It provides an updated, comprehensive analysis of the effects of obesity on foot and ankle surgical outcomes, with the ultimate aim of educating both surgeons and allied health professionals about the risks, benefits, and modifiable factors of operating on obese patients.

Key Words: Obesity; Foot and ankle surgery; Ankle fracture; Total ankle replacement; Achilles tendinopathy; Hallux valgus

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Core Tip: Obesity is a growing population. The impact of this is also reflected in fields such as Orthopedic Surgery including foot and ankle. Mobility is determinant in every aspect of life and in the obese population it reflects a greater challenge when addressing pathologies affecting the foot and ankle. Multiple factors can affect the outcomes of surgical treatments in this population and we believe that a greater understanding is needed to be prepared to treat these patients while trying to reduce the further complications that they face.

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INTRODUCTION

Obesity is a growing problem; it is predicted that by 2030, 48.9% of adults in the United States will be classified as obese[1] (Table 1). Causes of obesity are multifactorial, ranging from increasingly sedentary lifestyles, lower socioeconomic groups, as well as several genetic factors[1]. Obesity also contributes to healthcare costs, with an estimated $150 billion spent on direct impact costs per year in the United States [2]. Obese individuals have been found to have medical costs that are approximately 30% greater than their normal weight peers[3]. Worldwide costs of obesity continue to increase with an estimated two trillion dollars per year, or approximately 2.5% of the global Gross Domestic Product in 2014, spent solely on obesity related costs[4].

Obesity is defined as a body mass index (BMI) greater than 30 kg/m^2[1]. The importance of this lies in the physiologic changes of obesity presented by patients, both metabolic and biomechanical. Metabolically, hypertrophic adipocytes and adipose tissue-resident immune cells release increased levels of adipokines and lipokines, creating a chronic inflammatory state that exacerbates cardiovascular disease and insulin resistance, both of which adversely affect bone metabolism[5]. It has been shown that obese subjects who have one or two additional risk factors, like smoking and sedentarism, their risk of developing diabetes increases by nine times[5].

Bone mineral density is compromised in obese people by two mechanisms[6]. Firstly, increased levels of chemerin, an adipokine, correlates with an increased osteoporotic fracture risk[7]. Secondly, increased receptor activator of nuclear factor-kB (RANK)/RANK Ligand activity results in increased bone resorption by inducing increased osteoclast activity[8].

Forward progression forces are essential for normal gait. In obese subjects, energy usages tend to be lower in the anteroposterior plane and higher in the mediolateral plane indicating lower energy efficiency[9,10]. Other factors associated with abnormal gait include quadriceps weakening, knee osteoarthritis, poor balance, increased risk of falls, and skin irritation from poor shoe fit secondary to increased foot width and acquired flatfoot deformity[11-13]. Tibiotalar joints experience forces up to 5 times the body weight during the stance phase which is greater in an obese person[14,15]. With this knowledge in mind, it is no coincidence that there is an increased incidence of foot pain and higher rates of tendinitis, plantar fasciitis, and osteoarthritis in obese individuals[16-19].

Pre-operative weight loss seems the obvious solution for improving surgical outcomes. However, weight loss is difficult to achieve and to maintain[20,21]. Patients with foot and ankle pathologies often report pain as a limiting factor for successful weight loss. These patients have a higher risk of unsuccessful conservative treatment in conditions including Achilles' tendinopathy, plantar fasciitis and posterior tibial tendon dysfunction[22]. This leads to the belief that surgery will eliminate pain and finally allow them to lose weight as reported by MacMahon *et al*[23] where > 66% of obese patients had higher expectations than their surgeons, prior to surgical intervention[23].

The impact of obesity in orthopedic surgical outcomes has been extensively reported in total hip and knee arthroplasty studies, with strong evidence that obesity is highly associated with increased perioperative complications and higher revision rates[22,24-26]. A frequent complication present in this type of patients are wound complications which occur 3 times more often in obese individuals as shown in the literature[24]. In recent years, there has been more literature evaluating the implications of obesity in foot and ankle surgery[27]. This review will provide an updated, comprehensive analysis of the effects of obesity on foot and ankle surgical outcomes, provide insight into outcomes obese patients may expect from their surgeries, and highlight risks, benefits, and modifiable factors when operating on this cohort.

Table 1 Summary of foot and ankle surgical implications in obese patients

No.	Key points
1	By 2030, 48.9% of adults will be classified as obese, expanding surgical risk factors to a broad population
2	A chronic pro-inflammatory state faced by these patients, adversely affects bone metabolism
3	Factors associated with abnormal gait include quadriceps weakening, knee osteoarthritis, poor balance and an increased risk of falls
4	In obese subjects who have one or two additional risk factors like smoking and sedentary, their risk of developing diabetes increases by nine times
5	In Achilles tendon repairs, there is a significant increased rate of surgical site infection at the time of surgery if a comorbidity is present compared to those without a comorbidity
6	Patients with diabetes and vascular complications have the highest surgical site infection rate followed by obesity
7	Percutaneous hallux valgus procedures have found no difference in complication or re operation rates between normal weight and obese adults after surgery
8	There is an increased incidence of foot pain including higher rates of tendinitis, plantar fasciitis, and osteoarthritis in obese individuals
9	Compared with normal weight women, obese women have a three-fold increased risk of sustaining an ankle fracture after a fall
10	Obese patients have a greater proportion of chondral lesions when compared with normal weight subjects, 58% *vs* 30% respectively

IMPLICATIONS IN FOOT AND ANKLE SURGERY

Ankle fractures

A positive relationship between obesity and ankle fractures has been found in both men and women[28-31]. Compared with normal weight women, obese women have a three-fold increased risk of sustaining an ankle fracture after a fall[29].

Obesity has a direct correlation to ankle fractures in part due to altered gait changes as outlined above [32,33]. Mechanical loading is also affected in the obese population. Goodloe *et al*[34] found that after ankle fractures, obese patients have a significantly greater risk of needing repair of the syndesmosis[34]. They demonstrated an increased risk of 4.2% for each point increase in BMI for malleolar fractures, 3% for bi-malleolar fractures, and 3.4% for tri-malleolar fractures[29]. They proposed a biomechanical explanation where increased weight generates greater torque contributing to an increased risk of a more complex injury.

A greater risk of surgical site infections (SSIs) after open reduction internal fixation (ORIF) is a concern in obese patients. Specifically, Richardson *et al*[35] reported the greatest risk factors for SSIs were a BMI over 40 kg/m^2 [odds ratio (OR): 2.23, $P < 0.0001$] and the presence of peripheral vascular disease (OR: 2.16, $P < 0.0001$)[35]. Stavem *et al*[36] reported increasing BMI was associated with increased rates of venous thromboembolism (VTE) within 6 mo of ORIF for closed ankle fractures [OR: 1.15 per kg/m^2, 95% confidence interval (CI): 1.07-1.24, $P < 0.001$]. These complications arise from the fact that obese patients are at a constant inflammatory and immunosuppressed state[37,38].

Osteochondral lesions

Osteochondral lesions (OCLs) of the talus occur in approximately 70% of patients with an ankle sprain or fracture[37]. Frequently, a BMI greater than 25 kg/m^2 is associated with negative clinical outcomes [39].

Mardani-Kivi *et al*[14] performed a study of 26 obese patients and 10 nonobese patients evaluating the success of arthroscopic treatment of anterior ankle impingement in these groups. Patients underwent American Orthopaedic Foot and Ankle Society (AOFAS) scores at 6- and 12-mo follow-up demonstrating no difference in clinical outcomes. However obese patients were found to have a greater proportion of chondral lesions, when compared with normal weight subjects (58% *vs* 30% respectively) [40].

Ankle arthroscopy is more technically demanding in obese patients with significantly longer operative times[41]. This itself may be a risk factor for wound complications post-operatively, however further study is required.

Usuelli *et al*[42] studied arthroscopic autologous matrix-induced chondrogenesis for talar OCLs and found that overweight patients were more likely to have larger lesions based on preoperative magnetic resonance imaging scans. Despite this, they had similar clinical improvements and functional outcomes compared with normal weight patients. Koh *et al*[41] retrospectively evaluated 252 patients who underwent arthroscopic treatment for OCLs of the talus and found that a BMI > 25 kg/m^2 was not associated with worse post-operative and clinical outcomes when compared to non-overweight patients [43]. In contrast, a prospective study by Chuckpaiwong *et al*[44] investigating the relationship between lesion size and microfracture for OCLs found that higher BMI was a significant predictor of a negative outcome[44]. Younger patients with a shorter duration of symptoms and a lower BMI had better outcomes than older patients with a higher BMI and a more chronic symptomatic course[44].

Total ankle replacement

Total ankle replacement (TAR) surgery is increasingly performed for end stage arthritis to reduce pain and improve function and mobility to these patients. Obesity is important when considering TAR. These patients induce greater stress on prosthetic joints which may cause premature failure and subsequent surgery[45]. Werner *et al*[46] analyzed 5361 TAR procedures for end-stage arthritis and found obese patients had significantly more major and minor complications at 90 d post-surgery including infection and VET[46]. Comorbidity were more prevalent in the obese cohort compared to the nonobese cohort (P < 0.0001)[46]. While these may explain the higher complication rate and revision in obese patients following total ankle arthroplasty, multivariate regression analysis was not performed to determine if any of them were confounding variables.

Implant failure at mid and long-term follow up has been reported by Schipper *et al*[47]. Their study showed that a BMI 30 kg/m^2 was associated with a higher probability of implant failure (OR: 2.8, 95%CI: 1.04-7.53, P = 0.04), revision, and a significant decrease of 5-year survivorship when compared to nonobese patients (adjusted hazard ratio 3.73, 95%CI: 1.05-10.43, P = 0.04)[47].

Gross *et al*[48] carried out a prospective study of 455 primary TARs with a minimum follow-up of 2 years and reported no difference in complication, infection, or failure rates between obese and non-obese groups. While obese patients had high post-operative satisfaction and statistically significant improved clinical outcomes, they were all lower than their normal weight counterparts[48].

Ankle arthrodesis

Ankle arthrodesis remains the primary surgical approach in end-stage arthritis for many patients[49]. Using the United States Medicare database, Kamalapathy *et al*[50] evaluated the relationship between obesity, postoperative complications and hospital utilization following ankle arthrodesis[50]. They identified 5540 patients with normal BMI, 1108 patients who were obese and 1108 patients who were morbidly obese. Morbid obesity was associated with a statistically significant increased risk for acute kidney injury, urinary tract infection, VTE, readmission, and minor complications. Morbidly obese patients' length of stay was on average 2 d longer, and total hospital charge also correlated with increasing BMI, averaging $34335 more for morbidly obese and $28942 for obese patients compared to their normal weight counterparts[50].

Likewise, Werner *et al*[46] analyzed 17688 patients who underwent ankle arthrodesis and found that obesity was associated with a significant increase of thromboembolic events, infection and revision surgery[46]. Similar to TAR, complications can be related to additional medical comorbidities, intra operative factors and larger tissue envelopes[46].

Adult acquired flatfoot deformity

Obesity is a known risk factor for developing adult acquired flatfoot deformity (AAFD). The main stabilizer of the longitudinal medial arch is the posterior tibial tendon which, in obese patients, sustains greater axial load leading to insufficiency and finally collapse.

Soukup *et al*[51] performed a retrospective study comparing the outcomes of normal weight, overweight, and obese patients following AAFD reconstruction to treat stage II adult acquired flatfoot [51]. They identified 44 normal weight, 39 overweight and 44 obese patients with a mean follow up of 2.9 years. Obese patients reported more severe symptoms pre-operatively, but had similar clinical and radiological outcomes in the short-term when compared to the other two groups. They suggest that obese patients are still candidates for reconstruction with comparable short-term outcomes, but recognized that longer follow up and larger patient cohorts are needed to evaluate mid-term and long-term outcomes[51].

Fuhrmann *et al*[52] performed a retrospective analysis looking at clinical and radiological outcomes of hindfoot arthrodesis in patients with and without a flatfoot deformity showing that increased weight and BMI were predictors of recurrent deformity[52]. They suggested that when performing Stage 2 flatfoot deformity correction in obese patients, tissue reconstruction and corrective osteotomies should be augmented with a subtalar fusion, to enhance hindfoot stability[52].

Achilles tendinopathy

Achilles tendinopathy is a common condition associated with age greater than 50 years, male sex, increased BMI and lower extremity deformities[53]. Macchi *et al*[54] performed a meta-analysis of 22 studies comprising 18814 patients, 4010 of whom were obese (BMI ≥ 30 kg/m^2). They found that obese patients had increased rates of Achilles tendinopathy but not increased rates of rupture[54].

Some of the most common complications of Achilles tendon surgery are wound dehiscence and wound infection[53-55]. Dombrowski *et al*[55] identified that in a population of 24269 primary Achilles tendon repairs, there was a significantly increased rate of SSI if a medical comorbidity was present at the time of surgery compared to those without a comorbidity (17.96% *vs* 5.96%, P < 0.0001)[55]. Patients with diabetes and vascular complications had the highest SSI rate (OR: 7.85, 95%CI: 6.25-9.86, P < 0.001), followed by obesity (OR: 3.2, 95%CI: 2.9–3.6, P < 0.001)[55,56]. Bruggeman *et al*[53] also showed that patients with one or more risk factors had a greater rate of wound complications than patients without risk factors (P < 0.0001)[53].

Hallux surgery

Dufour *et al*[18] examined the association between obesity and foot problems in older adults and found that both men and women had an increased risk of morbidity with increasing BMI. Interestingly, severely obese women were less likely to develop hallux valgus (HV)[18]. Frey and Zamora[57] also identified that normal weight people had an increased likelihood of HV[57]. We suspect that shoe wear options in patients with large feet may have a wide toe-box and thus help prevent the development of HV.

Chen *et al*[58] found a 7-fold increase of re-operation in obese patients due to rates of non-union[58]. They proposed that fat-derived adipokines resulted in poor bone healing[58]. While obese patients had a poorer preoperative AOFAS Hallux Metatarsophalangeal-Interphalangeal scores, they were able to achieve functional outcome scores comparable to those of patients of normal weight, suggesting that obese patients can experience a greater improvement in function after HV surgery[58].

Percutaneous HV procedures have found no difference in complication or reoperation rates between normal weight and obese adults after surgery[59]. This may be due to the fact that surgeries on the forefoot are typically shorter, usually performed under regional anesthesia, and can allow for partial weight bearing operatively.

At present, it is unclear if BMI has an adverse effect in HV surgery. Although some studies suggest higher reoperation rates, and others state no correlation[60], most authors agree that while it is important to warn obese patients of the significantly higher risk of repeated surgery, these patients should not be excluded from undergoing HV surgery[58], and in most scenarios BMI should not influence prognosis[61].

LIMITATIONS

Obesity cannot be seen as an isolated risk factor for surgical procedures. Various clinical diseases arise from obesity and a better stratification of individuals should be contemplated when designing clinical studies to reach more significant clinical results according to each risk factor that englobes obesity. Large prospective studies are an urge in the field to identify associated risk factors and accurately stratify patients. This would enable choosing management adequately, including appropriate selection for surgery, in order to optimise the clinical outcomes.

CONCLUSION

Obesity significantly increases the risk of post-operative complications for many foot and ankle surgical procedures. However, these patients should not be excluded from undergoing surgery as improved functional outcomes can be achieved, relieving suffering for many patients. A multi-disciplinary pre-operative approach including different specialties should be considered to address the possible clinical implications such as wound infections, cardiovascular events and delayed functional recovery after these procedures. This way, risks can be reduced by preparing patients in the best way before a surgical procedure.

Future steps are necessary regarding better quality of evidence studies to examine how obesity and associated complications may contribute to unwanted surgical outcomes and how these risks can be managed.

FOOTNOTES

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MINIREVIEWS

Surgical strategy of the treatment of atypical femoral fractures

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Abstract

The atypical femoral fracture (AFF) has been attracting significant attention because of its increasing incidence; additionally, its treatment is challenging from biological and mechanical aspects. Although surgery is often required to manage complete AFFs, clear guidelines for the surgical treatment of AFFs are currently sparse. We reviewed and described the surgical treatment of AFFs and the surveillance of the contralateral femur. For complete AFFs, cephalomedullary intramedullary nailing spanning the entire length of the femur can be used. Various surgical techniques to overcome the femoral bowing common in AFFs include a lateral entry point, external rotation of the nail, and the use of a nail with a small radius of curvature, or a contralateral nail. In the case of a narrow medullary canal, severe femoral bowing, or pre-existing implants, plate fixation may be considered as an alternative. For incomplete AFFs, prophylactic fixation depends on several risk factors, such as a subtrochanteric location, presence of a radiolucent line, functional pain, and condition of the contralateral femur; the same surgical principles as those in complete AFFs can be applied. Finally, once AFF is diagnosed, clinicians should recognize the increased risk of contralateral AFFs, and close surveillance of the contralateral femur is recommended.

Key Words: Atypical femoral fracture; Surgical treatment; Surveillance; Contralateral femur; Femoral bowing

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Core Tip: For complete atypical femoral fractures (AFFs), cephalomedullary intramedullary nailing spanning the entire femur and various surgical techniques to overcome femoral bowing should be considered. For incomplete AFFs, the recognition of impending complete fractures is important. For the contralateral femur, close surveillance is recommended because of the increased risk of contralateral AFF.

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INTRODUCTION

The atypical femoral fracture (AFF) has attracted significant attention since Odvina *et al*[1] first reported non-traumatic subtrochanteric fractures in the femur in nine patients with the prolonged use of bisphosphonate therapy (BP). The treatment of AFFs is challenging, even for skilled orthopedic surgeons. Biologically, long-term use of anti-resorptive agents is associated with reduction of bone turnover and altered biomechanics[2]. The inhibition of the bone remodeling process by reducing the activity of osteoclasts causes changes in the mineral and matrix properties of the bone, consequently increasing the thickness of the bone cortex. As a result, bone strength and stiffness increase, making the bone more brittle and susceptible to fragility fractures. Also, biomechanical analyses indicate that tensile stresses are high in the lateral femoral cortex and these can predispose the AFFs[3]. In addition, it affects primary and secondary bone healing[2-4], resulting in delayed union or non-union[5]. In addition, AFFs are often encountered in unfavorable mechanical environments, such as anterolateral bowing of the femur[6], and intramedullary nailing (IMN) may not fit the femur[7-9]. As the incidence of AFF is rising owing to an increase in the aging population[4] and is often associated with the potential risk of poor bone healing, the treatment of AFF has become a major issue in the medical community, leading to convening a task force by the American Society of Bone and Mineral Research[10,11].

In general, AFF often requires surgical treatment depending on the fracture pattern (complete or incomplete), location (subtrochanter or diaphysis), and presence of symptoms (thigh pain), which is considered the standard treatment for both complete and incomplete fractures. However, as there has been a lack of randomized controlled trials demonstrating the optimal treatment of AFFs, clear guidelines for surgical treatment are currently scarce[12,13], and treatment for AFF is being performed according to a lack of consensus based on expert opinions.

In the current study, we reviewed the current surgical treatment methods for complete and incomplete AFF and highlighted the specific considerations to be observed in unique situations, such as concurrent severe bowing and surveillance of the contralateral femur. Finally, we summarized the context by providing a management algorithm for AFFs based on contemporary evidence in the literature.

SURGICAL TREATMENT OF COMPLETE FRACTURES

AFFs can be classified into complete and incomplete fractures, and surgical treatment is inevitable for complete fractures[14]. Randomized clinical trials have not yet been conducted to determine the optimal surgical method for complete fractures; however, long cephalomedullary IMN spanning the full length of the femur has been recommended[6,10].

Biomechanical aspect should be considered for the surgical treatment of AFFs. Previous reports have suggested several reasons why IMN is preferred for plate fixation in AFFs. First, from a mechanical aspect, IMN has advantages, including a better load-sharing capacity and less bending moment owing to its more medial location compared to plate fixation[15,16]. Thus, devices with greater load sharing have an advantage in AFFs in terms of early ambulation in elderly patients. Second, because of decreased bone remodeling and the subsequent poor bone quality, the stress concentration around the end of implants may induce peri-implant stress fractures[17]. While it is difficult to span the full length of the femur with open plating, IMN has the advantage of spanning the whole femur, and therefore, stabile fixation can be achieved without imbalance between tensile force and compressive force of the fracture site and it may be better than plating in reducing subsequent fatigue fractures[18]. Biologically, osteoclastic activity is suppressed by previous anti-resorptive medication in AFF patients, thereby rendering bone remodeling and subsequent direct bone healing difficult[1-4]. Although direct bone healing is important in plate fixation, IMN may induce indirect bone healing by endochondral ossification, and decreased osteoclastic function may affect the fracture healing process lesser compared to other methods[19]. Also, Basically, biological damage can be minimized by avoiding incision and

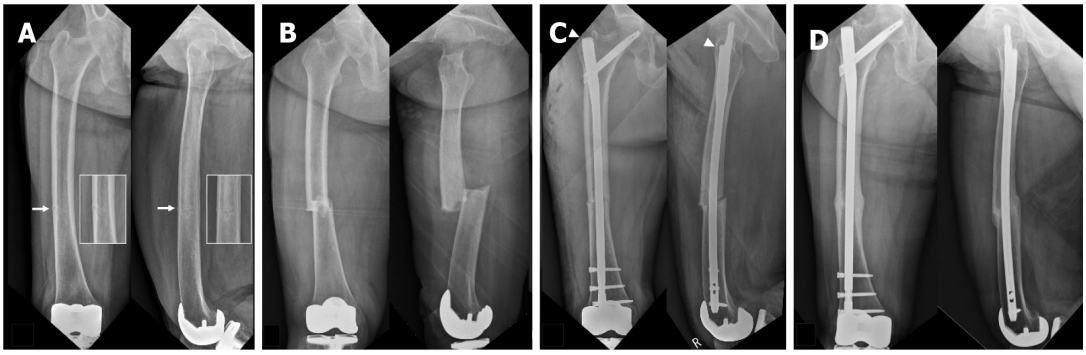
direct manipulation of the fracture site. In addition, Although intramedullary nailing can have detrimental effect on the cortical and the endosteal blood flow, it has important effect for bone healing with increased extraosseous circulation and the bone grafting effect from marrow reaming during IMN may enhance osteosynthesis in AFF patients with reduced fracture healing potential[20,21]. Finally, AFFs often accompany anterolateral bowing of the femur; however, contouring the plate to fit the three-dimensional (3D) curvature of the bowed femur during surgery requires additional time and a large incision for open plating itself in elderly patients[9]. Therefore, IMN has theoretical advantages over plating in terms of mechanical, biological, and practical aspects.

Systematic reviews have shown that a greater proportion of complete AFFs treated with plate fixation required reoperation compared to those individuals treated with IMN[11,22]. Egol *et al*[23] reported favorable functional outcomes with IMN in the treatment of AFFs. Shkolnikova *et al*[24] demonstrated that extramedullary fixation, such as plate fixation, resulted in a functional decline in the majority of patients with AFFs. Thus far, studies have shown that IMN provides better radiographic and functional outcomes when compared to plate fixation[11,22].

The selection of an IMN implant design is important for AFFs. The largest possible nail should be used to avoid distal perforation and iatrogenic fractures caused by IMN[25]. If accompanied by femoral bowing, it is recommended to use a nail with a small radius of curvature (ROC)[7,25]. The conventional standard IMN involves the oblique transverse orientation of the proximal interlocking screws across the proximal femur. However, because these interlocking screws do not cover the femoral neck, there is a potential risk of stress fractures around this unprotected area[26]. As cephalomedullary IMN incorporates one or two large proximal locking screws into the nail and places them in the direction of the femoral head, this method may protect the femoral neck from subsequent fragility fractures. A recent study showed that cephalomedullary IMN reduces the incidence of delayed peri-implant fragility fractures, newly developed AFFs, and non-unions in patients with AFF[27].

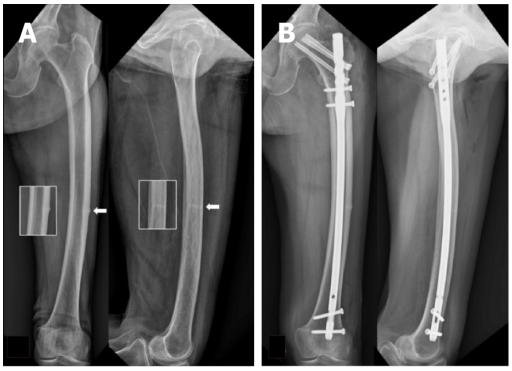
AFFs have been reported to have high complication rates with operative fixation because of their unique properties, including anterolateral bowing of the femur[4,28,29]. Although IMN follows the standard surgical technique for subtrochanteric or shaft fractures, meticulous surgical techniques may be necessary to treat complete AFFs. In AFFs, the lateral cortex of the femur at the fracture site is often thickened, which makes nail passage difficult. To overcome this, the medullary canal can be over-reamed by 2.5 mm to ensure good nail passage, stimulate fracture site healing, and reduce iatrogenic fractures[30]. The quality of fracture reduction is important for determining the healing of AFFs, and mal-alignment is strongly correlated with the healing time and failure rate[31,32]. Moreover, if the IMN straightens the curved femur, this not only affects the healing time but also induces limb length discrepancy (LLD)[9]. A previous study analyzed the factors affecting healing in complete AFFs and reported that IMN without cortical breakage around the fracture site and reduction of the fracture gaps anteriorly and laterally affected the healing of AFFs[33]. Since non-union may occur if there are residual fracture gaps anteriorly and laterally more than 2 mm, it is recommended to attempt narrowing of the gaps using the back-slapping method by applying the angular stable locking system (ASLS®, Synthes GmbH, Oberdorf, Switzerland) for distal interlocking. Another study reported that the quality of fracture reduction was the most important factor for achieving bone union; additionally, the cutoff points for the neck-shaft angle, differences in the neck-shaft angle, and sagittal angulation were 125.6, 4.4, and 5.5°, respectively[34]. If adequate alignment cannot be achieved with traction, particularly in subtrochanteric AFFs associated with strong muscle forces, percutaneous wiring or preliminary plating may be necessary[32,33]. The possible causes of failure include the position of the nail as well as the quality of reduction, and it is important to consider the respective starting points[35]. If loss of reduction occurs during nail passage, repositioning of the starting point should be considered.

IMN in AFF with severe anterolateral bowing is challenging, and various methods have been suggested to overcome this difficulty[8]. First, as mentioned above, if the bowing of the femur is severe, it is recommended to use a nail with as small ROC as possible[7,27]. Second, the entry point lateral to the greater trochanter or piriformis fossa can be used as a site of insertion (Figure 1)[36]. Third, an alternative method is to use the opposite side of the nail (Figure 2)[37]. Some femoral nails have an anterior curve as well as proximal lateral bending, and thus can be aligned with the anatomical axis of the femur with anterolateral bowing by rotating the zig 180° to the opposite side of the nail. The fourth method involves adjusting the alignment by externally rotating the nail. In this method, the anterior curvature of the nail is externally rotated to fit the anterolateral bowing of the femur, and the proximal lateral bending of the nail is matched to the anterior curvature of the femur[6]. However, this method requires the use of a standard nail with proximal screws in the transverse direction instead of the cephalomedullary nail in AFFs and demonstrates concerns related to femoral neck stress fractures. Finally, with the introduction of the minimally invasive plate osteosynthesis (MIPO) technique, which can facilitate indirect bone healing, plate fixation can be considered as an alternative to IMN in AFF with an extremely narrow canal, no nail match with severe femoral bowing, or pre-existing metal implants (Figure 3)[38]. When plate fixation is considered for AFF treatment, spanning the full length of the femur is recommended, and prophylactic screw fixation toward the femoral neck may be necessary to prevent peri-implant or femoral neck fractures (Figure 4)[18,39].



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Figure 1 Images of an 80-year-old woman. A: An 80-year-old woman was transferred from a spine clinic because of intractable right thigh pain for three months. Radiographs revealed a transverse radiolucent line (white arrows and insets) on the lateral and anterior cortex of the right femur with 10° of varus. The patient refused prophylactic surgery for incomplete atypical femoral fracture (AFF); however, medical treatment including a switch from bisphosphonate to teriparatide was initiated. According to a scoring system[11], the risk for impending complete AFF was scored as 10 points; B: Two months later, she visited the emergency department due to progression to a complete AFF; C: She underwent fixation with a long cephalomedullary nail (Trochanteric Fixation Nail-Advanced®, DePuy Synthes, Winterthur, Switzerland) spanning the whole length of the femur. It is to be noted that the entry point of the nail is lateral and anterior to the greater trochanter tip (arrowheads); D: Radiographs taken at 18 mo postoperatively showed healing of the fracture site.



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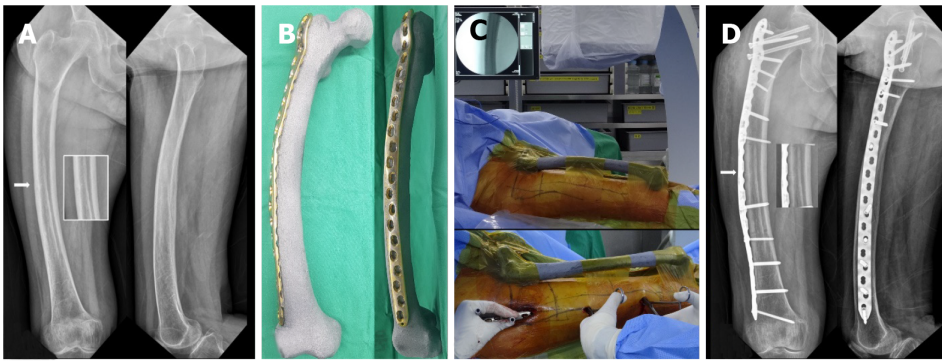
Figure 2 Images of an 81-year-old woman who had taken bisphosphonate for two years. A: An 81-year-old woman who had taken bisphosphonate for two years visited the outpatient clinic complaining of left thigh pain for two months. Radiographs revealed a transverse beak and radiolucent line (white arrows) on the lateral and anterior cortex of the right femur with 10° of varus and 7° of anterior angulation. According to a scoring system[11], the risk for impending complete atypical femoral fracture was scored as 11 points; B: She underwent fixation with an opposite-side (right side) standard nail (Sirus Femoral Nail®, Zimmer, Warsaw, IN, USA). Prophylactic screw fixation toward the femoral neck on her left femur was performed to prevent potential femoral neck fracture around the nail.

Delayed union, non-union, or implant failure has been a common complication reported after the surgical treatment of AFFs[11,22,40]. Among them, non-union is the most frequent complication, followed by implant failure. According to a recent systemic review including 348 complete AFFs, reoperation was required in 6 out of 38 (15.7%) extramedullary fixation devices used for treating AFF, whereas revision was required in 20 out of 310 (6.45%) IMNs[22]. This finding is consistent with the results reported by Koh *et al*[11]; a greater proportion of complete AFFs treated with plate fixation (31.3%) required reoperation than those treated with IMN (12.9%) (P<0.01). With regard to the clinical outcomes, the patients who underwent IMN demonstrated better functional scores[40]. A previous study reported that IMN returned to the baseline function in 64% and pain-free status in 66% of patients at postoperative 12 mo[23], while another study with a follow-up duration of up to 46 mo demonstrated a functional decline in 64% of the patients, the majority of whom had extramedullary fixation devices [24]. Unlike the increased mortality associated with typical osteoporotic fractures of the femur, a previous study reported that the mortality rate after treating AFFs was lower than that after treating ordinary femoral fractures[41]. Therefore, although the treatment of AFFs is often challenging, orthopedic surgeons may obtain promising outcomes if they choose a proper treatment option according to the individual and pay attention to meticulous surgical techniques.



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Figure 3 Images of a 75-year-old woman underwent a fixation with a long standard nail. A: A 75-year-old woman underwent a fixation with a long standard nail due to a complete atypical femoral fracture (AFF) on her right femur two years ago at another hospital and kept taking bisphosphonate (BP) until she visited our clinic; B: She reported left groin and thigh pain for six months. Radiographs revealed arthritis on her left hip joint (arrowheads) and transverse beaks with radiolucent lines ("dreaded black line") on the lateral and anterior cortex of the left femur (white arrows and insets). According to a scoring system[11], the risk for impending complete AFF was scored as 8 points and BP medication was discontinued; C: Before total hip arthroplasty (THA) to treat hip arthritis, a locking compression plate was pre-contoured along the shape of the bone model with 3D printing rapid prototyping; D: During THA, the sterile 3D-printed model was placed in the same position as that of the femur and used as a surgical navigation. Fixation with the pre-contoured plate *via* minimally invasive plate osteosynthesis was performed to treat incomplete AFF; E: Radiographs taken three years postoperatively showed complete healing of the AFF without progression of femoral bowing or implant-related complications.



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Figure 4 Images of a 75-year-old woman who had taken bisphosphonate. A: A 75-year-old woman who had taken bisphosphonate for a period of four years visited our clinic with right thigh pain for three months. Radiographs showed a transverse radiolucent line (white arrow and inset) on the apex of the lateral cortex of the right femur with 7° of varus. According to a scoring system[11], the risk for impending complete atypical femoral fracture (AFF) was scored as 9 points; B: Before the surgery, a locking compression plate was pre-contoured along the shape of the bone model with 3D printing rapid prototyping; C: During the surgery, the sterile 3D-printed bone model was placed in the same position as that of the femur and used as a surgical navigation; D: Fixation with pre-contoured plate fixation for incomplete AFF (white arrow and inset) with severe bowing was performed *via* minimally invasive plate osteosynthesis. It is to be noted that additional prophylactic screw fixation toward the femoral neck was performed to prevent potential femoral neck fractures.

SURGICAL TREATMENT OF INCOMPLETE FRACTURES

The natural history of incomplete AFFs has not yet been determined; therefore, taking decisions regarding whether or when to perform surgery is difficult[42]. Incomplete AFFs are easily misdiagnosed or undiagnosed before the fracture becomes complete (Figure 1)[43]. Meanwhile, a previous study reported that 10 of 14 (71.4%) incomplete AFFs were eventually treated surgically because of their progression to complete fractures or intractable pain[14]. The purpose of prophylactic surgery in incomplete AFFs is not only to reduce pain, but also to prevent progression to complete fractures, thereby avoiding commonly developed complications after complete AFFs, such as delayed union, non-union, implant failure, and LLD, as described above[11,44]. Therefore, it is important to assess whether the optimal option for treating incomplete AFFs is to perform prophylactic surgery or close observation. Recently, a scoring system was introduced to identify impending fractures among incomplete AFFs according to the fracture location, nature of pain, the extent of the radiolucent line, and condition of the contralateral femur (Table 1)[12]. If the score is equal to or greater than eight points, prophylactic fixation is recommended. Contrastingly, patients with a score of seven or less may be treated conservatively, and the responsible physician should carefully evaluate the patient's symptoms and radiographic findings to identify the changes during follow-up. In addition, some authors have recommended prophylactic fixation for incomplete AFFs in cases with the "dreaded black line" on radiographs, varus femoral bowing, a history of contralateral AFF, or failure to improve after two or

Table 1 A scoring system for the surveillance of impending complete atypical femoral fracture in an incomplete state[11]

Variables	Score		
	1	2	3
Pain	None	Mild	Functional
Site	Others	Diaphyseal area	Subtrochanteric area
Contralateral femur	Complete fracture	Incomplete fracture	Intact
Radiolucent line	Focal changes	Less than 1/2	More than 1/2

three months of conservative management[38,45].

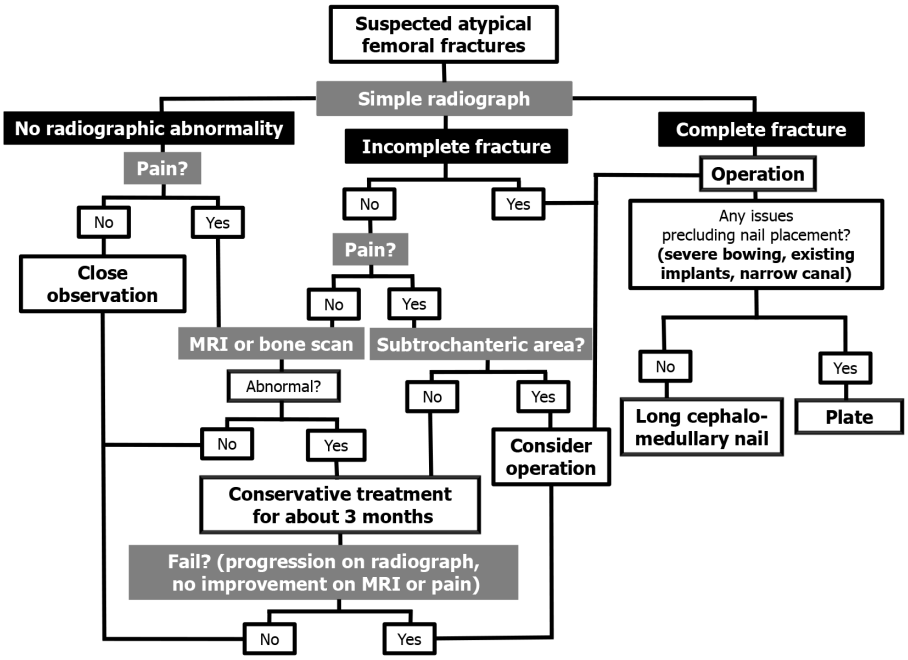
The same surgical principles as those for complete AFFs can be applied; thus, cephalomedullary IMN has been proposed as a standard prophylactic fixation for incomplete AFFs[46]. However, for those with severe femoral bowing, which is common in incomplete AFFs, care should be taken because IMN may lead to iatrogenic complete fractures and result in LLD, delayed- or non-union[11,46]. Recently, a report demonstrated that the use of a 3D printing technique could facilitate the reconstruction of severely bowed femurs with incomplete AFF, which were then fixed with a pre-contoured plate using an MIPO technique to match the shape of the femur (Figure 3 and 4)[9]. In this case, additional prophylactic screw fixation toward the femoral neck was required to prevent stress concentration and potential femoral neck fractures.

Although the indications or methods of prophylactic fixation for incomplete AFFs are still controversial, this approach has generally been associated with excellent results[23,47]. A previous study reported that incomplete AFFs treated with surgery showed radiographic healing in 100% and pain-free status in 81% of patients at a mean of 7.1 mo postoperatively[23]. In a systematic review of 109 incomplete AFFs treated with prophylactic fixation (78 fractures with IMN, 12 fractures with plate fixation, and the remaining by unspecified means), 106 fractures (97%) healed radiologically without any revision surgery at an average of 7 mo (range, 1.5–20 mo)[11].

SURVEILLANCE OF CONTRALATERAL FEMUR

Although the pathogenesis of AFFs remains unclear, patients with unilateral AFF have an increased risk of subsequent contralateral fractures[10]. Previous studies have reported that up to 62.9% of patients with AFFs had bilateral fractures or radiographic abnormalities in the contralateral femur[10,48]. However, as most patients with complete AFFs may have an asymptomatic contralateral femur at initial presentation, it is easy to underestimate the potential AFF in the contralateral femur until the fracture becomes complete (Figure 3)[49]. Several authors have investigated the natural course of the contralateral femur in patients with AFF and reported that up to 88.5% of contralateral femurs eventually progressed to an incomplete or complete fracture within a period of three years[50-52]. This is because reduced weight bearing in the fractured femur may propagate incipient stress fractures in the contralateral femur[9]. A recent report highlighted that the postoperative use of BP might influence the development of contralateral AFF[50]. Therefore, once AFF is diagnosed, a contralateral femur should be evaluated and appropriate medical treatment, including the discontinuation of BPs and initiation of calcium and vitamin D supplementation, must be initiated in addition to endocrine assessments, such as bone turnover markers[53]. When diagnosing a contralateral incomplete AFF, clinicians should decide whether to perform prophylactic surgery or conduct a close observation. As described in the surgical treatment of incomplete fractures, a history of contralateral AFF is a potential risk for an impending complete fracture; thus, the current consensus is that contralateral incomplete AFF may be considered an impending complete fracture[12,23,54].

In summary, orthopedic surgeons should be aware of the potential risk of contralateral AFF in patients with unilateral AFF and must evaluate the contralateral side. Although the validated guidelines to support the subsequent decision-making processes remain unclear, prophylactic fixation for contralateral incomplete AFF may be recommended in cases where the risk of impending complete AFF is increased (Figure 5)[55]. In the absence of such signs of incomplete AFF, close surveillance of the contralateral femur for at least two years may be required[50]. Once AFF is diagnosed, clinicians should discontinue BPs and provide calcium and vitamin D supplements. The use of bone-forming agents may promote healing and reduce the potential risk of complete AFF on the contralateral side[10].



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Figure 5 A proposed treatment algorithm for suspected atypical femoral fracture. MRI: Magnetic resonance imaging.

CONCLUSION

The incidence of AFFs is increasing, and their treatment is challenging in terms of the biological and mechanical aspects. For complete AFFs, the cephalomedullary IMN spanning the entire length of the femur can be primarily used. The various surgical techniques for IMN to overcome the femoral bowing common in AFFs include over-reaming, use of a lateral entry point, external rotation of the nail, and the use of a nail with a small ROC or contralateral nail. In cases of narrow canals, severe femoral bowing, or pre-existing metal implants, plate fixation may be considered as an alternative. For incomplete AFFs, prophylactic fixation depends on potential risk factors such as subtrochanteric location, the presence of a radiolucent line, functional pain, and condition of the contralateral femur, and the same surgical principles as those in complete AFFs can be applied. Finally, once AFF is diagnosed, the clinicians should recognize the increased risk of contralateral AFF, and close surveillance of the contralateral femur is recommended.

FOOTNOTES

Author contributions: Shim BJ performed the majority of the writing, prepared the figures and tables; Won H provided the input in writing the paper; Kim SY performed data accusation and writing; Baek SH designed the outline and coordinated the writing of the paper.

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MINIREVIEWS

Amputation in diabetic foot ulcer: A treatment dilemma

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Abstract

Diabetic foot is a clinical manifestation of diabetes with a wide range of symptoms, including ulceration, osteomyelitis, osteoarticular destruction, and gangrene, as a consequence of advanced disease. Some diabetic foot cases present general indications for amputation, including dead limb, threat to the patient's life, pain, loss of function, or nuisance. Various tools have been introduced to help decision-making in amputation for diabetic foot. However, it remains a conundrum because diabetic foot involves multiple pathomechanisms and factors that hinder its outcomes. Sociocultural issues often impede treatment from the patient's side. We reviewed different perspectives in diabetic foot management, particularly related to amputation. In addition to deciding whether to amputate, physicians should address amputation level, timing, and ways to avoid patient deconditioning. Surgeons should not be autocratic in these circumstances and should be aware of beneficence and maleficence when considering whether to amputate. The main goal should be improving the patients' quality of life rather than preserving the limb as much as possible.

Key Words: Diabetic foot; Ulcer; Amputation; Decision-making; Perspective

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Core Tip: Making a decision regarding amputation for diabetic foot patients is not as simple as following guidelines, such as scoring systems. There are many influential factors that come from different perspectives and are sometimes contradictory. Decision-making should consider other clinical and sociocultural factors, with the improvement of patient quality of life as the main goal.

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INTRODUCTION

The rising prevalence of diabetes represents a major public health and socioeconomic burden on society. Diabetes presents relatively mild symptoms that generally go unnoticed at early stages. Patients commonly seek medical treatment in later stages when complications occur. Diabetic complications are associated with poor glycemic control[1].

Diabetic foot is one clinical manifestation of diabetes with a wide range of symptoms, including ulceration, osteomyelitis, osteoarticular destruction, and gangrene, as a consequence of advanced disease (Figure 1). Some diabetic foot cases present general indications for amputation, including dead limb, threat to the patient's life, pain, loss of function, or nuisance[2]. Various scoring systems are applicable for clinicians to determine whether the indication for amputation is present, such as the mangled extremity severity score or diabetic ulcer severity score[3,4]. However, clinicians must address various factors that are not resolvable by these scoring systems in many cases. Therefore, decision-making is complicated. This article reviewed the contributing factors that are often encountered during decision-making in diabetic foot management, especially when it is related to amputation.

CLINICAL CONSIDERATIONS

The etiology of diabetic foot ulcer is multifactorial. Poor glycemic control is the major underlying cause of advanced glycation end product (AGE) accumulation circulating in the body, which affects various organs. AGE formation is one of the main mechanisms responsible for vascular damage in diabetes patients, and it alters the angiogenic reaction[5]. Angiopathy indicates a vascular defect that is associated with angiogenic abnormalities. Angiogenesis itself results from the balanced functions of pro- and antiangiogenic molecules. Defects in this angiogenic balance may result in excessive or antiangiogenesis[6]. The activity of various regulators determine this angiogenesis switch. Vascular endothelial growth factor (VEGF) is a signal protein responsible for blood vessel formation. Hypoxia-inducible factors (HIFs) are transcription factors that respond to decreases in cellular hypoxia. Exposure to high glucose inhibits HIF and VEGF expression in normal cells[6].

Peripheral artery disease (PAD) may be described as atherosclerotic occlusive disease of the lower extremities. Chronic hyperglycemia, dyslipidemia, and insulin resistance in diabetes mellitus patients are responsible for vascular wall derangements *via* promotion of vascular inflammation, endothelial cell dysfunction, abnormalities in blood cells, and factors affecting hemostasis[7]. AGEs contribute to impaired angiogenesis *via* a reduction in collateral vessel development. AGEs also participate in the modification of extracellular matrix molecules, which promote atherosclerotic lesion development[8,9].

Macroangiopathy or microangiopathy has a tendency to inhibit nutrient/oxygen supply. These conditions put the foot at risk for ulceration and hinder the wound-healing process[6]. These vascular problems in combination with increased plantar pressure due to fibrosis-related Achilles tendon contracture and loss of protective sensory function result in recalcitrant complicated foot ulceration[10]. The involvement of infrapopliteal vessels is commonly found in diabetes patients with PAD. When ischemia is established, the restoration of pulsatile blood flow by revascularization is paramount for limb salvage. The treatment options are angioplasty, surgical bypass, or subintimal recanalization with varied results[11,12].

Infection is a common complication in diabetes, and it is particularly attributable to hyperglycemia-related immunosuppression in which polymorphonuclear lymphocyte activity is hindered. Infection results in prolonged inflammation that prevents wound healing and keeps the microorganism portal of entry open, which eventually causes further infections[13]. Diabetic foot infection is difficult to manage. Timely diagnosis and appropriate intervention are essential in management strategies. Diabetic foot osteomyelitis (DFO) is the consequence of a soft tissue infection that spreads into the bone, and it involves the cortex first then the marrow. DFO showed an increase in multidrug-resistant organisms, primarily methicillin-resistant Staphylococcus aureus or extended-spectrum beta-lactamase-producing



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Figure 1 A complicated diabetic foot ulcer which required a careful decision-making.

bacteria[14,15]. The presence of osteomyelitis impedes infection control and raises the further need for medical treatment and surgeries[16]. Osteomyelitis requires surgery to remove portions of bone that are infected or dead. Although an aggressive surgical approach may be mandatory, retrospective studies showed that conservative treatment effectively promoted wound healing and reduced the risk of major amputations[14,17]. Recurrent ulcers are a significant cause of hospitalization and amputation[18].

Although diabetic foot ulcer is generally painless, it is viewed as the main reason for ulcer formation due to the loss of protective sensory function, and as many as 27% of patients experience painful diabetic peripheral neuropathy (DPN) to various degrees[19]. However, severe neuropathy is not the only cause of pain because there are other causes precipitating pain, including ischemia, infection, and oxidative stress-related mechanisms. Other than clinical findings, DPN may be diagnosed using several adjunct examination tools, such as nerve conduction studies. One of the newest tools is the assessment of transcutaneous oxygen pressure ($TcPO_2$), in which the sitting-supine position difference in $TcPO_2$ is higher in DPN patients than control subjects[20]. Various drugs have been introduced to address this problem, including selective serotonin and norepinephrine reuptake inhibitors, anticonvulsant agents, and opioid receptor agonists, but pain relief remains poor for most patients[21].

Longstanding diabetic foot, particularly when treated insufficiently, may produce some disabling deformities. The wound may be healed in this condition, but functional gait or ambulation is hindered. When physical activity is decreased, static positioning with fibrotic changes within the muscle will lead to contracture formation. Considering the muscle imbalance between the anterior and posterior groups, equinus contracture will likely develop[10]. Combined with muscle atrophy resulting from disuse and neuropathy, deformity and function loss may occur and result in a condition called damned nuisance, in which the limb is functionless, and amputation followed by prosthesis application would be a better solution. The deformity can also occur from osteoarticular destruction or prior autoamputation.

AMPUTATION AND COMMON CONUNDRUMS

Amputation is generally the last choice for the treatment of non-salvageable limbs[22]. The main indications for amputation include various conditions, such as posing a threat to the body, such as the spreading of infection or tumors, the presence of necrotic tissue that constitutes a medium for pathological microorganism growth and a functionless limb, and some situations in which the patient and clinician believe that amputation will yield better results in overall function and quality of life in the absence of dead or dangerous limbs. Clinical decision-making on whether to amputate or to determine the amputation level frequently deviates from the factors that the patient and surgeon initially considered when the patient first presented with diabetes.

Amputation is divided into major or minor, according to its level. Major amputation is defined by any ankle disarticulation, transfemoral amputation, or transtibial amputation, and minor amputation is defined as a toe or transmetatarsal amputation[23]. Determining the amputation level is critical to the

efficacy of management. Amputation should be performed at a level with sufficient blood supply for wound healing. Arterial angiography, Doppler ultrasonography, and perfusion pressure are acceptable methods. The latest advanced examination tools, such as transcutaneous oxygen pressure measurement, are reliable in predicting wound healing in diabetic foot[24]. Soft tissue coverage should also be considered in deciding the amputation level. For great toe gangrenes, ray amputation is preferred over metatarsophalangeal joint disarticulation despite good blood supply and biomechanical advantages of the latter. Less soft tissue bulk and higher pressure at the distal part result in eventual wound breakdown. Exposed cartilage following disarticulation may be a source of infection *via* necrotic tissue formation[22]. In addition to local vascular status, systemic condition will also determine the result. Lower albumin and higher glycated hemoglobin, C-reactive protein, white blood count, and creatinine levels are determinants of failed amputations that need subsequent reamputation[25]. Amputation is contraindicated in these situations and delayed until systemic improvement is achieved, except in emergency situations.

Despite the clear clinical findings prompting amputation, the negative perception of amputation remains, which results in hesitation to undergo amputation[22]. The ability to cope with an amputation is affected by clinical measurements, cosmesis, cultural issues, social support, and the patients' pre-amputation coping style[26]. Although many patients refuse amputation and are discharged against medical advice, they often request that the surgeon perform amputation as distally as possible without understanding the indications. The fact that amputation may be perceived as a taboo makes discussion with patients and their relatives difficult[27].

Leg amputation is related to increased dependence. In addition to the medical benefit obtained from well-indicated amputation, function may be restored using proper prosthetics to regain the patient's independence. However, the recovery of function is not solely based on prosthetics. Older age, poor balance, previously low function level, and higher amputation level are some determinants of disability status[26]. Considering the physical demands, amputee patients spend more energy during walking than able-bodied persons. The energy expenditure of transfemoral amputees is higher than transtibial amputation[28]. Therefore, choosing the amputation level should also be in concordance with further postoperative rehabilitation plans.

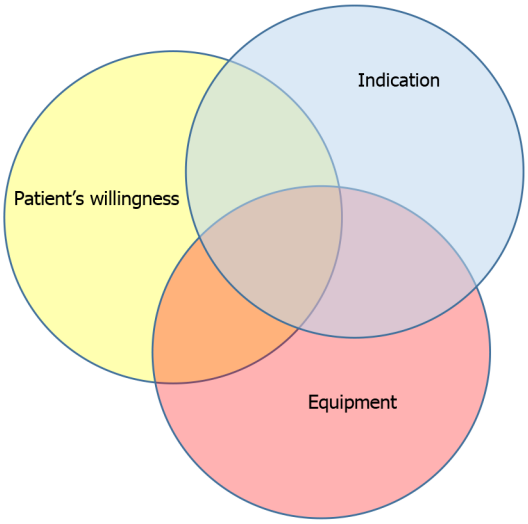
DECISION-MAKING

In regard to decision-making for amputation, various factors may be determinants. Choosing the level of amputation is the mainstay of treatment, but the timing of surgery is also important.

While establishing the indication is paramount, its contraindication is also critical. The general contraindication for amputation is the patient's inability to tolerate anesthesia or the surgery itself, such as the accompanying systemic problems. Amputation at a particular level is contraindicated when inadequate blood supply for wound healing is encountered, when the infarcted area is undetermined, or when malnutrition occurs that hinders wound healing. Therefore, amputation is contraindicated when the quality of life is reduced afterward.

PAD and infections are the main causes of lower-leg amputations. Limb salvage in diabetic patients with PAD requires comprehensive management, including medical therapies. Other than glucose-lowering and lipid-lowering drugs, these patients need medications that aim to improve vascular functions, including antiplatelet therapy, protease-activated receptor-1 antagonists, anticoagulants, or vasodilators[29]. Due to ischemic and neuropathic pain, many diabetic foot patients continually consume analgesics, including several anticonvulsants[21]. Antihypertensive and antithrombotics are the major medications related to polypharmacy management for the elderly population, which increase the risk of adverse drug reactions (ADRs)[30]. Chronic kidney disease occurs as a diabetic complication *via* renal fibrosis. Therefore, longstanding drug administration in limb preservation should be monitored carefully. Deprescription should be considered to avoid ADRs. PAD is difficult to treat in diabetes patients due to various comorbidities. Atherosclerotic lesions are multilevel with a high prevalence of long occlusions. New techniques and technologies have been introduced for addressing PAD with various results that were likely related to the individual patient conditions[31,32].

Revascularization is a procedure to restore blood supply to the tissue by addressing the blocked blood vessels. The aim is to salvage the limb by healing the trophic disorder. The indications included critical ischemia with some suggestive vascular examination findings (arterial pressure < 50 mmHg or $TcPO_2$ < 30 mmHg). However, prerequisite conditions must be met, including a satisfactory support bed, a distal artery of a good caliber, and the presence of a plantar arch[11]. Vascular surgeons generally choose between endovascular procedures (transluminal or subintimal), bypasses, or hybrid techniques that include both procedures. The choice of revascularization technique depends on the type of lesion, the presence or absence of stenosis, and thrombosis and their length[11]. Iatrogenic injuries were reported but were mostly self-limited and of minimal clinical significance. Some life-threatening complications may occur, including ruptures, perforations, and pseudoaneurysms. Patient subpopulation selection is important to avoid unpredicted complications[33]. The main objective of revascularization is wound healing and limb salvage. At the one-year follow-up, 60% or more ulcers had healed



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Figure 2 Contributing factors in decision-making process for amputation.

with endovascular procedures or open bypass surgery. However, the overall results demonstrate improved rates of revascularization compared to conservative treatment[31].

Revascularization is mandatory in ischemic limbs for wound healing and as a prerequisite for further surgical procedures, including debridement and amputation. Otherwise, re-amputation will likely be needed[22]. Many patients presented contraindications for minor or major amputation, systemic or local, including unfeasible revascularization. Autolytic debridement may be an option in this setting, or major amputation at the safe level. Autolytic debridement itself is safe because it uses the natural ability of the body's own enzymes to remove dead tissues. To achieve autolytic debridement, the maintenance of a moist local wound environment is paramount[34].

Regarding limb salvage options, wound bed preparation *via* serial debridement is important, initially to limit the spread of infection. There are various advanced treatment options for recalcitrant diabetic foot wounds, such as hyperbaric oxygen therapy and platelet-rich gel treatment. Hyperbaric oxygen therapy involves the patient entering a pressurized room and breathing almost pure oxygen, which increases the amount of oxygen in the bloodstream and eventually boosting oxygen flow to the wound. Hyperbaric oxygen therapy offers great benefit in diabetic foot ulcer treatment and the reduction of amputation[35,36]. Autologous platelet-rich gel therapy is another option that effectively improves the healing of diabetic foot ulcers by increasing the concentration of platelets and growth factors in the wound and improving the surrounding microenvironment[37]. When the infection is controlled and granulation induces healing, limb reconstruction can proceed. Therefore, vascular flow is predominant. Thorough evaluation and approaches are needed to ensure this reconstructive procedure. Small, vascularized areas with no bone exposed may be grafted for nonbearing areas or local flaps in weight-bearing areas. Complex wounds are considerable for limb reconstructive procedures. Either decision must be made by the team and family[38].

Other than clinical measurements, patients' quality of life is an important factor to evaluate. Diabetic foot has a negative impact on patient quality of life. Pain from ischemia, dependent status, daily ulcer dressing, and unemployment stress were some the major causes of decreased quality of life[39]. Considering the frustrating circumstances and physical deconditioning caused by prolonged immobilization, early major amputation may be a viable option. With early major amputation followed by appropriate prosthesis use, particularly in patients who had lower possibility of successful limb salvage, deconditioning may be avoided, and quality of life is preserved or even improved. Cost analysis must also be considered. Earlier amputation may decrease the costs from the length of hospital stay, repeated surgery, medications, and daily expense. However, patients undergoing major amputation will need proper rehabilitation exercise and prostheses that may be costly as well[40]. Therefore, decisions should be made carefully and promptly.

CONCLUSION

Amputation is an option for patients with diabetic foot ulcers. Although there are absolute or relative indications for amputation, there is also a clinical decision algorithm to determine whether a limb can be salvaged. However, various influencing factors should also be considered (Figure 2). The objective is to reach an immediate optimum state for the patient and increase their quality of life. In contrast to clinical

discussion, cultural values also played a role in patients' willingness to undergo amputation, as suggested. Surgeons should not be autocratic in these circumstances and should be aware of beneficence and maleficence when considering the decision of whether to amputate.

FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Rotator cuff repair with an interposition polypropylene mesh: A biomechanical ovine study

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Abstract

BACKGROUND

Chronic large to massive rotator cuff tears are difficult to treat and re-tears are common even after surgical repair. We propose using a synthetic polypropylene mesh to increase the tensile strength of rotator cuff repairs. We hypothesize that using a polypropylene mesh to bridge the repair of large rotator cuff tears will increase the ultimate failure load of the repair.

AIM

To investigate the mechanical properties of rotator cuff tears repaired with a polypropylene interposition graft in an ovine ex-vivo model.

METHODS

A 20 mm length of infraspinatus tendon was resected from fifteen fresh sheep shoulders to simulate a large tear. We used a polypropylene mesh as an interposition graft between the ends of the tendon for repair. In seven specimens, the mesh was secured to remnant tendon by continuous stitching while mattress stitches were used for eight specimens. Five specimens with an intact tendon were tested. The specimens underwent cyclic loading to determine the ultimate failure load and gap formation.

RESULTS

The mean gap formation after 3000 cycles was 1.67 mm in the continuous group, and 4.16 mm in the mattress group (P = 0.001). The mean ultimate failure load was significantly higher at 549.2 N in the continuous group, 426.4 N in the mattress group and 370 N in the intact group (P = 0.003).

CONCLUSION

The use of a polypropylene mesh is biomechanically suitable as an interposition graft for large irreparable rotator cuff tears.

Key Words: Rotator cuff repair; Massive tear; Interposition graft; Biomechanics; Polypropylene mesh

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Core Tip: Our ex-vivo ovine model demonstrates that the use of a polypropylene mesh is mechanically suitable as an interposition graft for large irreparable rotator cuff tears. Its use results in a repair that is at least as robust as an intact rotator cuff tendon. When paired with a continuous suturing technique, its resultant superior mechanical properties may potentially reduce re-tear rates after repairing large or massive rotator cuff tears.

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INTRODUCTION

Rotator cuff tears are one of the most common shoulder conditions that orthopaedic surgeons treat. Chronic large to massive tears are difficult to treat due to development of tendon retraction, muscle atrophy and fatty infiltration. In addition, re-tear after primary repair of large to massive tears are common, reportedly between 40%[1] to 94%[2].

Complete, anatomic rotator cuff repair with restoration of the tendon footprint is the preferred treatment option, but it is often not possible in up to 20% of patients with large to massive rotator cuff tears[3]. Numerous joint-preserving procedures have been attempted to address this group of patients with an irreparable tear – tendon transfers of the latissimus dorsi or pectoralis major, superior capsular reconstruction and patch augmentation are among the salvage procedures described[4].

Several materials have been investigated for the purpose of augmenting the rotator cuff repair. The ideal material should provide a biomechanical advantage, be biocompatible and allow for ingrowth of host tissue. The fascia lata and human dermal allografts have been used in clinical practice to repair massive rotator cuff tears. Fascia lata autograft[5] or allograft[6], and human dermal allografts[7,8] have been used as interposition grafts and are also commonly used for superior capsular reconstruction[9]. Commercially available human dermal allograft has an ultimate load of 313 N at 1.4 mm thickness, while fascia lata allograft had a higher ultimate load of 350 N at 1 mm thickness[10]. In clinical studies, the healing rates when human dermal allograft is used is only between 59% to 74%[7,11].

To improve the healing rates, we propose using a synthetic polypropylene mesh to increase the tensile strength of the repair. The polypropylene mesh has been widely used in ventral abdominal and inguinal hernia repair for decades, and its safety and efficacy are well established[12]. However, the use of polypropylene mesh in rotator cuff repair is not well studied. A clinical study by Ciampi *et al*[13] found that the use of polypropylene patch augmentation for rotator cuff repair resulted in better function and strength, as well as lower re-tear rates compared to collagen patch augmentation or cuff repair alone.

We hypothesize that using a polypropylene mesh to bridge the repair of large rotator cuff tear is a biomechanically sound concept. If proven to be biomechanically viable, it will be the first step towards adopting this widely available, relatively inexpensive material in the clinical setting. Thus, we aim to investigate the time-zero mechanical properties of a rotator cuff repaired with a polypropylene interposition graft in an ovine infraspinatus ex-vivo model. In addition, we aim to compare if continuous stitching of the mesh to the remnant tendon on the greater tuberosity results in higher failure load compared to mattress stitching.

MATERIALS AND METHODS

Specimen preparation

Twenty fresh shoulders from skeletally mature sheep were procured from a local abattoir and used in this study. Ethics approval was not required for this study as it involved commercially available animal specimens. The supraspinatus muscle and tendon, as well as the subscapularis tendon and gleno-

humeral joint capsule were detached to isolate the infraspinatus muscle. In five specimens, the infraspinatus tendon was left intact in order to determine the ultimate failure load of intact tendon (Intact group).

The infraspinatus tendon was sharply detached from its insertion on the greater tuberosity to simulate a full thickness tear in the remaining fifteen specimens. This was followed by resecting a section of tendon 20 mm in length (medial-to-lateral dimension) to further simulate tendon retraction and actual loss of tendon substance due to degeneration at the tendon insertion (Figure 1).

Tendon repair

A polypropylene mesh (PROLENE™, ETHICON, NJ, United States) was cut to match the width of the remnant infraspinatus tendon. The length of the mesh was fixed at 60 mm to provide consistency in the test results. The mesh was then folded lengthwise over the tendon on the infraspinatus end and sutured together with four mattress stitches using Prolene 2-0. On the greater tuberosity side, the mesh was secured to the remnant tendon by continuous stitching with Prolene 2-0 in seven specimens (Continuous group). In eight specimens, the mesh was secured to the remnant tendon at the greater tuberosity by mattress stitches (Mattress group) (Figure 2).

Biomechanical testing

A custom-designed fixture was used to secure the specimens to a universal testing machine (Instron 5566, Instron, MA, United States) with a 10 kN load cell. A hole with diameter 6.5 mm was drilled through the scapula to mount the specimen onto the fixture. A two-piece clamp was used to secure the humerus at the desired abduction angle of 45° (Figure 3). The abduction angle represents the angle the humeral shaft makes with the vertical axis in the direction of cyclic loading.

Biomechanical testing was carried out in three phases – firstly, pre-cycle loading was conducted between 5 and 10 N for 10 cycles to account for the muscle's elastic elements which are pre-stretched by the load. This was followed by cyclic loading between 10 and 180 N at a cross-head velocity of 8.33 mm/s for a total of 3000 cycles. The change in distance of the tendon lateral edge with loading is regarded as the amount of gap formation and this was measured at every 500 cycles. To record the gap formation, a ruler with marking pieces was mounted beside the test specimen's tendon for reference (Figure 3). A digital camera mounted on a tripod with its lens facing the tendon perpendicularly was placed in front of the universal testing machine. After each 500 cycles, a high-resolution digital picture of the tendon was taken. The image is processed in ImageJ (version 1.53a) (National Institutes of Health, Bethesda, MA, United States) where a 50 mm line is drawn parallel to the ruler. The measurements were calibrated by comparing the image pixel value of the 50 mm line to 50 mm on the ruler. This was then used to measure the amount of gap formation in each image.

After 3000 cycles of cyclic loading, the specimen was loaded to failure at a cross-head velocity of 1 mm/s to determine the ultimate failure load. The universal testing machine was stopped manually at the first sign of rotator cuff repair failure, and the mode of failure was identified and recorded. For the intact tendon group, testing was terminated once a tear was observed in the tendon.

Statistical analysis

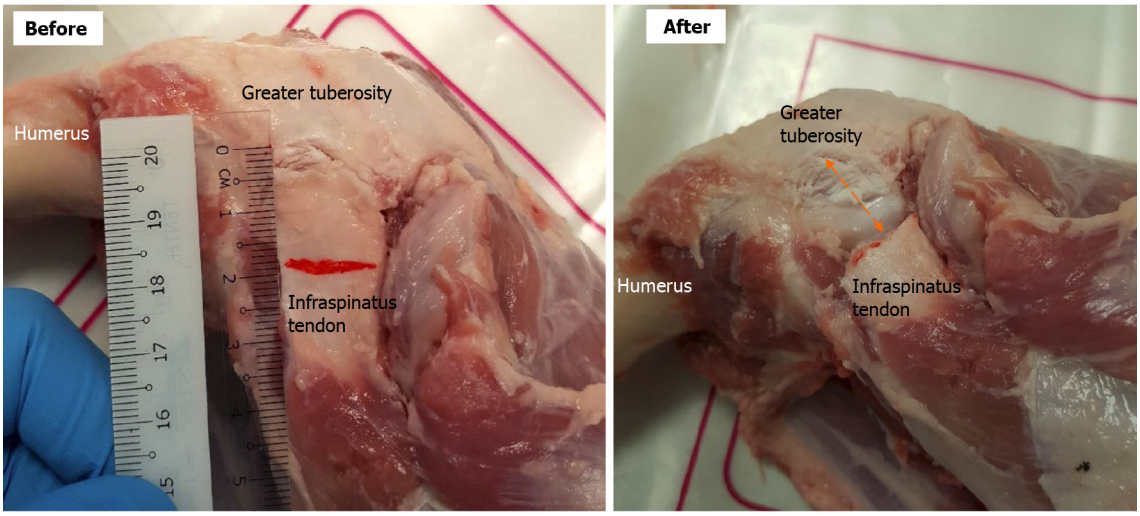
Statistical analysis was performed with SPSS v23.0 (IBM, SPSS Statistics, Armonk NY, United States) statistical software. Student's *t*-test was used to compare gap formation between the two methods of stitching. One-way analysis of variance was used to compare the ultimate failure load between all three groups. Post hoc test was performed using Tukey honest significant difference if one-way analysis of variance was found to be significant. A P value of 0.05 was considered statistically significant.

RESULTS

The mean ultimate failure load in intact tendon was 370 (range 300 N to 425 N, standard deviation 48.1). For the intact group, 3000 cycles of loading could not be completed as tears appeared in the tendons after a mean of 590 cycles and testing was terminated.

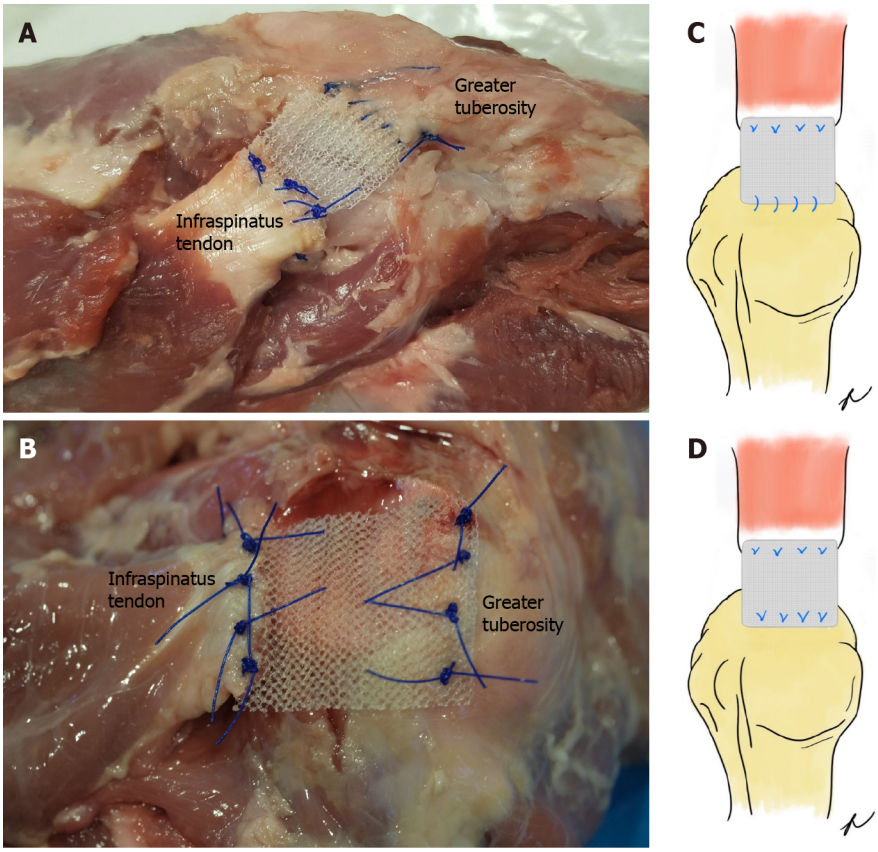
In all fifteen specimens which underwent tendon repair, gap formation increased with progressive cyclic loading through the 3000 cycles. At each interval after 500 cycles, the mean gap formation was significantly lower in the continuous group compared to the mattress group (Figure 4). The mean gap formation after 3000 cycles was 1.7 mm (standard deviation 0.3) in the continuous group, while it was 4.2 mm (standard deviation 1.3) in the mattress group (P = 0.001).

All specimens in the Mattress and Continuous group failed through suture pull-out at the greater tuberosity end of the repair. There was no record of any mesh failure or suture breakage. The ultimate failure load in the continuous group ranged from 416.7 N to 755.9 N and ranged from 403.2 N to 466.1 N in the mattress group. The mean ultimate failure load for the continuous group and mattress group was 549.2 N (standard deviation 127.3) and 426.4 N (standard deviation 106.1) respectively.



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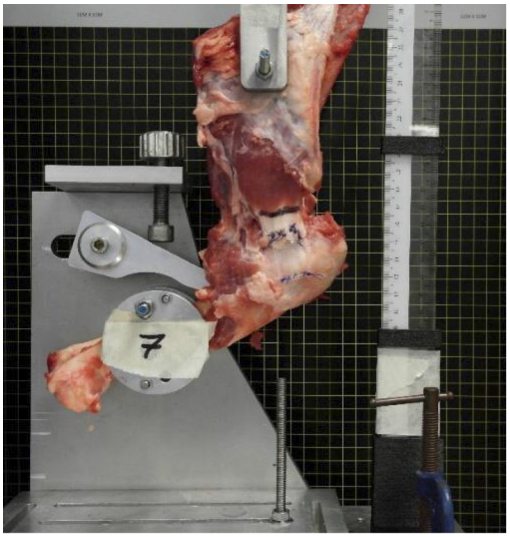
Figure 1 Specimen preparation with arrows indicating 2 cm section of tendon removed.



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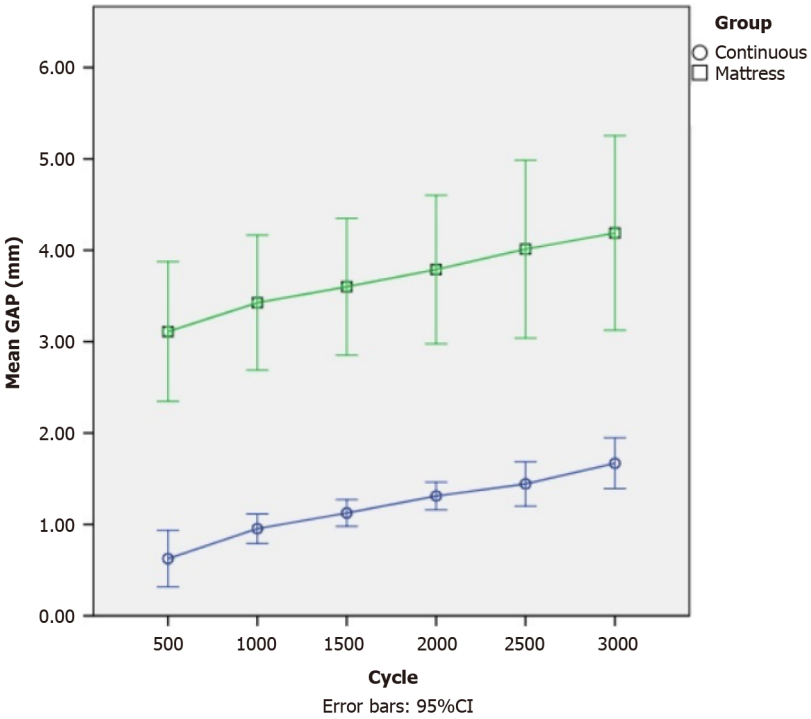
Figure 2 Tendon repair with Prolene mesh interposition graft. A: Continuous stitching; B: Mattress stitching; C: Schematic representation of continuous repair; and D: Schematic representation of mattress repair.

The ultimate failure load in the continuous group was significantly higher when compared to the mattress group (P = 0.02) and intact group (P = 0.004). There was no statistically significant difference in ultimate failure load between mattress and intact group (P = 0.45) (Figure 5).



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Figure 3 Mounted specimen for testing.

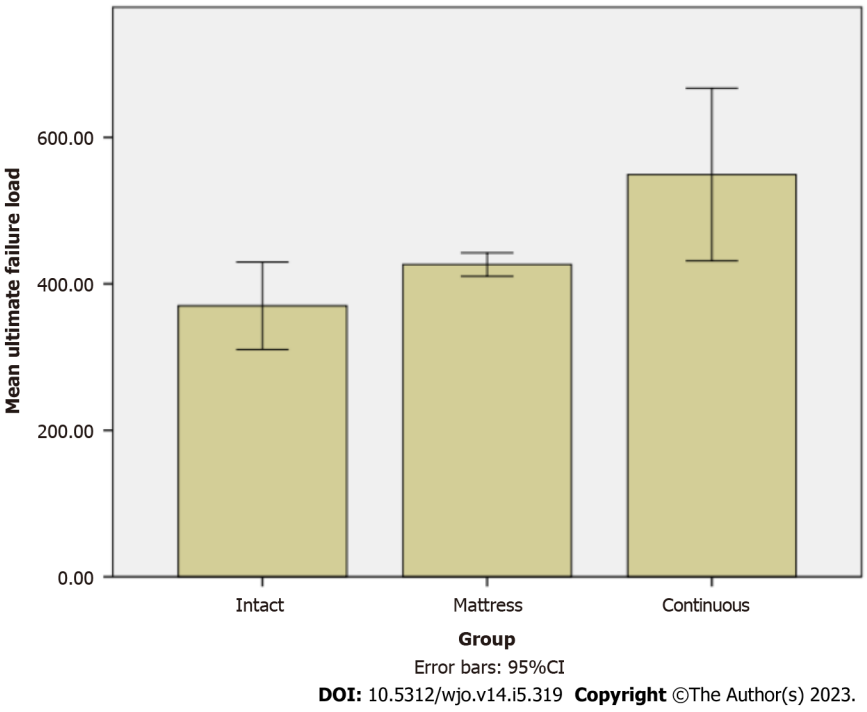


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Figure 4 Mean gap formation at 500 cycle interval (error bars 95% confidence interval).

DISCUSSION

Large or massive rotator cuff tears continue to pose a challenge to shoulder surgeons. The use of scaffolds may play a role in the treatment of such tears. These scaffolds can be used to augment or reinforce an anatomically repairable tear. It can also be used to as an interposition graft, where the scaffold bridges the gap between the irreparable cuff and the humerus[14]. Allografts and xenografts extra-cellular matrix scaffold devices provide mechanical support during the early phases of rotator cuff healing but are eventually degraded to be replaced by a mixture of organized muscle cells, collagenous connective tissue and adipose connective tissue[15]. Mihata's biomechanical analysis of grafts used in superior capsular reconstruction found that human dermal allografts would elongate by 15% with loading, while fascia lata grafts did not change significantly after testing and was also able to completely restore superior glenohumeral joint stability[16]. Due to the stiffness of fascia lata grafts, post-operative shoulder stiffness would be a concern. In addition, there are concerns that biologic grafts may



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Figure 5 Mean ultimate failure load of specimens (error bars 95% Confidence interval).

potentially incite a host inflammatory response that may cause breakdown of the repair[15,17].

Synthetic materials, such as those made of polyurethane, polypropylene or expanded polytetrafluoroethylene (PTFE) are able to maintain their mechanical properties over a long period of time, thus stabilizing the repair till tissue healing occurs. Our study suggests that using a polypropylene mesh to augment rotator cuff tendon repair is at least as strong as an intact tendon. When continuous suturing is performed, the ultimate failure load is significantly increased compared to intact tendon.

One of the technical aims of a good rotator cuff repair is to achieve sufficient strength to withstand the pull of the rotator cuff during early passive motion. Burkhart calculated that the maximal contraction force across the rotator crescent to be 302 N[18]. Mall suggested that tendon repairs resist 300 N to 350 N of tensile force to allow for early post-operative motion to help prevent stiffness and maximize healing potential[19]. All our repaired specimens were able to withstand at least 350 N of cyclic loading. Our study also demonstrated that continuous suturing at the greater tuberosity was superior to mattress sutures, with lesser gap formation and higher ultimate failure load.

Several authors have suggested a gap formation of 5 mm at the repair site to be clinically significant [20,21]. In our study, only two specimens in the mattress group exceeded 5 mm of gap formation. In a rodent model, Killian found that the greater the gap between the post-repair tendon-to-bone attachment, the greater the scar formation and presence of disorganized tendon insertion to bone[22]. This suggests that gap formation plays an important role in repair outcomes. It is promising that our mean gap formation was only 1.7 mm in the continuous group, however, *in vivo* studies using relevant large ovine animal models are still required to determine if this will translate into better tendon-to-bone healing.

Clinical studies of interposition synthetic grafts have been encouraging. Nada *et al*[23] reported on the use of a polyester Dacron ligament in 21 patients with chronic massive rotator cuff tears. The mean Constant and Murley score increased from 46.7 pre-operatively to 84.5 post-operatively. Petrie *et al*[24] used the polyester Ligament Augmentation and Reconstruction System in 31 shoulders and reported a mean improvement of Oxford shoulder score from 46.7 to 30.6. Audenaert *et al*[25] also used a polyester (ethylene terephthalate) mesh in 41 patients and the mean Constant and Murley score increased from 25.7 pre-operatively to 72.1 post-operatively. Hirooka *et al*[26] used a Gore-Tex expanded PTFE patch in 28 shoulders and reported the average total Japanese Orthopaedic Association score increased from 57.7 to 88.7. Our study suggests that the inexpensive, widely available polypropylene mesh may have a potential role in strengthening the repair of chronic large rotator cuff tears. The polypropylene mesh may even be used in combination with a fascia lata graft to improve graft healing rate as demonstrated by Kholinne when done for superior capsular reconstruction[27].

There are limitations to an ex-vivo animal study. While our study has demonstrated that the polypropylene mesh has good mechanical properties, there have been concerns over its potential to incite a vigorous foreign body and chronic inflammatory response. This may lead to contracture, scar and adhesion formation and chronic pain, particularly troubling in up to 3.6% patients who undergo mesh repair for abdominal hernia[28-30]. However, it is encouraging to note that Ciampi's study reported no

adverse events such local inflammation, fibrosis, and subacromial adhesions affecting joint function in 52 patients with polypropylene mesh augmented rotator cuff repair[13]. Our study did not attempt to undertake histological analysis of the specimens to examine for host-tissue maturation and host-implant biocompatibility as the study was not performed on live animals.

Another limitation of our study is our use of healthy rotator cuff specimens from sheep. While the sheep infraspinatus tendon has similar geometry and mechanical properties to human supraspinatus tendon[31], the healthy rotator cuff specimens may not be representative of the typical degenerate tendon seen in patients with massive rotator cuff tears. In addition, the use of suture anchors to secure the mesh to the tuberosity side could have provided greater biomechanical strength to the repair and prevent suture pull out from the tuberosity, which was the mode of failure in all our specimens. Our study serves as a proof of concept that a polypropylene mesh as an interposition graft may be an option in rotator cuff repairs. Further studies such as comparing the biomechanical properties of the polypropylene mesh to other types of commercially available grafts, and an *in-vivo* ovine study should be undertaken before adopting its use in human patients.

CONCLUSION

The use of a polypropylene mesh is mechanically suitable as an interposition graft for large irreparable rotator cuff tears. Its use results in a repair that is at least as robust as intact rotator cuff tendon. When paired with a continuous suturing technique, its resultant superior mechanical properties may potentially reduce re-tear rates after repairing large or massive rotator cuff tears.

ARTICLE HIGHLIGHTS

Research background

Augments and scaffolds are increasing in importance in patients with large to massive cuff tears. There is limited data on the mechanical properties of such materials.

Research motivation

The polypropylene mesh is a time tested, bio-compatible material with strong mechanical properties that may be used in rotator cuff repairs to improve the strength of the repair.

Research objectives

To investigate the mechanical properties of rotator cuff tears repaired with a polypropylene interposition graft in an ovine ex-vivo model.

Research methods

We used a polypropylene mesh as an interposition graft between the ends of the tendon to repair a tear in the infraspinatus of fresh sheep shoulders. The mesh was secured to remnant tendon by continuous stitching in seven specimens while mattress stitches were used for eight specimens. Five specimens with an intact tendon were tested. The specimens underwent testing to determine the ultimate failure load and gap formation.

Research results

The mean gap formation after 3000 cycles was significantly lower in the continuous group than the mattress group. The mean ultimate failure load was also significantly higher in the continuous group when compared to mattress stitching or intact tendon.

Research conclusions

The use of a polypropylene mesh is biomechanically suitable as an interposition graft for large rotator cuff tears.

Research perspectives

Further studies such as comparing the biomechanical properties of the polypropylene mesh to other types of commercially available grafts, and an *in-vivo* ovine study should be undertaken before adopting its use in human patients.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Mid-term results of sub-trochanteric valgus osteotomy for symptomatic late stages Legg-Calvé-Perthes disease

Khaled M Emara, Ramy Ahmed Diab, Ahmed K Emara, Mohamed Eissa, Mostafa Gemeah, Shady Abdelghaffar Mahmoud

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Abstract

BACKGROUND

The treatment of late stages of Legg-Calvé-Perthes disease (LCPD) is controversial. Although the concept of femoral head containment is a well-established technique of treatment, its use remains debatable in the late stages of the disease, as it does not improve symptoms in terms of limb length discrepancy and gait.

AIM

To assess the results of subtrochanteric valgus osteotomy in symptomatic patients with late-stage Perthes disease.

METHODS

From 2000 to 2007, 36 symptomatic patients with late stage of Perthes disease were surgically treated with subtrochanteric valgus osteotomy and followed-up for 8 to 11 years using the IOWA score and range of motion (ROM) variables. The Mose classification was also assessed at the last follow-up to reflect possible remodeling. The patients were 8 years old or older at the time of surgery, in the post-fragmentation stage, and complaining of pain, limited ROM, Trendelenburg gait, and/or abductor weakness.

RESULTS

The preoperative IOWA score (average: 53.3) markedly improved at the 1-year post follow-up period (average: 85.41) and then slightly improved at the last follow-up (average: 89.4) (P value < 0.05). ROM improved, with internal rotation

increased on average by 22° (from 10° preoperatively to 32° postoperatively) and abduction increased on average by 15.9° (from 25° preoperatively to 41° postoperatively). The mean Mose deviation of femoral heads was 4.1 mm at the end of the follow-up period. The tests used were the paired *t*-test and Pearson correlation test, where the level of significance was a *P* value less than 0.05.

CONCLUSION
Subtrochanteric valgus osteotomy can be a good option for symptomatic relief in patients with late-stage of LCPD.

Key Words: Legg-Calvé-Perthes disease; Femoral head avascular necrosis; Valgus osteotomy; Deformity correction; Post fragmentation stage; Late stage Perthes

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Core Tip: This is a retrospective study on 36 patients with ages ranging from 8 to12 years with late stage Perthes disease (re-ossification and healing stages) underwent femoral valgus osteotomy with rotational component which result in pain relief, improved gait, and increased range of motion. In addition, relative neck lengthening is also achieved that can correct limb length discrepancy resulting from head deformity associated with the disease which for many patients may be the only problem encountered Preoperative hip arthrography is done to see the sphericity of the hip and whether there are lateral osteophytes or not.

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INTRODUCTION

Legg-Calvé-Perthes disease is the childhood onset of osteonecrosis of the femoral head and its etiology remains poorly understood. The incidence of the disease among children varies from 0.2 per 100000 to 19.1 per 100000, with white populations being the most affected and East Asians being the least affected [1]. The prognosis of Perthes disease is controversial, with some studies showing a benign long-term outcome[2,3], while others suggest that it may lead to poor long-term sequalae (Stulberg classification type IV and V)[4-6]. Consequently, the optimal treatment approach for this condition remains debatable.

Although varus femoral osteotomy[7-10] and pelvic osteotomy[11-16] are well-established techniques for enhancing femoral head containment in the treatment of Perthes disease, their use in the late stages of the disease is controversial. They do not appear to improve symptoms such as limb length discrepancy (LLD) and may even worsen them[17-20]. Therefore, head containment should not be the primary target of treatment, particularly in the late stages of Perthes disease[7-9]. The prognosis depends more on the disease stage rather than the type of surgery performed[21], and there is no significant difference in outcomes using Stulberg radiographic criteria between conservative treatment and containment surgery in late Perthes disease[17,22].

Valgus femoral osteotomy is usually described for treatment of hinged abduction that is associated with late stages of Perthes disease[23-26]. The benefits are gained by moving the abutting epiphyseal fragment away from the acetabulum and lateralizing the greater trochanter increasing the abductor lever arm and the offset, and hence the abductor function. This results in pain relief, improved gait, and increased range of motion (ROM). In addition, relative neck lengthening is also achieved that can correct LLD resulting from head deformity associated with the disease[25]. Valgus osteotomy is also used to treat severely deformed Perthes disease, Herring classification system type B-C and C, in the fragmentation stage that showed greater congruency with adduction with improved clinical and radiological outcomes[27].

To our knowledge, no prior studies have investigated the role of femoral valgus osteotomy in the symptomatic late stages (re-ossification and healing) of Perthes disease in the absence of hinged abduction. Our hypothesis is that this approach can improve symptoms and function without targeting remodeling, as it is not possible after the fragmentation stage. We conducted a study to evaluate the clinical and radiological outcomes of this approach, with an average follow-up period of nine years.

MATERIALS AND METHODS

This retrospective cohort case series study was conducted on human participants from 2000 to 2007, performed by a single surgeon at an institutional hospital, and followed-up over 8-11 years (mean 9.36). It was conducted in accordance with the 1964 declaration of Helsinki and its later amendments/clarifications and with approval from the ethics and search committee, approved and analyzed prior to invitation of the study. Inclusion criteria were: (1) Ages 8 years or older; (2) femoral heads in the re-ossification or healing stages according to the Waldenström classification[28]; and (3) exhibition of symptoms in the form of Trendelenburg gait, abductor weakness, limping, LLD, pain, and/or limited ROM. Exclusion criteria were: (1) Patients below 8 years of age; (2) a Waldenström classification of initial or fragmentation stages; (3) asymptomatic patients; (4) patients with hinge abduction deformity; and (5) history of previous hip or pelvic surgeries.

The study included 36 patients, 23 males and 13 females, with Perthes disease in re-ossification or healing stage, 11 and 25 respectively, presented by symptoms. The symptoms varied and included pain, abductor weakness (Trendelenburg gait), external rotation gait, LLD, and/or limited abduction (Table 1). Asymptomatic Perthes disease (20 cases) was excluded from the study. None of the patients included had hinged abduction deformity confirmed by examination under general anesthesia according to Kruse *et al*[14] and Rhienker *et al*[29] definitions. The age range was between 8-12 years (mean 9.41). All the patients in the study group were treated with subtrochanteric valgus osteotomy and fixation was by pre-contoured plate in 23 cases (63.9 %) or dynamic hip screw (DHS) in 13 cases (36.1 %) (Table 2)[30-32]. All patients reached skeletal maturity at the time of last follow up.

The patients underwent a thorough clinical assessment focusing on functionality and pain history, as well as clinical examination that addressed gait, ROM, and deformity. Hence, the IOWA hip score[33] and ROM were evaluated once preoperatively and twice postoperatively (1st at 1 year postoperative and 2nd at the end of the follow-up period). The IOWA hip score is a 100-point scale that evaluates the hip by assessing different functional activities (35 points), freedom from pain (35 points), gait abnormality (10 points), deformity (10 points), and ROM (10 points), with the highest point scale indicating the best function[33]. Data collection was performed by the 2nd, 3rd, and 4th authors.

Surgical technique

The extent of limb deformity was carefully evaluated both clinically and radiologically (using plain X-rays, computed tomography scans, and intraoperative arthrography) to plan for the required planes and degrees of correction and to identify the most deformed part of the femoral head, with the goal of unloading it (Figure 1). The degree of valgus and rotation performed was measured by using the unaffected limb as a reference. If the patient was affected bilaterally, we relied on hip arthrography and neck shaft angle (NSA) and performed the valgus and rotation to the degree that brought lateral osteophytes away from the required range of motion and made the NSA more than 130 degrees. Therefore, the degree of correction was tailored to each patient individually.

Patients were placed supine on a radiolucent table. A direct lateral approach was utilized to access the femur. First, hip arthrography is done to confirm the sphericity of the head and to see whether there are lateral osteophytes or not, also the hip arthrography determines the direction of our osteotomy according to the site of osteophytes as mentioned above (Figure 2). The level of osteotomy was determined under an image intensifier, which was always subtrochanteric. In some cases, a pre-contoured plate (narrow plate) was used, and the plate was contoured to the desired degree of valgus and loosely fixed with a screw to the neck. In cases involving DHS, the desired degree of valgus was achieved by adjusting the inclination of the guide wire of the lag screw accordingly. The osteotomy was performed using multiple drill holes to weaken the cortex then completed by an osteotome. The osteotomy aimed to perform valgus, internal rotation, lateral translation, and extension of the distal femur if any limitations in the preoperative flexion range were discovered. Additionally, the osteotomy was oblique to provide inherent stability, and a de-rotation element was added to unload the affected portion, thereby relieving pain and correcting the external rotational deformity that is frequently associated with Perthes disease. After plate fixation, frequent irrigation was performed, followed by tissue closure in layers (Figures 3 and 4).

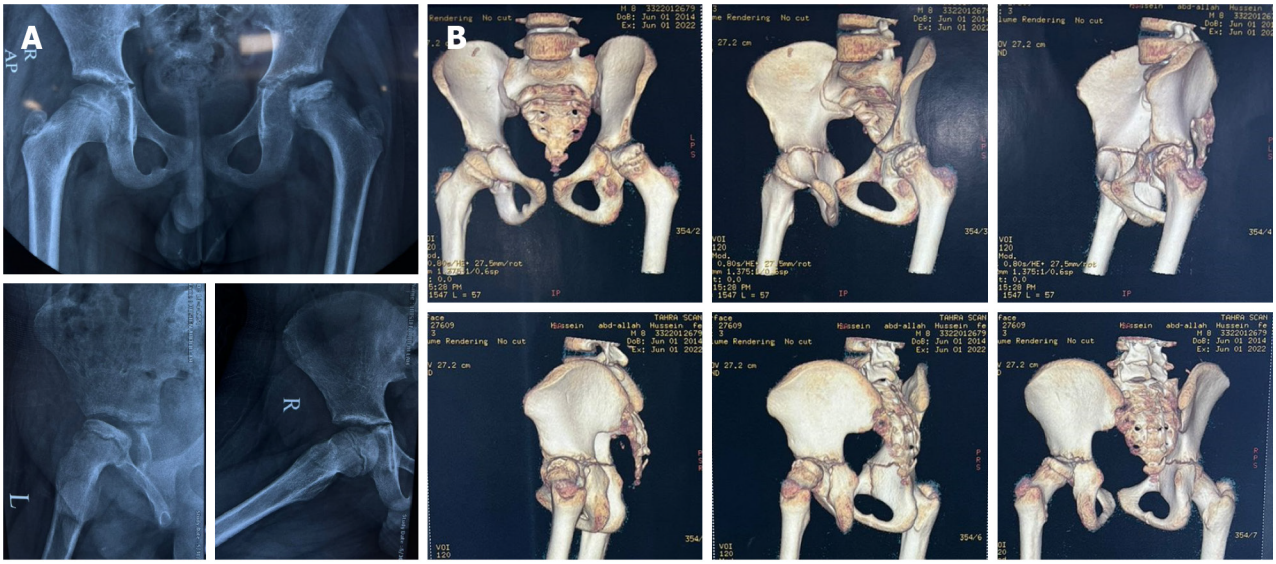
Postoperative protocol included non-weight bearing for 6 wk, followed by physical therapy for gait training, balance, and abductor muscle strengthening. Subsequently, partial weight bearing was allowed with crutches, which was then progressed to full weight bearing without crutches.

Statistical analyses

Statistical analysis was conducted to determine the significance of functional outcomes, patients' age at the time of surgery, and the follow-up period for the improvement of symptoms. IBM SPSS statistics (version 24.0, IBM Corp., United States, 2016) was used for data analysis. The data were presented as mean ± SD for quantitative parametric measures and as numbers and percentages for categorized data. The following tests were performed: (1) Paired t-test was used to compare two dependent groups for parametric data; and (2) Pearson correlation test was used to analyze the possible association between each two variables among each group for parametric data. The level of significance was set at $P < 0.05$.

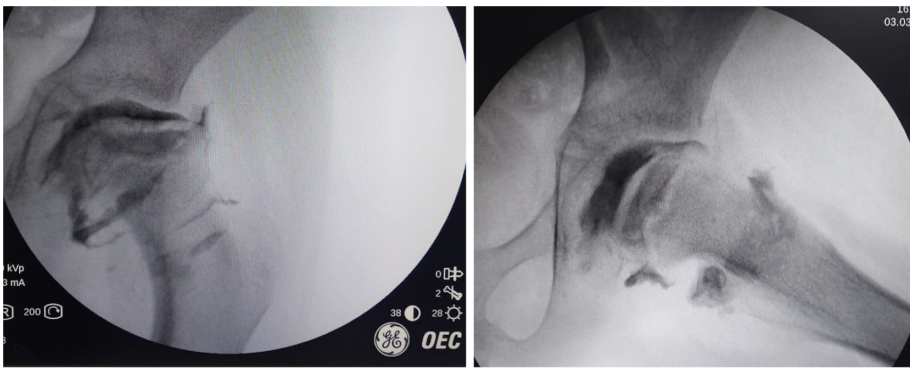
Table 1 The clinical picture of the surgically treated patients with their proportions, *n* (%)

Clinical picture	Count
Pain	31 (86.1)
Trendlenburg gait and abductor weakness	30 (83.3)
External rotation gait	29 (80.5)
Limb length discrepancy	34 (94.4)
Limited abduction	3 (8.3)
Fixed flexion deformity	9 (25)



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Figure 1 The extent of limb deformity. A: Preoperative Plain X ray of 11 years male patient with left Perthes disease (Waldenström: Healing stage); B: Preoperative 3D-computed tomography scan.



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Figure 2 Intraoperative arthrography of the previous patient showing that the head is aspherical with lateral osteophytes.

RESULTS

ROM

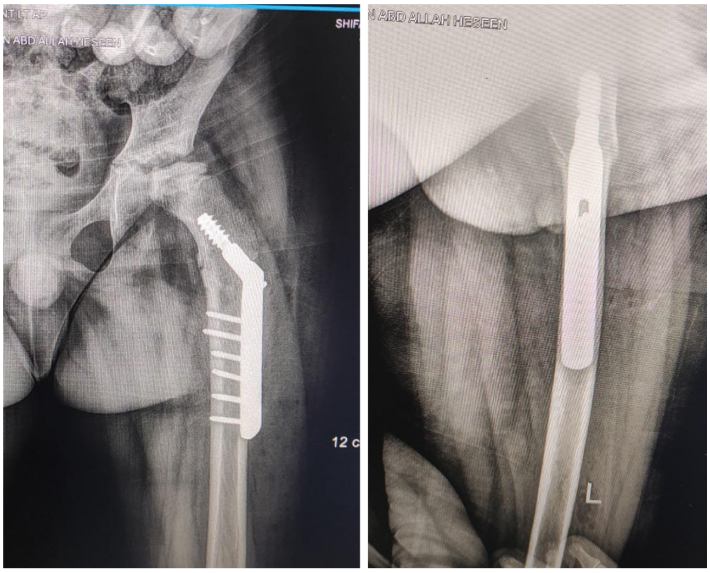
On average, the internal rotation increased by 22° (range: 10°-40°), from an average of 10° preoperatively to an average of 32° postoperatively with SD 5.72. Abduction increased by an average of 15.9° (range: 10°-35°) from an average of 25° preoperatively to an average of 41° postoperatively with SD 5.18. LLD improved in 30 cases (average improvement 0.9 cm) and remained unchanged in 6 cases. LLD was measured using the tape method and approximated to 0.5 cm, 1 cm, 1.5 cm, and so on. The difference

Table 2 Details of patients treated by femoral valgus osteotomy

Case	Sex	Age at surgery	Waldenström classification	Joseph classification[30]	Catterall classification[31]	Stulberg classification	Mose[32] at last F.U. (mm)	Follow up period	Implant
1	M	9	Re-ossification	IIIb	III	III	3	9	Contoured plate
2	M	8	Re-ossification	IIIa	III	III	2	8	Contoured plate
3	F	9	Healing	IV	IV	IV	5	10	DHS
4	M	11	Re-ossification	IIIb	III	IV	8	11	DHS
5	F	10	Re-ossification	IIIb	IV	III	5	9	Contoured plate
6	F	8	Healing	IV	III	III	6	9	Contoured plate
7	M	9	Re-ossification	IIIb	II	II	1	8	Contoured plate
8	M	9	Re-ossification	IIIa	II	II	2	9	Contoured plate
9	M	12	Healing	IV	IV	III	4	10	DHS
10	F	10	Healing	IV	IV	III	5	9	Contoured plate
11	M	9	Re-ossification	IIIa	III	IV	9	8	Contoured plate
12	F	8	Healing	IV	II	II	1	8	DHS
13	M	9	Healing	IV	III	III	3	9	Contoured plate
14	M	10	Re-ossification	IIIb	III	III	4	10	Contoured plate
15	F	11	Re-ossification	IIIb	IV	III	4	9	Contoured plate
16	M	10	Re-ossification	IIIb	III	IV	8	9	DHS
17	F	11	Healing	IV	II	II	1	8	Contoured plate
18	M	9	Healing	IV	IV	IV	7	11	Contoured plate
19	F	8	Re-ossification	IIIa	III	III	2	9	DHS
20	M	9	Healing	IV	III	III	4	10	Contoured plate
21	M	8	Healing	IV	II	II	1	11	DHS
22	M	9	Re-ossification	IIIb	III	II	2	9	Contoured plate
23	F	9	Re-ossification	IIIa	II	III	6	8	DHS
24	M	8	Re-ossification	IIIa	III	III	5	9	Contoured plate
25	F	10	Healing	IV	IV	IV	8	10	DHS
26	F	11	Healing	IV	III	II	1	9	Contoured plate
27	M	9	Healing	IV	IV	IV	5	9	Contoured plate
28	M	9	Re-ossification	IIIa	III	III	2	9	Contoured plate
29	F	8	Re-ossification	IIIa	II	II	2	9	DHS

30	M	8	Healing	IV	III	III	4	10	Contoured plate
31	M	9	Re-ossification	IIIb	III	III	5	8	DHS
32	M	10	Re-ossification	IIIb	III	IV	4	8	DHS
33	M	11	Re-ossification	IIIb	II	II	2	9	Contoured plate
34	M	10	Healing	IV	IV	IV	6	9	Contoured plate
35	M	9	Healing	IV	IV	IV	10	9	DHS
36	F	12	Healing	IV	III	II	1	10	Contoured plate

DHS: Dynamic hip screw; F: Female; M: Male.



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Figure 3 Immediate post operative pregnane X receptor of the previous patient fixed with dynamic hip screw. 10° valgus, 10° extension and 15° internal rotation were done.

between the preoperative and postoperative measures was statistically significant ($P < 0.05$) (Table 3).

IOWA score

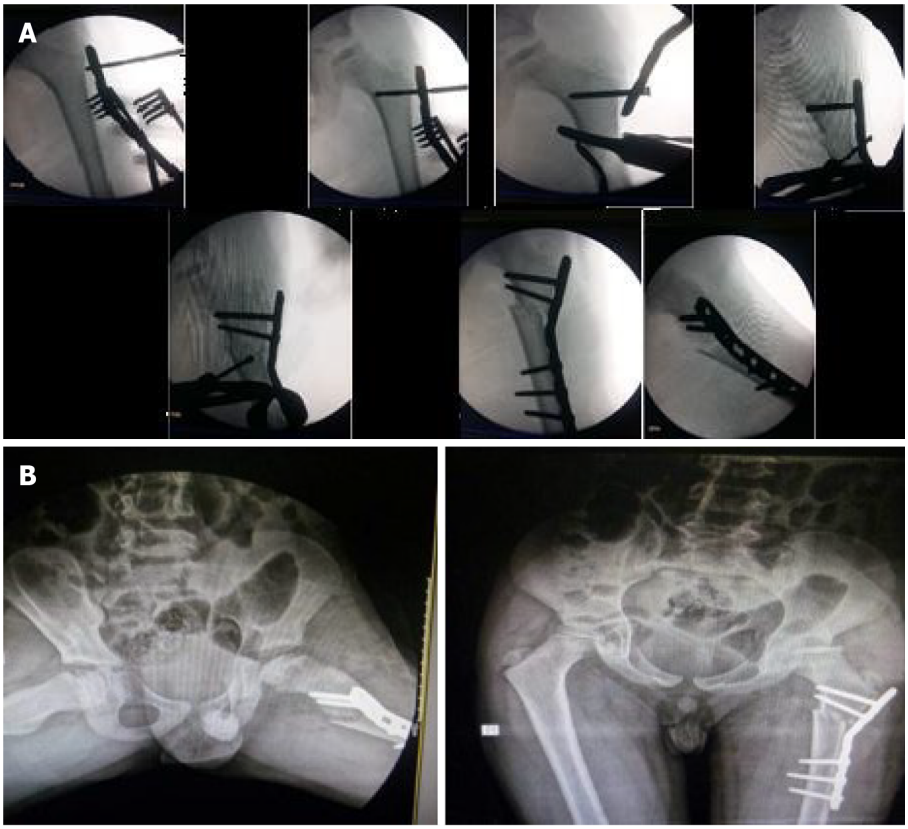
Twenty-three boys and 13 girls underwent unilateral subtrochanteric valgus osteotomies. The average age was 9.4 years (range 8-12) with an average follow-up period of 9.1 years (range 8-11). Clinical outcomes were assessed using the IOWA hip score[33] preoperatively, at 1-year postoperative, and at the last postoperative follow-up. The preoperative IOWA score had an average of 53.3 and SD 10.1, and it showed a marked improvement at the 1-year postoperative follow-up, with an average of 85.4 and SD 5.4. There was a slight improvement at the final follow-up, with an average of 89.4 and SD 5.2. The improvement was significant in pain, with an average of 22.4 preoperative to an average of 36.2 postoperative, walking tolerance, with an average of 4.7 preoperative to an average of 8.7 postoperative, gait, with an average of 3.5 preoperative to an average of 12.9 postoperative, shortening, with an average of 1.2 preoperative to 2.6 postoperative, and Trendelenburg absence, with an average of 2 preoperative to 0 postoperative. The difference between preoperative and final outcomes was statistically significant ($P < 0.05$).

Mose's circles

At the end of the follow-up period, Mose classification[32] was evaluated to assess any remodeling, with physis closure ensured. The mean Mose deviation was 4.11 mm, ranging from 1-10 mm.

Table 3 Statistical analysis of valgus osteotomy case series

Descriptive statistics	*n*	Min	Max	mean ± SD
Age	36	8	12	9.4 ± 1.5
Follow up	36	8	11	9.36 ± 2.2
IOWA score preoperative	36	30	70	53.3 ± 10.1
Postoperative after 1 yr	36	77	100	85.4 ± 5.4
Final	36	79	100	89.4 ± 5.2
Internal rotation degree	36	10	40	22.1 ± 5.26
Abduction degree	36	10	35	15.7 ± 6.2



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Figure 4 Treatment of a femoral valgus osteotomy in a 10-year-old man with left Pertes disease. A: Intra-operative surgical steps of another 10 years old male patient with left Perthes disease (Waldenström: Re-ossification stage) treated with femoral valgus osteotomy using pre-contoured plate. Note the extension component of the osteotomy was evident in the lateral shot to compensate associated fixed flexion deformity of the hip; B: Immediate post operative pelvic X-ray of the same patient.

Complications

Superficial infection occurred in four cases, which were treated with daily dressings and a parenteral antibiotic course with no sequels. Six cases required hardware removal due to pain.

DISCUSSION

The optimal treatment approach for late stages of Perthes disease is still debatable. Although achieving proper femoral head containment (such as varus femoral osteotomy and pelvic osteotomy) to promote head remodeling and delay the need for total hip replacement (THR) has been widely accepted in the surgical treatment of the disease, there are many clinical and pathological aspects that raise concerns about the use of this surgical method in late symptomatic stages[34]. Firstly, the relationship between Perthes disease and osteoarthritis (OA) is atypical. According to Stulberg classification[4], only

aspherical incongruent cases carry a risk of severe OA, which usually doesn't develop before the 5th decade. Additionally, there is no correlation between symptom severity and osteoarthritic radiographic changes in Perthes disease. Furthermore, Perthes OA affects the medial joint compartment rather than the superior compartment, which is typically affected in age-related degenerative joint diseases. This different pattern of OA carries a better prognosis than the typical superior compartment one[5,22]. Larson *et al*[17] studied the outcomes of conservative management on 58 hips with a mean follow-up of 20.4 years, where only three patients required hip arthroplasty, and one patient required a pelvic osteotomy. This study supports the atypical relationship between Perthes disease and OA. Regarding varus femoral osteotomy, its use in treating Perthes disease has many limitations. Its effectiveness in providing the desired remodeling potential is restricted to cases in the early avascular and fragmentation stages. Therefore, its use in the re-ossification or healing stages is of questionable value[7, 9]. It is also limited to cases with a skeletal age of 8 years or more at onset, particularly Herring classification system group B and B/C border[5,21]. Sponseller *et al*[10] even concluded that the use of varus femoral osteotomy in patients older than 10 years yielded poor results, indicating that its use may be restricted to Herring classification system group B and B/C border in patients aged 8-10 years in the early avascular or fragmentation stages. Moreover, although varus femoral osteotomy may relieve pain associated with the disease by providing containment, it exacerbates the symptoms of limping due to the shortening of the affected limb[8]. It also worsens the Trendelenburg gait by increasing the abductor weakness[18,20]. Watanabe *et al*[19] studied gait analysis after varus femoral osteotomy and found that the stance phase was shorter, cadence was faster, and the strength ratio of hip abductor muscles was lower in operated patients *vs* non-operated and healthy subjects.

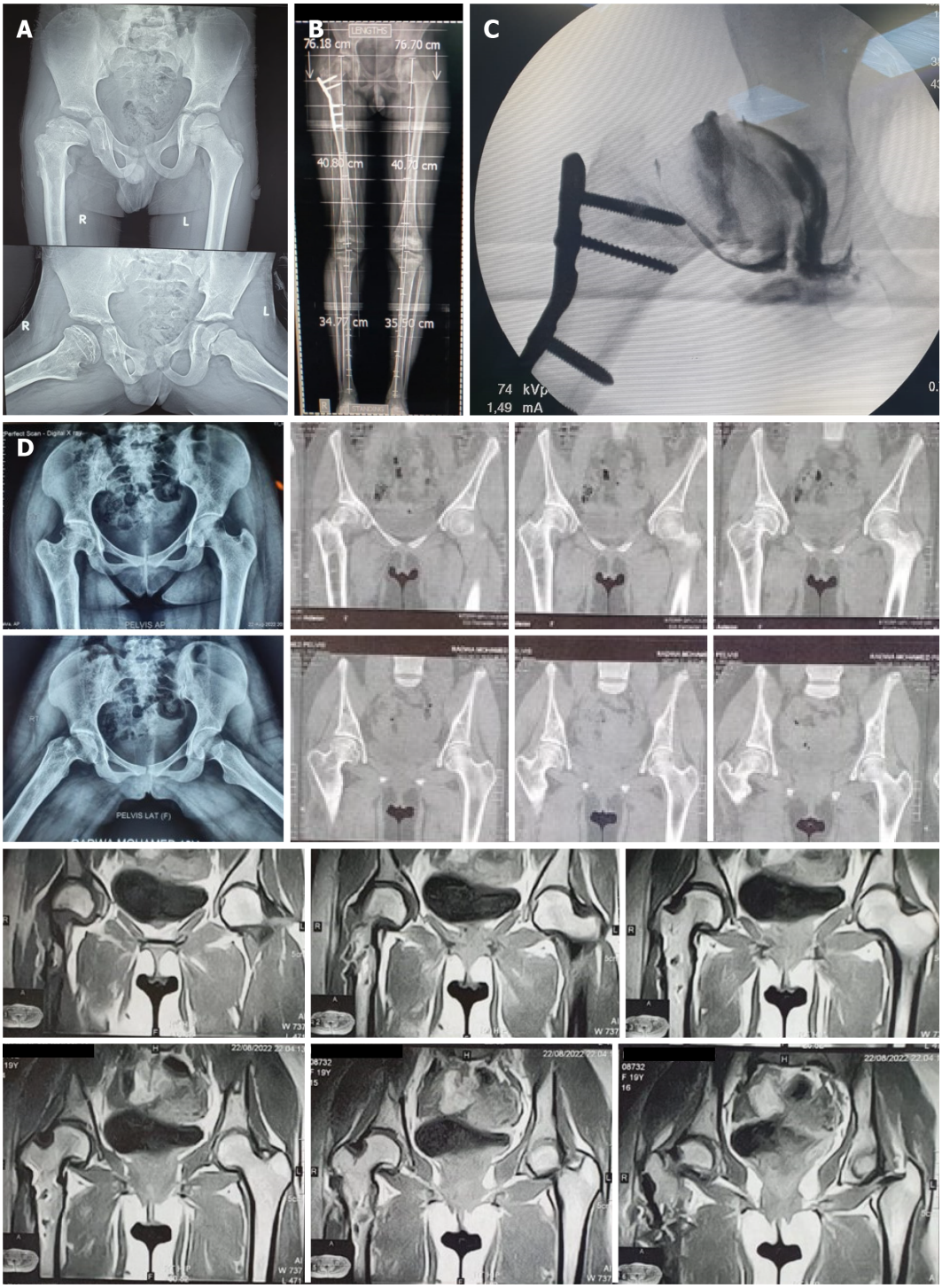
Arthrodiastasis has been studied in cases of late-stage Perthes disease with advanced Catterall stages and has shown satisfactory clinical and radiological outcomes. However, its effect is most significant when the disease is in the early avascular or fragmentation stages, as it can prevent head collapse and speed up recovery[27,35].

Two surgical approaches have been utilized to treat patients with healed Perthes in adulthood; safe surgical dislocation and combined acetabular and femoral osteotomies[36-38]. Safe surgical dislocation has been used to treat complex femoral deformities resulting from Perthes disease, with positive outcomes and statistically significant results. Trochanteric advancement and osteochondroplasty have been performed to address short neck, chondral and labral lesions, and femoro-acetabular impingement that may complicate Perthes disease in adulthood[36-38]. Clohisy *et al*[37] described a combined periacetabular osteotomy and intertrochanteric valgus osteotomy to treat femoral head deformities complicated by acetabular dysplasia. The procedure was performed on 42 cases (mean age 22.7 years) and followed up over 4.5 years, with statistically significant improvement in the Harris hip score. However, none of these procedures were used to treat Perthes disease before healing during childhood.

In addition, head remodeling is not limited to the containment concept. Yoo *et al*[24] studied the effect of valgus extension osteotomy on remodeling potential in hinge abduction cases and observed favorable remodeling in young cases that were at the fragmentation or early re-ossification stages. This is supported by Kim *et al*[27], who studied valgus osteotomy on patients at the fragmentation stage who had better containment by adduction. All femoral head roundness measures and the Shenton line were improved, with the best results demonstrated in severely deformed heads with Herring classification type C. This indicates that patient characteristics and disease stage at the time of intervention are the main determinants of head remodeling, rather than the type of surgery performed[24]. In delayed stages of Perthes disease, such as re-ossification and healing stages, containment can no longer be achieved, and the potential for remodeling is lost[39]. Many of these cases develop hinged abduction, and several studies have described the use of valgus femoral osteotomy in an attempt to move the abutted head away, with good outcomes[23-26]. Bankes *et al*[25] described the use of extension valgus osteotomy in 48 cases in the re-ossification stage, resulting in improved symptoms with a ten-year follow-up, but no prospective scoring system was used to quantify the improvement. Yoo *et al*[24] added sagittal and coronal rotational components to accurately accommodate different hinging patterns, resulting in improved mean IOWA score from 71 to 92 in a long-term study on 31 patients. The same results were achieved by Myers *et al*[26] in a short-term study, with an improved mean Harris hip score by 41.

However, no studies have discussed valgus femoral osteotomy among symptomatic late-stage Perthes disease in the absence of hinged abduction. We conducted a retrospective study on such a population group with ages ranging from 8 to 12 years. Our chosen operative intervention was femoral valgus osteotomy with a rotational component, and we observed the patients over a period of 8-11 years, assessing them clinically using the IOWA score[33] (Figure 5). Preoperative hip arthrography was done to assess the sphericity of the hip and the presence of lateral osteophytes. This simple surgical procedure, femoral valgus osteotomy, can relieve existing symptoms such as pain, limping, limb length discrepancy, limited ROM, and abductor weakness, which for many patients may be the only problem encountered.

On the other hand, we considered the re-ossification and healing stages to be critical periods, as we could not guarantee containment *via* varus femoral or pelvic osteotomy, and the potential complication of OA later on was uncertain to have a significant impact on the functional activity of the diseased patients compared to other patients who might eventually develop it. The controversies regarding the prognosis of Perthes disease compelled us to focus on relieving existing symptoms and improving the



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Figure 5 Clinical evaluation for 8-11 years in patients with femoral valgus osteotomy with a rotational component. A: Preoperative pelvic X-ray (PXR) of 9 years old male patient with right Perthes disease (Waldenström: Healing stage); B: Follow up scanogram after 10 years showing no limb length discrepancy nor hip arthritis; C: Intraoperative hip arthrography just before plate removal that show smooth head with no osteophytes; D: Post removal PXR, computed tomography and magnetic resonance imaging respectively that show normal hip.

quality of life of these patients. In this study, the clinical outcomes significantly improved from an average IOWA score of 53.3 preoperatively to 89.4 at the end of the follow-up period, with a highly significant *P* value ($P < 0.01$). ROM increased, which is reflected in the patient's quality of life. Internal rotation and abduction improved by an average of 22° and 15.9° degrees, respectively. The mean Mose deviation was 4.11 mm, reflecting the lack of remodeling in these stages, and this is consistent with results of Yoo *et al*[24], which showed no improved radiographic indices in such an entity. There was a positive relationship between the age at the time of surgery and functional improvement, with a *P* value of 0.001, making it a potential good option in the treatment of older symptomatic patients with Perthes disease. There was no correlation between the duration of the follow-up period and functional

improvement, with a *P* value of 0.979. This necessitates further evaluation by long follow-up studies.

There is no proof that other types of surgery could change the natural history of late-stage Perthes disease or add value in improving patient symptoms, articular impingement, weak abduction, and limb length discrepancy. Therefore, our protocol to deal with symptomatic late-stage Perthes disease is either to leave the patient with no surgery, just conservative treatment for symptoms, or to do valgus de-rotation osteotomy to bring the osteophyte away from the joint articular surface. Hip arthrography is needed for proper dynamic assessment of the articular surface.

The limitations of this study include its retrospective nature and lack of control groups that receive other treatments such as conservative and other surgical procedures. Longer follow-up periods are also needed to assess the end fate of the hips and the risk of OA development, although the mid-term outcomes display promising efficacy and safety. It is also important to determine whether the deformity of the proximal femur would remodel or have any impact on future THR surgery. Further studies to tailor the use of sub-trochanteric valgus osteotomy according to the patient's age of onset and the disease stage are also required.

CONCLUSION

We hypothesize that valgus femoral osteotomy is a valid option for patients with late-stage Perthes disease. This procedure can effectively alleviate symptoms such as pain, limping, and limb length discrepancy, which may be the only problems encountered by many patients for an extended period of time. Therefore, valgus femoral osteotomy could be used beyond its role as a salvage option in hinge abduction cases.

ARTICLE HIGHLIGHTS

Research background

Legg-Calvé-Perthes disease is a condition that affects the hip joint, most commonly in children between the ages of 4 and 10. In this disease, the blood supply to femoral head. The treatment of late-stage Perthes disease remains controversial, and there is debate about the most effective techniques for managing symptoms and improving long-term outcomes.

Research motivation

The motivation for this study was to contribute to the ongoing debate about the most effective treatment approaches for late-stage Perthes disease, and to evaluate the potential benefits of subtrochanteric valgus osteotomy in improving symptoms and long-term outcomes.

Research objectives

The objective of this study was to evaluate the outcomes of subtrochanteric valgus osteotomy in patients with late-stage Perthes disease.

Research methods

The study included 36 symptomatic patients with late-stage Perthes disease who underwent subtrochanteric valgus osteotomy between 2000 and 2007. The patients were aged 8 or older at the time of surgery, in the post-fragmentation stage of the disease, and experiencing pain, limited range of motion, Trendelenburg gait, and/or abductor weakness.

Research results

The results of the study showed that subtrochanteric valgus osteotomy significantly improved hip function and range of motion in patients with late-stage Perthes disease.

Research conclusions

The study concluded that subtrochanteric valgus osteotomy can be an effective treatment option for relieving symptoms and improving hip function and range of motion in patients with late-stage Perthes disease. The results of the study suggest that this surgical technique can be a valuable addition to the range of treatment options available for this condition.

Research perspectives

The study provides important insights into the potential benefits of subtrochanteric valgus osteotomy for patients with late-stage Perthes disease. However, further research is needed to confirm the findings of this study and to evaluate the long-term outcomes of this treatment approach.

FOOTNOTES

Author contributions: Emara KM designed the study, analyzed the data, done the operations, and reviewed the manuscript critically; Diab RA analyzed the data, reviewed the manuscript critically, approved the final version to be published; Emara AK and Eisa M analyzed the data and reviewed the manuscript critically; Gemeah M collected the data reviewed the manuscript critically; Mahmoud SA collected the data, designed the study, and wrote the manuscript.

Institutional review board statement: This study has been reviewed and approved by the Institutional Review Committee at Ain Shams University School of Medicine.

Informed consent statement: As our study is a retrospective study, signed informed consent form is not needed. However, the institutional Hospital has given permission to access data and conduct this study.

Conflict-of-interest statement: Authors declare that they have no conflict of interest.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Spinal fusion is an aerosol generating procedure

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Abstract

BACKGROUND

Transmission of severe acute respiratory syndrome coronavirus 2 can occur during aerosol generating procedures. Several steps in spinal fusion may aerosolize blood but little data exists to quantify the risk this may confer upon surgeons. Aerosolized particles containing infectious coronavirus are typically 0.5-8.0 μm.

AIM

To measure the generation of aerosols during spinal fusion using a handheld optical particle sizer (OPS).

METHODS

We quantified airborne particle counts during five posterior spinal instrumentation and fusions (9/22/2020-10/15/2020) using an OPS near the surgical field. Data were analyzed by 3 particle size groups: 0.3-0.5 μm/m^3, 1.0-5.0 μm/m^3, and 10.0 μm/m^3. We used hierarchical logistic regression to model the odds of a spike in aerosolized particle counts based on the step in progress. A spike was defined as a > 3 standard deviation increase from average baseline levels.

RESULTS

Upon univariate analysis, bovie (P < 0.0001), high speed pneumatic burring (P = 0.009), and ultrasonic bone scalpel (P = 0.002) were associated with increased 0.3-0.5 μm/m^3 particle counts relative to baseline. Bovie (P < 0.0001) and burring (P < 0.0001) were also associated with increased 1-5 μm/m^3 and 10 μm/m^3 particle counts. Pedicle drilling was not associated with increased particle counts in any of the size ranges measured. Our logistic regression model demonstrated that bovie

(OR = 10.2, $P < 0.001$), burring (OR = 10.9, $P < 0.001$), and bone scalpel (OR = 5.9, $P < 0.001$) had higher odds of a spike in 0.3-0.5 μm/m^3 particle counts. Bovie (OR = 2.6, $P < 0.001$), burring (OR = 5.8, $P < 0.001$), and bone scalpel (OR = 4.3, $P = 0.005$) had higher odds of a spike in 1-5 μm/m^3 particle counts. Bovie (OR = 0.3, $P < 0.001$) and drilling (OR = 0.2, $P = 0.011$) had significantly lower odds of a spike in 10 μm/m^3 particle counts relative to baseline.

CONCLUSION

Several steps in spinal fusion are associated with increased airborne particle counts in the aerosol size range. Further research is warranted to determine if such particles have the potential to contain infectious viruses. Previous research has shown that electrocautery smoke may be an inhalation hazard for surgeons but here we show that usage of the bone scalpel and high-speed burr also have the potential to aerosolize blood.

Key Words: Optical particle sizers; Aerosol; COVID-19; Orthopaedic procedures; Spinal fusion; SARS-CoV-2

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Core Tip: In this study we use a handheld optical particle sizer to measure the generation of aerosols during surgical steps in spinal fusion because of the risk this may confer upon surgeons in regards to the airborne transmission of severe acute respiratory syndrome coronavirus 2. Several steps in spinal fusion, specifically the bone scalpel and high-speed burr, were found to be associated with increased airborne particle counts in the aerosol size range.

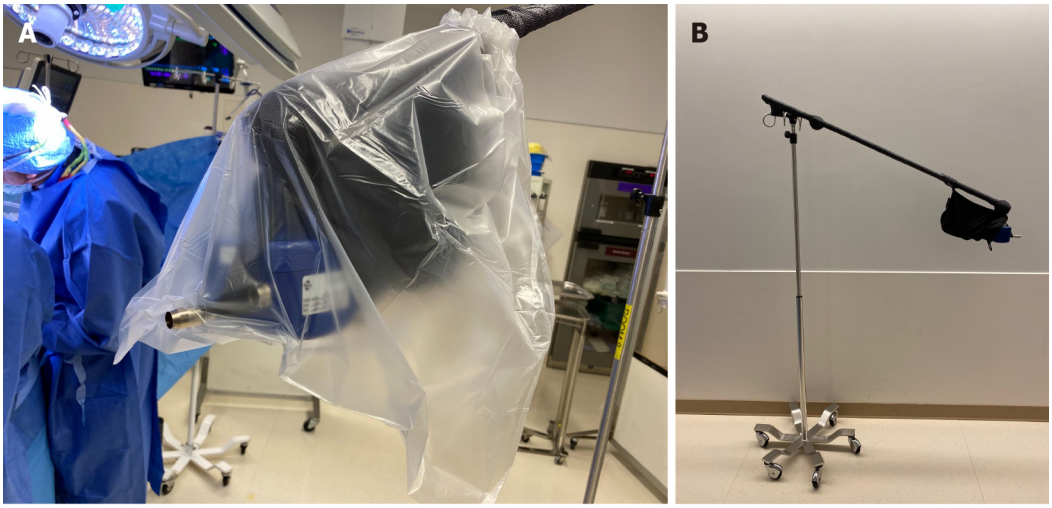
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INTRODUCTION

The World Health Organization has warned that airborne transmission of severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019, COVID-19) can occur during medical procedures that generate aerosols, especially those involving the airway[1]. Instrumentation of the upper and lower airways is often considered high risk and some research has indicated that these procedures are aerosol-generating procedures (AGPs)[2]. Certain tools used in orthopaedic surgery have previously been shown to generate blood containing aerosols less than 5 μm in diameter[3]. Despite this potential hazard, there are no previous reports describing the risk of aerosolization of body fluids during spinal fusion.

The naked COVID-19 virus is 0.06-0.14 μm in diameter but aerosolized particles containing infectious virus are typically 0.5-8.0 μm. Particles greater than 5 μm are generally considered droplets whereas those less than 5 μm represent aerosols that remain suspended for periods of time and travel significant distances, though there is some controversy over these definitions[4]. In a 2010 study researchers found that electrocautery, bone saws, reamers and drills appear to produce aerosols[5]. Other authors have raised the theoretical concern that aerosolized blood during spine surgery could put members of the surgical team at risk for exposure to infectious viral particles, but there is little *in vivo* data to help quantify this risk[6].

The current guidelines for personal protective equipment during orthopedic surgery vary by institution but generally providers are advised to wear N95 masks during intubation and other procedures considered to be aerosol generating[7-9]. However, controversy remains over which procedures or components of procedures should be considered AGPs, leaving policy makers with a lack of evidence to guide decisions related to infection control. Here we present a pilot study using handheld optical particle sizers (OPSs) to evaluate the potential for various surgical steps during spinal fusion to aerosolize blood and other body fluids. We hypothesize that surgical steps of interest, mainly bovie electrocautery, burring, drilling, and harmonic bone scalpel, will significantly increase airborne aerosol particle counts during spinal fusion.



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Figure 1 Aerotrak handheld airborne particle counter. A: In a sterile bag; B: Suspended in a hanger.

MATERIALS AND METHODS

Study design

We quantified airborne particle counts throughout the course of five posterior spinal instrumentation and fusions (9/22/2020-10/15/2020). The University Institutional Review Board (IRB No. 58206) granted an IRB waiver with a determination that no human subjects were involved in this study. This pilot study was designed as a quality improvement assessment for our institution.

Device/sampling

An Aerotrak Handheld Airborne Particle Counter (Model 9306-V2) from TSI Incorporated (Shoreview, Minnesota) was used as the OPS. Before each procedure, a Zero Check was performed in the operating room on the OPS by attaching the high efficiency particulate air (HEPA) zero filter assembly to the inlet nozzle and running a two-minute purge. This step was repeated until one or less particles of any size were counted. The zero filter was then removed and the Stainless-Steel Isokinetic inlet was attached for sampling. The OPS was secured to a hanger to ensure consistent sampling height and distance to the patient and stabilized with a sandbag (Figure 1A).

A sterile bag was placed over the OPS and hanger. The vented aspects of the OPS used for sampling remained uncovered (Figure 1B).

Because this study is primarily evaluating the risk to the surgical team, the OPS was positioned next to the surgical staff hanging over the central operating area at a comparable height and distance to the wound as the surgeon's face.

Throughout the procedure, the OPS took continuous 30-s samples and reported the sum of particles sizes 0.3 μm/m^3, 0.5 μm/m^3, 1.0 μm/m^3, 3.0 μm/m^3, 5.0 μm/m^3, and 10.0 μm/m^3 in each 1.4 L sample. Based on the usage of high-speed power tools and shear forces, the following surgical steps were identified for study: Bovie, burring, drilling, and bone scalpel. As the OPS sampled, researchers recorded the start and end times of each surgical step of interest, the approximate distance from the wound/central operating area to the particle sensor, and the maximum number of people in the operating room at any point during the sampling period (excluding the patient). The operating rooms used for sampling in this study have an airflow of 25 air exchanges per hour with laminar flow ceilings that create an air curtain about four feet on each side of the patient. There were two low wall returns in each room that used a recirculated system with HEPA filtration.

Statistical analysis

The data was downloaded using the TSI TrakPro Lite Secure 3.1 software in an XML format and analyzed in RStudio version 1.1.456 using a two-sided level of significance of 0.05. Each 30 s sample was labeled with the surgical step of interest that was occurring. If there was more than one step occurring during a 30 s sample, this was labeled as multiple steps. Each 30 s sample labeled with a surgical step of interest was compared to baseline samples when there were no steps of interest occurring. In addition, the 30 s samples before and after a sample with a step of interest occurring were removed from the analysis to reduce the potential of biasing the data with leftover aerosols.

Multivariable hierarchical logistic regression models were used to model the odds of a spike in particle counts, accounting for within-surgery variability and autocorrelated errors. Surgical steps, the sensor distance, and the maximum number of people in the operating room were included in these

Table 1 Logistic regression analysis of surgical steps of interest for 0.3-0.5 μm/m³ particle counts

Variable	OR	Lower 95%	Upper 95%	Z score	*P* value
Bovie	10.20	7.80	13.30	16.80	< 0.001
Burring	10.90	6.60	18.00	9.40	< 0.001
Drilling	0.50	0.20	1.10	-1.70	0.099
Bone scalpel	5.90	3.20	10.90	5.70	< 0.001
Max in room	1.40	0.90	2.00	1.60	0.116
Sensor distance	0.03	0.01	0.10	-4.70	< 0.001

OR: Odds ratios.

Table 2 Logistic regression analysis of surgical steps of interest for 1-5 μm/m³ particle counts

Variable	OR	Lower 95%	Upper 95%	Z score	*P* value
Bovie	2.60	2.00	3.5	6.5	< 0.001
Burring	5.80	3.40	10.2	6.2	< 0.001
Bone scalpel	4.30	2.00	9.3	3.7	0.005
Max in room	1.40	0.90	2.4	1.3	0.179
Sensor distance	0.05	0.01	0.4	-2.9	0.004

OR: Odds ratios.

models. A spike in particle counts was defined as a greater than 3 standard deviations increase in particles from baseline levels. Data were analyzed by grouping the particle sizes into 0.3-0.5 μm/m³, 1.0-5.0 μm/m³, and 10.0 μm/m³. This division in particle sizes was not alterable and based on the internal settings of the OPS. To adjust for potential confounding, we used a regression model to control for the variables of sensor distance to the surgical field and the maximum number of people in the room during sampling.

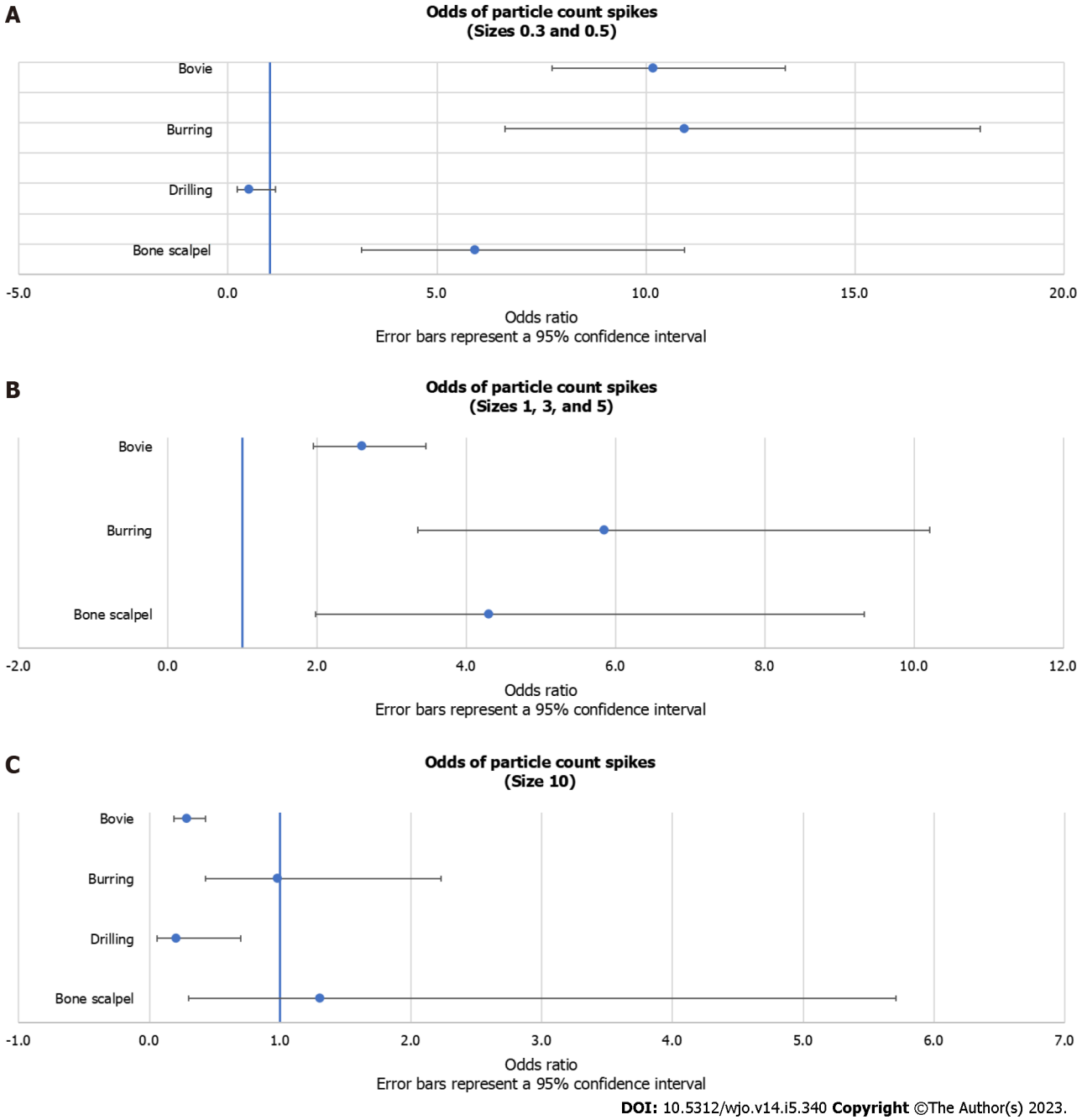
RESULTS

The logistic regression analysis revealed that bovie (OR = 10.2; 95%CI: 7.8, 13.3; $P < 0.001$), burring (OR = 10.9; 95%CI: 6.6, 18.0; $P < 0.001$), and bone scalpel (OR = 5.9; 95%CI: 3.2, 10.9; $P < 0.001$) had significantly higher odds of a spike in 0.3-0.5 μm/m³ particle counts ("spike" being defined as a greater than 3 standard deviation increase from average baseline levels) (Table 1). Drilling was not significantly associated with a spike in 0.3-0.5 μm/m³ particle counts (OR = 0.5; 95%CI: 0.2, 1.1; $P = 0.099$).

Bovie (OR = 2.6; 95%CI: 2.0, 3.5; $P < 0.001$), burring (OR = 5.8; 95%CI: 3.4, 10.2; $P < 0.001$), and bone scalpel (OR = 4.3; 95%CI: 2.0, 9.3; $P = 0.005$) had significantly higher odds of a spike in 1-5 μm/m³ particle counts (Table 2). Drilling was excluded in this analysis because no spikes in the 1-5 μm/m³ particle size range were recorded during drilling.

Bovie (OR = 0.3; 95%CI: 0.2, 0.4; $P < 0.001$) and drilling (OR = 0.2; 95%CI: 0.1, 0.7; $P = 0.011$) had significantly lower odds of a spike in 10 μm/m³ particle counts (Table 3). Burring (OR = 1.0; 95%CI: 0.4, 2.2; $P = 0.962$) and the bone scalpel (OR = 1.3; 95%CI: 0.3, 5.7; $P = 0.724$) were not significantly associated with a spike in 10 μm/m³ particle counts. All logistic regression results are visually presented as forest plots (Figure 2).

In addition, using generalized least squares (GLS) regression models, we compared average particle counts found within a certain step to the baseline defined before and after the steps. The results from this analysis are highly consistent with those of the logistic regression. The bovie ($P < 0.001$), burring ($P = 0.009$), and bone scalpel ($P = 0.002$) were associated with an increase in the average 0.3-0.5 μm/m³ particle counts relative to baseline, while drilling was not ($P = 0.323$). Bovie ($P < 0.001$) and burring ($P < 0.001$) were associated with an increase in the average 1-5 μm/m³ particle counts, while drilling ($P = 0.748$) and bone scalpel ($P = 0.110$) were not. Bovie ($P = 0.032$) was associated with a decrease in the average 10 μm/m³ particle counts, while burring ($P < 0.001$) was associated with an increase in the average 10 μm/m³ particle counts. Drilling ($P = 0.403$) and the bone scalpel ($P = 0.638$) were not



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Figure 2 Forest plot. A: Odds ratios (ORs) for each surgical steps of interest for 0.3-0.5 μm/m^3 particle counts; B: ORs for each surgical steps of interest for 1-5 μm/m^3 particle counts; C: ORs for each surgical steps of interest for 10 μm/m^3 particle counts.

associated with changes in the average 10 μm/m^3 particle counts.

DISCUSSION

Handheld OPSs are common tools used to quantify particles present in an air sample. OPSs have previously been employed in the healthcare setting to quantify aerosol generation during medical and surgical procedures[10-14]. In this study we use an OPS to demonstrate that several steps in spinal fusion are associated with increased airborne particle counts in the aerosol size range. Specifically, bovie, burring, and the bone scalpel showed consistently higher odds of spikes, while drilling did not. Although bovie and drilling had lower odds of a spike in 10 μm/m^3 particle counts, this was likely due to the large number of 10 μm/m^3 particle counts at baseline, which may have influenced our ability to recognize a spike in this range.

Table 3 Logistic regression analysis of surgical steps of interest for 10 μm/m³ particle counts

Variable	OR	Lower 95%	Upper 95%	Z score	*P* value
Bovie	0.3	0.2	0.4	-6.0	< 0.001
Burring	1.0	0.4	2.2	0.0	0.962
Drilling	0.2	0.1	0.7	-2.5	0.011
Bone scalpel	1.3	0.3	5.7	0.4	0.724
Max in room	1.7	0.9	3.5	1.6	0.111
Sensor distance	0.02	0.001	0.2	-3.0	0.003

OR: Odds ratios.

CONCLUSION

It is well established that the bovie produces large clouds of aerosolized particles[9]. This study has confirmed this finding and given validity to our methodology of identifying aerosol producing surgical steps. Previous research has shown that electrocautery smoke may be an inhalation hazard for surgeons but here we show that usage of the high speed burr and bone scalpel have the potential to aerosolize blood and other body substances[11,15]. Of note, burring confers less heat than bovie and bone scalpel, potentially making the aerosol particles it produces a larger risk if they are carrying infectious agents. These steps generate an abundance of particles in a size range that has been established to carry infectious particles. Multiple lines of evidence have confirmed that viral particles are detectable in the blood, but further research is warranted to determine if such particles have the potential to contain infectious viruses. Furthermore, if aerosolized blood has the potential to transmit the COVID-19 virus further research would be needed to determine if and whether the blood aerosolized through the surgical techniques described here is an infectious hazard or if particles are heated up to the point that they are no longer infectious[12,16-18].

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) pandemic has raised awareness of aerosol generation during medical procedures as an occupational hazard. Several authors have speculated that certain steps during spinal fusion have the potential to generate aerosols, however there is a dearth of data to quantify this risk. Publishing the type of data, we present here is critical to help hospitals create evidence-based workplace safety policies. As such, we believe that the findings presented here will be of interest to the readership of your journal and will hopefully inform future research and clinical care.

Research motivation

Several steps in spinal fusion are associated with increased airborne particle counts in the aerosol size range. Further research is warranted to determine if such particles have the potential to contain infectious viruses.

Research objectives

Upon univariate analysis, bovie ($P < 0.0001$), high speed pneumatic burring ($P = 0.009$), and ultrasonic bone scalpel ($P = 0.002$) were associated with increased 0.3-0.5 μm/m³ particle counts relative to baseline. Bovie ($P < 0.0001$) and burring ($P < 0.0001$) were also associated with increased 1-5 μm/m³ and 10 μm/m³ particle counts. Our logistic regression model demonstrated that bovie (OR = 10.2, $P < 0.001$), burring (OR = 10.9, $P < 0.001$), and bone scalpel (OR = 5.9, $P < 0.001$) had higher odds of a spike in 0.3-0.5 μm/m³ particle counts. Bovie (OR = 2.6, $P < 0.001$), burring (OR = 5.8, $P < 0.001$), and bone scalpel (OR = 4.3, $P = 0.005$) had higher odds of a spike in 1-5 μm/m³ particle counts.

Research methods

We quantified airborne particle counts during five posterior spinal instrumentation and fusions (9/22/2020-10/15/2020) using an optical particle sizer (OPS) near the surgical field. Data were analyzed by 3 particle size groups: 0.3-0.5 μm/m³, 1.0-5.0 μm/m³, and 10.0 μm/m³. We used hierarchical logistic regression to model the odds of a spike in aerosolized particle counts based on the step in progress.

Research results

In this study we use a handheld OPS to measure the generation of aerosols during surgical steps in spinal fusion because of the risk this may confer upon surgeons in regards to the airborne transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Research conclusions

Several steps in spinal fusion may aerosolize blood but little data exists to quantify the risk this may confer upon surgeons.

Research perspectives

Transmission of SARS-CoV-2 can occur during aerosol generating procedures. Several steps in spinal fusion may aerosolize blood but little data exists to quantify the risk this may confer upon surgeons.

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FOOTNOTES

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Does orthotics use improve comfort, speed, and injury rate during running? A randomised control trial

Alice E Fortune, Jonathan M G Sims, George Ampat

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Abstract

BACKGROUND

Running is a hugely popular sport. Unfortunately, running-related injury (RRI) rates are high, particularly amongst amateur and recreational runners. Finding ways to reduce RRI rates and maximise comfort and performance for runners is important. Evidence regarding whether orthotics can successfully improve these parameters is limited and contradicting. Further research is required to provide runners with clearer guidance on the usefulness of orthotics.

AIM

To investigate the effect of Aetrex Orthotics on comfort, speed and RRI rates during recreational running.

METHODS

One hundred and six recreational runners were recruited on a voluntary basis *via* running clubs and social media pages and randomised into either the intervention or control group. Participants in the intervention group ran with Aetrex L700 Speed Orthotics inserted in their usual running shoes, whilst participants in the control group ran in their usual running shoes with no orthotics. The study ran for an 8-wk period. Participants provided data relating to running comfort, distance, and time during weeks 3-6. Participants provided data relating to any RRIs they sustained during all 8 wks. Running distance and time were used to calculate running speed in miles *per* hour (mph). For each outcome variable, 95% confidence intervals and *P* values were calculated to assess the statistical significance between the groups. For comfort and speed data, univariate multi-level analysis was performed, and for outcome variables with significant between

group differences, multi-level multivariate analysis was performed to evaluate any confounding effects of gender and age.

RESULTS

Ninety-four participants were included in the final analysis (drop-out rate = 11%). Comfort and speed from 940 runs and 978 injury data reports were analysed. Participants who ran with orthotics reported, on average, speeds 0.30 mph faster (P = 0.20) and comfort scores 1.27 points higher ($P \leq 0.001$) than participants who ran with no orthotics. They were also 2.22 times less likely to sustain an injury (P = 0.08) than participants who ran with no orthotics. However, findings were only significant for comfort and not for speed or injury rates. Age and gender were found to be significant predictors of comfort. However, the improvements in comfort reported by participants who ran with orthotics were still significant after adjusting for age and gender.

CONCLUSION

This study found orthotics to improve comfort and speed and prevent RRIs whilst running. However, these findings were only statistically significant for comfort.

Key Words: Running; Foot orthoses; Running related injuries; Pain; Patient comfort; Athletic performance.

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Core Tip: Running-related injuries are common, necessitating research into ways to prevent injury. Foot orthotics have been suggested as a method to reduce running-related injury rates and improve comfort and performance, which are important components of running. Previous evidence regarding this is limited and mixed. This randomised control trial finds that running with Aetrex L700 Speed Orthotics inserted into normal running shoes reduces the rate of running-related injuries and improves both comfort and speed. These findings were only statistically significant for comfort. Providing increased comfort may encourage individuals to take up running, improving their health and decreasing the demand on healthcare systems.

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INTRODUCTION

Running is a highly popular sport, likely due to its accessibility and wide range of health benefits. It has been found to prevent many common health conditions and reduce overall mortality[1-5]. However, amongst people who run, there are high rates of injuries reported[6,7]. Several studies have found running-related injury (RRI) rates to be particularly high amongst amateur and recreational runners compared to professional runners[8-11]. Common RRIs include medial tibial stress syndrome, Achilles tendinopathy and plantar fasciitis[12-14]. RRIs frequently lead to pain and discomfort and may cause individuals to stop running or seek medical treatment[14]. The high prevalence of RRIs necessitates research into prevention, especially when considering the need to encourage individuals to run in order to gain the many health benefits.

Comfort is an important factor whilst running. It has been shown that increased comfort of running can, in turn, lead to improved running performance[15]. Additionally, the experience of pain and injury overlaps with the experience of discomfort and therefore comfort. Hence, improving comfort may reduce pain and subsequently reduce reported injury rates and time taken off work or any activity due to injury. There is, therefore, a substantial incentive to improve comfort for runners.

Orthotics are a type of shoe insert often used within the running community. They can be prefabricated or custom-made to fit an individual's foot shape and size. Orthotics act to correct lower limb alignment by reducing foot pronation[16], whilst also providing enhanced cushioning, support and comfort for the foot[17]. As well as injury and comfort, another factor important to many runners is performance: Typically measured as running speed. Previous research into the benefits of orthotics on running performance, comfort and injury rates is limited and, at times, contradicting. Some studies have found orthotics to improve running performance and comfort, whereas others have shown orthotics to negatively impact these parameters[18-22]. Evidence regarding the impact of orthotics on RRI rates is also mixed[23-25]. Hence, further research is required to determine the relationship between orthotics and running comfort, running speed and RRI rates. Exploring modalities to improve comfort,

performance and injury rates whilst running is important and valuable, as this would hopefully encourage more people to take up running, leading to substantial health benefits. Exploring ways to prevent RRIs in amateur and recreational runners is particularly relevant as these groups are thought to have the highest injury rates[8-11].

The aim of this study is to explore the effects of prefabricated Aetrex[26] Orthotics on running comfort, running speed and RRI rates compared to running with no orthotics. The results of this study will add to the current evidence concerning orthotics usage in running, building on previous work by Ampat *et al*[27]. This will provide runners with enhanced guidance on the possible benefits of orthotics and, hopefully, if the results are positive, encourage non-runners to take up running, thereby improving their health[1].

This article presents the findings from the full study cohort, building on the findings in the preliminary study report[28]. The study design was previously registered in clinical trials (https://www.ijclinicaltrials.com/index.php/ijct/article/view/586) in May 2021 (NCT04901442) and published [29].

MATERIALS AND METHODS

This study was conducted as a randomised control trial. The primary objective was to investigate whether running with prefabricated orthotics inserted into participants' usual running shoes *vs* running without would improve comfort and speed and reduce injury rates.

Recruitment

Results of our previous study found an improvement of two points on the comfort scale when using orthotics compared to usual running trainers with no orthotics[27]. For the sample size estimate for this study, a conservative improvement of 1.5 points, with a standard deviation of 2.45, was used. Based on this, a target sample size of one hundred and six participants was determined through a sample size calculation, using a target significance level of 5%, target power of 80% and allowing for a 20% dropout rate. All 106 participants were recruited between July 2021 and April 2022 on a voluntary basis *via* advertisements displayed on social media pages and at local running clubs. Individuals who contacted the research team were screened for eligibility and provided with a participant information sheet (PIS). Recipients were allowed sufficient time to read and understand the PIS in full. If, following this, they were willing to participate, a phone call with the lead investigator was arranged to answer any remaining questions. Following this, individuals willing to participate provided informed, written consent, either by post or online *via* legalesign.com.

Inclusion criteria for the study were: Aged 18 and over and used to completing runs of at least 5km distance during the last year. Exclusion criteria were: Current use of prescription orthotics, having any ongoing pain or deformity in the foot, having any serious health condition which had led to a doctor advising them not to exercise or having undergone any surgery in the past six months or any surgery to the feet during their lifetime. Participants were informed that they could withdraw from the study at any time if they wished to, without needing to provide a reason.

Randomisation

Following recruitment, participants were randomised into one of two groups using a 1:1 allocation: Group A (intervention group), in which participants ran with Aetrex[26] L700 Speed Orthotics inserted into their usual running shoes, or Group B (control group), in which participants ran in their usual running shoes with no orthotics. Randomisation and group allocation occurred using pre-filled and sealed envelopes, each containing a note to assign a participant to either Group A (intervention group) or Group B (control group). All envelopes were shuffled thoroughly before opening and randomly selected and opened by an individual independent of the study. Blinding of participants and researchers to group allocation was not possible due to the nature of the study intervention.

Participants allocated to Group A (intervention group) received a pair of Aetrex[26] L700 Speed Orthotics in their correct shoe size *via* post. They also received an instruction sheet clearly explaining how to use the orthotics. The Aetrex[26] L700 Speed Orthotics provided to Group A (intervention group) in this study are pictured in Figure 1.

Data collection

Upon recruitment to the study, basic demographic information was collected from each participant. Collection of data for all three primary outcomes (comfort, speed, and injury rate) then took place over an 8-wk period. To minimise confounding variables and risk to participants, participants were asked to run as they usually would during the 8-wk study period, with no changes made other than the addition of the orthotics for the intervention group. Participants provided all data remotely and could choose whether they wished to provide data *via* an online or a paper survey provided to the researchers *via* post. All participants opted to provide data *via* the online method.



Figure 1 Aetrex L700 Speed Orthotics. Image of Aetrex L700 Speed Orthotics, provided to participants in the intervention group. Reprinted with permission of Aetrex, Inc. © 2022.

The majority of data collection took place during weeks 3, 4, 5 and 6 of the 8-wk data collection period. Weeks 1 and 2 were allocated as an 'acclimatisation period' to allow individuals in the intervention group to become familiar with using the orthotics. Weeks 7 and 8 were allocated as a 'run-through period' with the purpose of collecting data regarding any injuries that occurred following the main data collection weeks. During weeks 3, 4, 5, and 6, participants provided data relating to running comfort, running duration, and running distance immediately after every run they completed. Participants were asked to complete and provide data from at least 10 runs during this 4-wk period. Comfort was scored using a self-report visual analogue scale (VAS) of 0 to 10, where 0 represented "No Comfort" and 10 represented "Maximum comfort". VAS was selected as this is a widely used and validated method of scoring patient-perceived comfort[30,31]. Running duration was reported in hours and minutes, and running distance was reported in miles/kilometres. Running duration and distance were used to calculate running speed in miles *per* hour (mph). Speed was used to represent running performance in this study, in line with the way that running performance is measured in running events around the world.

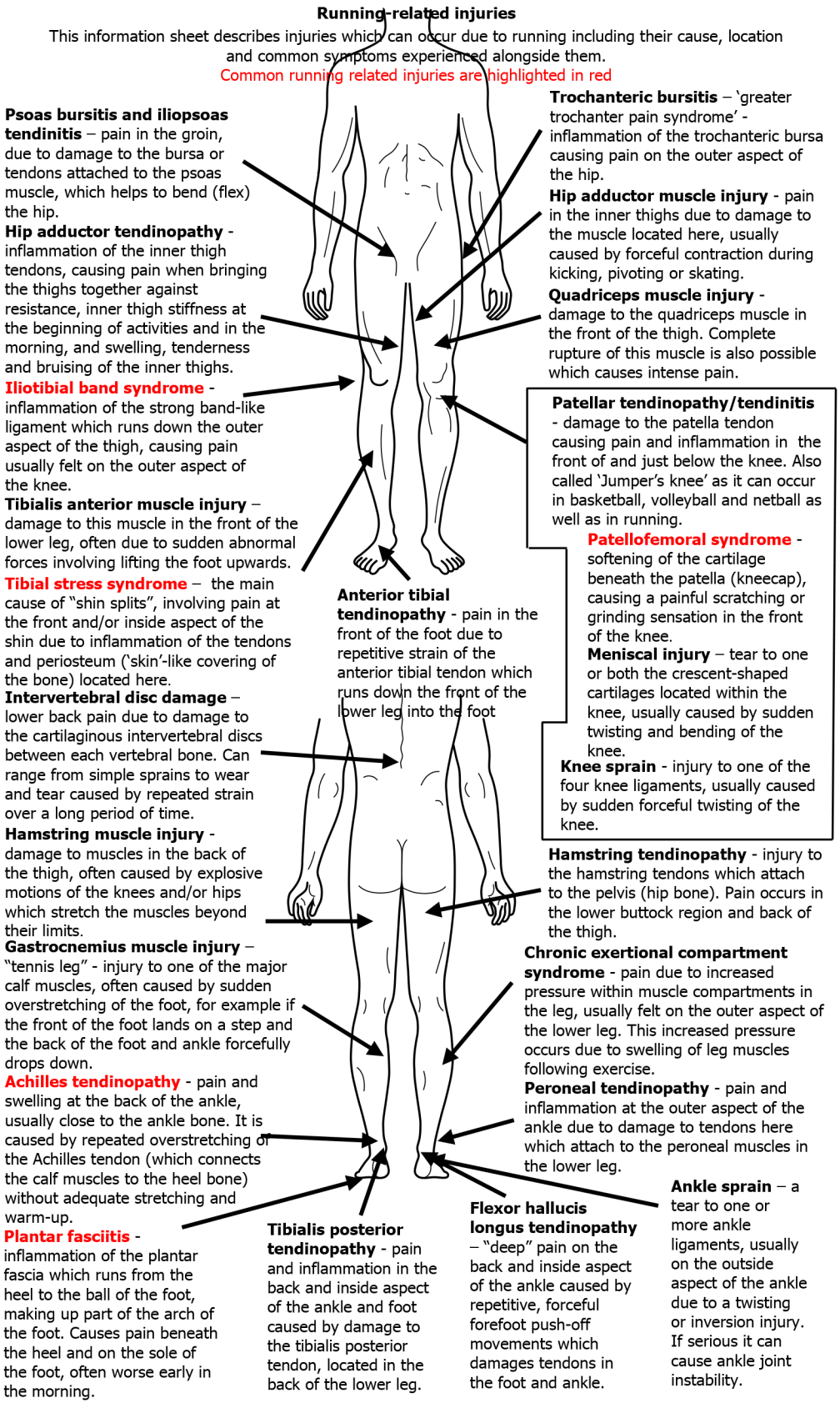
Participants were asked to provide data relating to any RRIs they had sustained at least once *per* week during the whole 8-wk period. This data was reported *via* a self-report survey, and all participants were provided with an injury identification sheet about common RRIs to assist them in providing this data, as depicted in Figure 2. Data was submitted regarding whether the injury led to disruption of running (disruption of distance, speed, duration, or frequency of running), and if so, how long for. Participants also self-reported the nature of the injury (*e.g.*, iliotibial band syndrome, Achilles tendinopathy) based on the injury identification sheet and whether the injury was new or pre-existing. For an injury to be included in analysis, it had to meet the definition "running-related musculoskeletal pain in the lower limbs that causes a restriction or stoppage of running (distance, speed, duration, or training) for at least 7 d or 3 consecutive scheduled training sessions". This is the consensus definition presented by Yamato *et al*[32] following their work on defining RRIs. Pre-existing injuries were included only if they flared up during the study period.

Data collection was monitored by a data monitoring committee consisting of an orthopaedic surgeon, a patient and a statistician, all independent of the research team.

All individuals who took part in the study were provided with a free pair of Aetrex[26] L700 Speed Orthotics to thank them for their time and participation in the study. Those in Group B (control group) were provided these after the data collection period.

Statistical analysis

All participants were analysed (intention to treat) within their original assigned groups. The primary outcomes comfort and speed data were analysed using multi-level univariate analysis. This was done to group together the data provided by each individual (*i.e.*, runners having data on multiple runs), allowing any internal correlations to be accounted for. 95% confidence intervals and *P* values were calculated for each outcome variable to determine if between-group differences were statistically significant. This was done using the Chi-squared test for comfort and speed data and Fisher's exact test for injury data. Statistical significance was considered if $P < 0.05$. For outcome variables with significant findings, multi-level multivariate analysis using a logistic regression model was performed to evaluate any confounding effects of gender or age on the findings.



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Figure 2 Injury identification sheet. Injury identification sheet regarding common running-related injuries provided to participants to assist them in reporting injuries.

All statistical analysis was reviewed by a National Institute for Health and Care Research-funded statistician from the Department of Biostatistics, University of Liverpool.

RESULTS

One hundred and six individuals were recruited to the study; 53 were randomised to the intervention group and 53 to the control group. During the study, 12 participants withdrew (6 from the intervention group, and 6 from the control group), two due to illness, two due to injury and eight stopped responding. This left a total of 94 participants to be included in the analysis (drop-out rate of 11%). Full details of participant flow, including reasons for withdrawal, are detailed in Figure 3.

The final study cohort (n = 94) ranged in age from 19 to 66 years old, with an overall mean age of 39 and a higher proportion of males than females. The intervention group contained slightly more women than men (n = 24 *vs* 23), whereas the control group contained more men than women (n = 29 *vs* 18). On average, participants in the intervention group were older than those in the control group, with mean ages of 40.8 and 37.9, respectively. Complete demographic data for the study population can be found in Table 1.

All the 94 participants included in the analysis provided data from at least 10 runs across weeks 3, 4, 5 and 6, and injury data at least once *per* week during weeks 1-8. The first 10 runs provided by each participant were included in the analysis. From these, comfort, and speed data for runs over two hours long were considered outlier variables and excluded from the analysis. Such runs, of which there were 65 in total (6.91%), were removed because the purpose of this study is to investigate amateur and recreational runners, for whom a run longer than two hours is not considered typical. The injury data of the two participants who withdrew from the study due to injury was removed from the analysis. This left a total of 875 sets of comfort and speed data and 978 sets of injury data in the final analysed dataset.

Regression coefficients, 95% confidence intervals and P values for comfort and speed data are provided in Table 2. On average, participants who ran with Aetrex[26] Orthotics reported comfort scores that were 1.27 points higher than those who ran with no orthotics. This finding was statistically significant, with a P value of < 0.001. Running speeds reported by participants in the intervention (orthotic) group were, on average, 0.30 mph faster than those reported by participants in the control (no orthotic) group. However, this finding was not statistically significant (P = 0.20).

Numbers of injuries reported by both groups and the odds ratios, 95% confidence intervals and P values calculated for injury data are provided in Table 3. Participants in the intervention group were 2.22 times less likely to report an injury that disrupted running for ≥ 7 d compared with participants in the control group). However, these findings were not statistically significant (P = 0.08).

Table 4 reports data for injuries lasting ≥ 7 d in more detail, showing the frequency of injury at different sites and overall injury rates. Upper leg and knee injuries were rarely reported in the intervention group, whilst they were the most common injured sites in the control group. Overall, injuries occurred less frequently in the orthotic group; however, of the injuries that did occur, a large proportion of these was in the ankle. One participant from each group experienced two injuries that lasted ≥ 7 d. Hence, 5 participants reported 6 injuries lasting ≥ 7 d in the orthotic group, and 10 participants reported 11 injuries in the control group.

The orthotic group reported three ankle injuries, all of which were ankle sprains. Conversely, the control group reported no ankle sprains. To explore the potential reason for this discrepancy, all participants who experienced an ankle sprain were contacted to enquire about the type of terrain on which they were running when the ankle sprain occurred (on or off road). All three participants reported that they were running off-road at the time of the injury.

Multilevel multivariate analysis of comfort scores is provided in Table 5. Age and gender were found to be significant predictors of comfort scores. Male participants provided scores that were, on average, 0.55 points higher than females (P = 0.039), and comfort scores increased by 0.04 points for every one-year increase in participant age (P = 0.003). However, the increase in comfort scores in the intervention group remained significant after adjusting for the effects of gender and age ($P \leq 0.001$).

Generally, the spread of data for all variables was broad, reflected by wide confidence intervals, and this was wide enough to produce non-significant findings for injury and speed.

It was ensured that no participants experienced any additional harm or injury by participating in the study. This was mitigated by instructing all participants to run as they normally would, without changing the running frequency, speed, or duration. The only alteration was the addition of orthotics in intervention group, who were shown to have a reduced RRI rate as compared to the control group. Two participants withdrew from the study due to injury. However, the participants did not require any medical intervention other than cessation of running.

DISCUSSION

This randomised control trial explores the effect of orthotics on running comfort, speed and RRI rates. It finds that participants who ran with Aetrex[26] L700 Speed Orthotics reported, on average, higher comfort scores, higher running speeds and lower injury rates over the 8-wk study period than participants who ran with no orthotics. These findings, however, were statistically significant for comfort only and not for injury or speed.

Table 1 Basic demographic information for participants included in analysis, *n* (%)

	Intervention (orthotic) group	Control (no orthotic) group	Both groups
Sex			
Male	23 (48.94)	29 (61.70)	52 (55.32)
Female	24 (51.06)	18 (38.30)	42 (44.68)
Age (yr)			
< 20	1 (2.1)	1 (2.13)	1 (1.06)
20-29	9 (19.1)	9 (19.15)	16 (17.02)
30-39	10 (21.3)	15 (31.91)	26 (27.66)
40-49	16 (34.0)	13 (27.66)	30 (39.91)
50-59	8 (17.0)	7 (14.89)	16 (17.02)
60-69	3 (6.4)	2 (4.26)	5 (5.32)
Mean age	40.79	38.49	38.97
Total	47	47	94

Table 2 Findings and multi-level analysis of comfort and speed data for both groups

Outcome measure	Regression coefficient (95%CI)	*P* value
Comfort	1.27 (0.69 - 1.84)	< 0.001
Speed	0.30 (-0.16 - 0.75)	0.20

Table 3 Findings and statistical analysis of injury data for both groups

Outcome measure	Participants experiencing outcome in intervention (orthotic) group	Participants experiencing outcome in control (no orthotic) group	Odds ratio (95%CI)	*P* value
Injury	5	10	2.27 (0.71 - 7.25)	0.26

Table 4 Frequency of injuries lasting > 7 d for both groups classified by injury site

Injury site	Injury frequency		
	Intervention (orthotic) group	Control (no orthotic) group	Both groups
Upper leg	0	6	6
Knee	1	3	4
Lower leg	1	1	2
Ankle	3	1	4
Foot	1	0	1
All sites	6	11	17

Previous studies have similarly found that orthotics provided non-significant improvements in injury rates and/or speed but significant improvements in comfort[27,33]. Ampat *et al*[27], reported on 37 participants who ran with and without the orthotics on alternate weeks, reporting distance, time, comfort and RRIs. In line with the current findings, Ampat *et al*[27] found significant improvements in comfort only and non-significant improvements in both injury rate and performance. Mündermann *et al*[33] assessed the effects of various shoe inserts on comfort and injury frequency in military personnel. As compared to the control condition (no insert), all shoe inserts allowed for significantly higher comfort ratings. The incidence of injury and pain at various locations was also reduced, albeit not significantly. However, this study assessed these effects during general physical activity, and not exclusively whilst running. Whilst these studies found somewhat similar findings to the current,

Table 5 Findings from multivariate analysis of comfort data

Outcome measure = comfort		
Variable	**Regression Coefficient (95%CI)**	***P* value**
Group (Intervention *vs* control)	1.22 (0.67 - 1.78)	< 0.001
Gender	0.55 (0.03 - 1.07)	0.039
Age	0.04 (0.01 - 0.06)	0.003

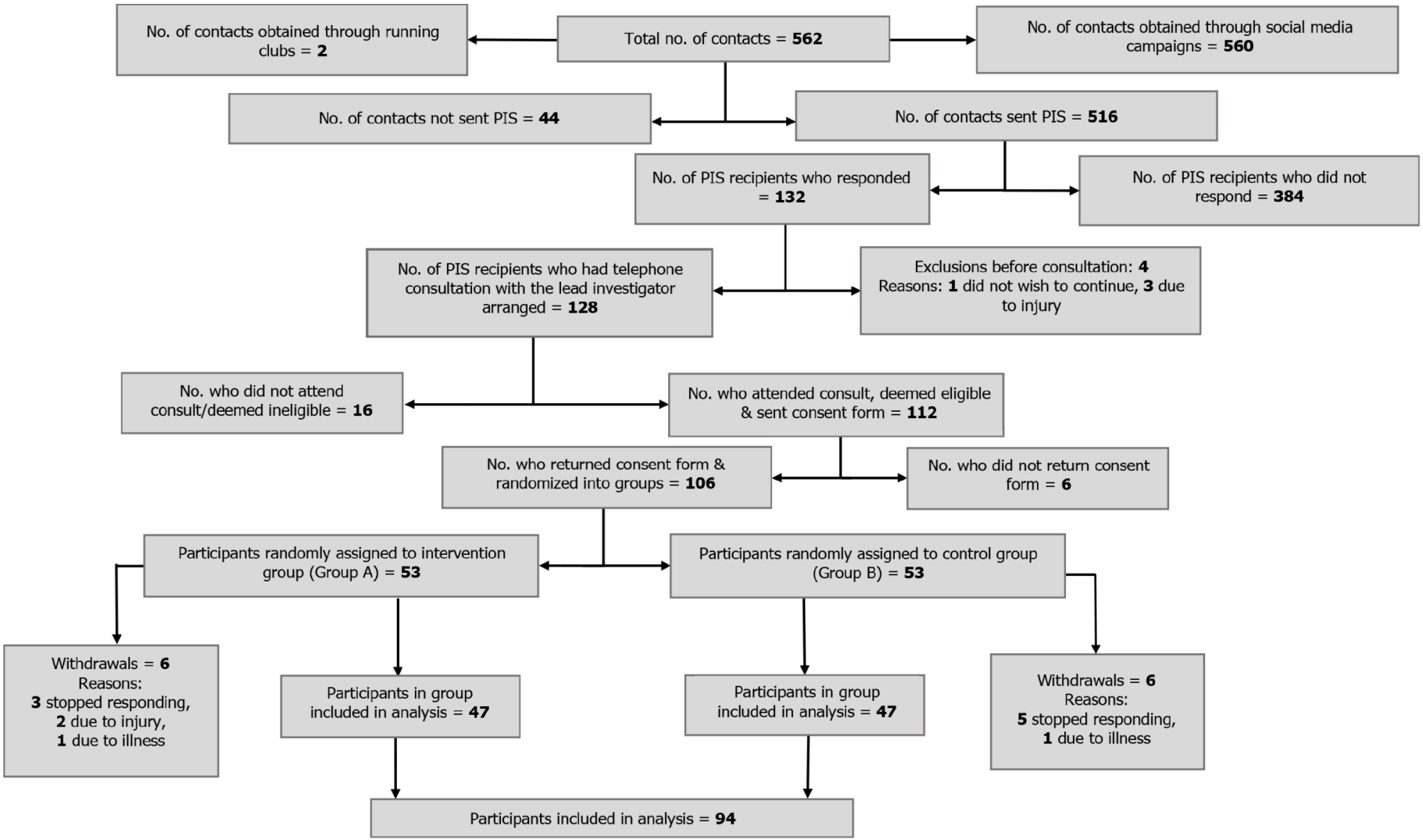
discrepancies in findings exist within the literature. For instance another study found only non-significant improvements in comfort[20]. However, unlike the current study, this assessed the effects of custom-made orthotics on well-trained male athletes in a controlled setting, in which participants ran on a treadmill for six minutes at high and low speeds in three footwear conditions; standardized footwear (control), custom made orthotics made from ethyl-vinyl acetate, and custom-made orthotics made from expanded thermoplastic polyurethane. Although not significant, arch height comfort and medio-lateral control comfort were improved in both orthotic conditions[20]. Additionally, a 2017 systematic review found significant reductions in overall injury rates with orthotics but non-significant reductions in injury rates when data for individual types of injury were analysed[23]. Contrastingly, a 2007 meta-analysis found orthotics to significantly reduce rates of lower limb overuse injuries specifically[30]. In summary, findings in the literature vary greatly. A likely factor contributing to this is the variation in RRI definitions used between studies. This has led to wide variation in reported RRI rates, ranging from 15.6% to 79.3% in previous studies[7,10,34]. For comparison, the overall number of participants who experienced a RRI in this study was 16%. Another likely contributor to the heterogenicity between study findings is the influence of various confounding variables. These variables include terrain, speed, experience, history of previous injury and distance. This study could have been improved by exerting greater control over confounding variables, such as those listed above. However, a strength of this study was the use of the consensus definition for a RRI, which was agreed upon in work done by Yamato and colleagues[32].

In this study, the rate of injuries lasting ≥ 7 d was lower in the intervention group at all sites except for the foot and ankle, where injuries were more common amongst individuals running with orthotics. Such findings from the orthotic group are harmonious with the findings of a 2012 systematic review which investigated the incidence and prevalence of running-related musculoskeletal injuries and found that foot and ankle injuries may be some of the most prevalent[35]. The higher rate of ankle injuries with the orthotic, namely ankle sprains, may also be explained by the fact that all participants in the orthotic group who experienced such injuries did so when running off-road. Ankle sprains are the most common injury to occur during off-road running[36]. This suggests that the terrain might have contributed to the injury, rather than the use of orthotics.

Unlike barefoot runners, who experience more accurate proprioceptive input from the feet during running and usually land on the ball of the foot[37], individuals who wear trainers whilst running have poorer proprioception and often land with their heels hitting the ground first. This causes overpronation of the foot and internal rotation of the lower limb joints, with simultaneous external rotation of the patella, which can lead to injury. The current working principle is that orthotics act to reduce this, as well as to distribute pressure more evenly across the foot[38-40]. The redistribution of pressure is illustrated in Figure 4. Additionally, orthotics are thought to provide impact cushioning, absorbing some of the forces that pass through the foot and lower leg during running, thereby reducing injury[17]. It would be beneficial for the running population that such orthotics are readily accessible and affordable. Prefabricated orthotics, which are at least 2.5 times less costly than custom-made orthotics, would be preferred[27]. This preference is supported by the results of previous research, which suggest that there is no significant difference when using pre-fabricated orthotics instead of customised orthotics to prevent RRIs[30].

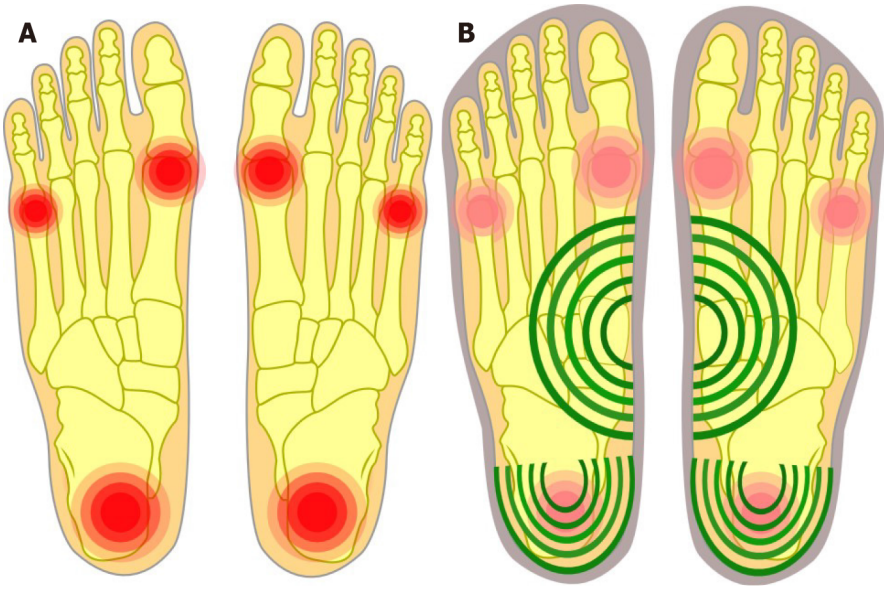
The strengths of this study include power analysis prior to commencement, achievement of target sample size, and a drop-out rate of just 11%, well below the drop-out rate allowed for, in the study size calculation. This allowed data collection of sufficient quantity and power to produce statistically significant findings. The wide range of ages of participants in this study increases its applicability to the broader running population. Additionally, the collection of data detailing the length of disruption to running following an injury, and injury sites, allowed more detailed exploration into the effect of orthotics usage on RRIs.

The study was not without limitations. No blinding of researchers or participants to group allocation took place. Some participants in the intervention group may have expected that the orthotics would improve their running experience, which could have created bias. This risk of bias is further emphasized when taking into consideration the newly developed 'comfort filter' paradigm, which suggests that injury risk is automatically reduced if a shoe or insert is deemed more comfortable by the runner as assessed by their own 'comfort filter'[41]. Additionally, comfort could have been explored in more



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Figure 3 Participant flow. Participant flow, including randomised group assignment and any withdrawals. No.: Number; PIS: Participant information sheet.



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Figure 4 Comparison of pressure in the feet with and without orthotics. A: Increased pressure at three points without orthotics compared to; B: Reduced pressure using orthotics with arch support and a cupped heel.

depth by assessing comfort in various parts of the foot, as done in other studies[33], rather than simply an overall comfort measure. Furthermore, the study results may have benefited from all participants being queried further regarding their running experience. Recreational runners have been defined as individuals with over 3 mo of running experience, whilst anyone with less than 3 mo of running experience is referred to as novice runners[8]. Experienced runners have been defined as runners who have been running for over a year[9]. It has been found that the incidence of RRIs is significantly higher in novice than experienced runners, with one study finding that novice runners experience 8.78 RRIs *per* 1000 hours of running, as compared to 4.24 *per* 1000 hours for experienced runners[9]. Hence, whilst the current study aimed to focus on recreational runners, the use of these definitions to sub-group participants would have been advantageous, as it would have allowed for further analysis into the relationship between running experience and its effects on injury rate. It would have also been beneficial for the researchers to evaluate participants history of previous RRIs, as this has been associated with an increased likelihood of a further injury and a poorer prognosis following a new injury[42]. Again, the inclusion of this data would have allowed sub-group analysis, enabling any existing correlations to be identified. The collection of data regarding each participant's usual running terrain is also a consideration for future studies as, once more, it would have allowed sub-group analysis to ascertain the relationship between the terrain on which participants ran and their injury types and injury rate. The lack of data collection concerning the participants running footwear could also be viewed as a limitation. Gathering this data would have allowed for sub-group analysis to determine if differences in footwear effected running performance or injury rate, as bias may exist. However, the researchers did not wish to control the participants running shoes, as the aim of the study was to ascertain the level of benefit orthotics can provide to general runners, irrespective of their usual running footwear. To improve the clarity of findings, it could also be favorable if future studies request a maximum of one weekly injury report and one comfort report for the entire week.

In this study, there was a much higher proportion of males (n = 29) than females (n = 18) in the control group. The UK running population is estimated to contain more males than females[43], but not at such an extreme ratio as in this participant group. In contrast, the intervention group contained slightly more females (n = 24) than males (n = 23). This difference in numbers of males and females in each group is relevant as it will have confounded the study findings, as demonstrated in the multivariate analysis of comfort. Closer monitoring of the participant recruitment process in future studies and using a sampling technique, such as stratified sampling, would prevent discrepancies like this from occurring in the future.

The wide confidence intervals found during the analysis of all outcomes demonstrate a wide spread of data from the mean values for each outcome and each group. These confidence intervals were wide enough to cause the improvements in speed and injury rate to be non-significant. This broad spread of data may be partially explained by the nature of the outcomes explored by this study. Natural tendencies for injury, running speeds and expectations for comfort vary between individuals, which may have led to a wider spread of data.

The burden of cardiovascular diseases, cancers and diabetes mellitus within the general population is substantial, and lack of exercise is a significant contributor to this[2-5,44-46]. Recreational running is an accessible, affordable way to exercise and reduces the risk of these health conditions[47,48]. This study finds that Aetrex L700 Speed Orthotics allows at least some improvements in performance and injury reduction and significant improvements in comfort.

This study advances current knowledge regarding the use of prefabricated orthotics in reducing RRI rates and improving running comfort and speed. However, the lack of significant findings for injury and speed necessitates further research. This is particularly important as reducing discomfort and injury may encourage more individuals to take up running and improve their health thereby decreasing the strain on healthcare services.

CONCLUSION

This randomised control trial finds that running with Aetrex[26] L700 Speed Orthotics improves comfort and speed whilst running and reduces RRI rates compared to running with no orthotics. However, data were only significant for comfort and not for injury rate or speed.

ARTICLE HIGHLIGHTS

Research background

Current evidence regarding the effect of orthotics on comfort, speed and injuries during running is limited and mixed.

Research motivation

Running is a highly popular sport; however, the rate of running-related injuries is high. Exploring the ability of orthotics to reduce injury and improve speed and comfort during running would be valuable to runners and, if the results are positive, encourage individuals to take up running, thereby improving their health.

Research objectives

To explore whether running with Aetrex[26] Orthotics inserted into normal running shoes reduces the rate of running-related injuries and improves comfort and speed.

Research methods

In this randomised control trial, participants were recruited on a voluntary basis and allocated to either the intervention (orthotic) group or the control (no orthotic) group. Participants in the intervention group were asked to run with a pair of Aetrex[26] L700 Speed Orthotics inserted into their normal running shoes, whilst participants in the control group were asked to run in their normal running shoes with no orthotics. Data for any related running-related injuries was collected over an 8-wk period. Comfort scores and run duration and distance data were collected immediately after any run performed during weeks 3-6. Univariate multi-level analysis was performed for comfort and speed data. Odds ratios were calculated for injury data, and 95% confidence intervals and *P* values were calculated for all three outcomes. Multilevel multivariate analysis was performed for outcomes with significant findings between groups to evaluate any confounding effects of gender and age.

Research results

Data from 94 participants were included in the final analysis. On average, participants in the intervention (orthotic) group reported higher comfort scores, faster running speeds and fewer injuries. This data was significant for comfort but not for injury rates or running speed. Gender and age were found to significantly affect comfort, but significant improvements in comfort when wearing the orthotic were still present after adjusting for gender and age.

Research conclusions

This study provides evidence that running with prefabricated orthotics inserted into normal running shoes increases comfort and speed and reduces the rate of running-related injuries. However, data were only significant for comfort and not for speed or injury rates.

Research perspectives

Further research on this subject is required due to the ongoing need to find a cost-effective way to reduce injury rates in recreational runners and encourage individuals to take up running to improve their health. Future studies should consider collecting data regarding the tendency for running injury

and usual running speeds to allow adjustment of results for these confounding variables.

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FOOTNOTES

Author contributions: Fortune AE, Sims JMG, and Ampat G designed the research study; Sims JMG was involved in recruitment and data collection; Ampat G performed telephone consultations with all participants on enrolment to the study; Fortune AE and Sims JMG analysed the data. Fortune AE, Sims JMG and Ampat G wrote the manuscript; All authors have read and approved the final manuscript.

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Clinical trial registration statement: This study is registered at https://clinicaltrials.gov/ct2/show/NCT04901442. The registration identification number is: NCT04901442.

Informed consent statement: All study participants gave their informed, written consent (*via* an online e-form) prior to study inclusion.

Conflict-of-interest statement: George Ampat and Jonathan M G Sims are Directors/employees of Talita Cumi Ltd. Talita Cumi Ltd has a commercial relationship with Aetrex, Inc. 414 Alfred Avenue Teaneck, NJ 07666, USA. Alice E Fortune has no conflict of interest.

Data sharing statement: The anonymised dataset is available from the corresponding author at g.ampat@liverpool.ac.uk. Participants gave informed consent for sharing of anonymised data.

CONSORT 2010 statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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CASE REPORT

Intra-abdominal myositis ossificans - a clinically challenging disease: A case report

Gabriele Carbone, Valentina Andreasi, Paola De Nardi

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Peer-review model: Single blind

Peer-review report's scientific quality classification

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Abstract

BACKGROUND

Myositis ossificans (MO) is an uncommon disorder characterized by heterotopic ossification within soft tissues. Only a few cases of intra-abdominal MO (IMO) have been described in the literature. Histology could be difficult to understand and a wrong diagnosis could lead to an improper cure.

CASE SUMMARY

We herein report the case of IMO in a healthy 69-year-old man. The patient presented with an abdominal mass in the left lower quadrant. A computed tomography scan showed an inhomogeneous mass with multiple calcifications. The patient underwent radical excision of the mass. Histopathological findings were compatible with MO. Five months later the patient showed a recurrence causing hemorrhagic shock due to intractable intralesional bleeding. The patients eventually died within three months since recurrence.

CONCLUSION

The case described could be classified as post-traumatic MO that developed close to the previously fractured iliac bone. The subsequent surgical procedure was ineffective and the disease rapidly recurred. The misleading intraoperative diagnosis led to improper surgical treatment with a dramatic evolution.

Key Words: Myositis ossificans; Post-traumatic; Diagnosis; Surgical treatment; Prognosis; Case report

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Core Tip: Myositis ossificans (MO) is a rare condition of heterotopic bone formation within muscle or soft tissues. Intra-abdominal MO is even rarer usually arousing following abdominal surgery or trauma. Its presentation is non-specific and physical examination is usually unremarkable until the mass reaches large dimensions. Laboratory examinations are within normal limits. Computed tomography scan is essential for the diagnosis, since it can show the typical "zonal patterns" of the calcifications. Histopathology can differentiate MO from infections and malignancies. However, histology could be misinterpreted for fibromatosis or sarcoma, thus leading to improper cure. The treatment may be complex and should be based on patients' symptoms. Most patients can be treated conservatively and surgical procedures should be reserved for selected patients since repetitive surgery promotes further and more aggressive calcifications.

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INTRODUCTION

Myositis ossificans (MO) is a rare and benign connective tissue disorder characterized by non-neoplastic heterotopic ossification in the context of soft tissues. MO tends to be secondary to trauma. It is mostly found in adolescents or young adults and the lesions are predominantly located in the large skeletal muscles of the arms and thighs. This form, also known as post-traumatic MO (PTMO), is usually self-limiting thus not requiring specific surgical treatment. However, the clinical, radiological, and histological presentation of MO is often non-specific and can mimic a soft tissue malignancy, resulting in misdiagnosis and inappropriate management. We herein report a very rare case of intra-abdominal MO (IMO) and review the main features of this rarely encountered, but clinically demanding condition.

CASE PRESENTATION

Chief complaints

A 69-year-old man presented at the surgical clinic with a painless abdominal lump, located in the left iliac fossa. The patient did not refer any systemic symptom.

History of present illness

The mass had slowly increased in size over the last couple of months.

History of past illness

His past medical history included an appendectomy during his childhood. Four years earlier a car accident occurred resulting in abdominal trauma and left iliac bone fracture.

Personal and family history

The patient denied any family or personal history of malignancies.

Physical examination

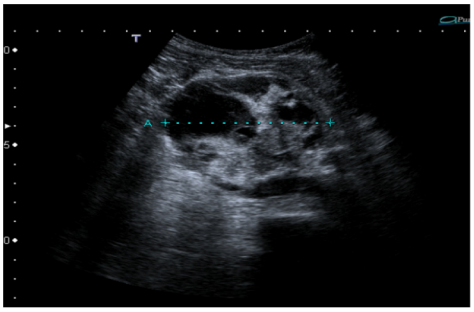
Clinical examination revealed a non-tender, firm, oval-shaped abdominal mass with smooth surface in the left lower quadrant.

Laboratory examinations

Laboratory findings were within normal range.

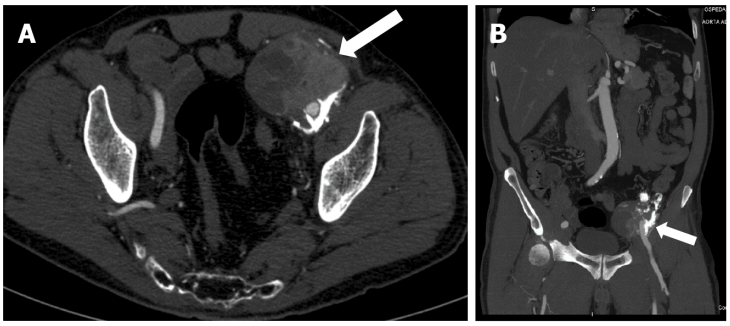
Imaging examinations

An abdominal ultrasound showed a 7-cm ovoidal lesion with a mixed echo structure, diffuse calcifications and increased vascular density at the color-Doppler control (Figure 1). A computed tomography (CT) scan was obtained with evidence of an 8 cm × 6.5 cm × 7 cm, highly inhomogeneous mass composed by multiple calcifications at the periphery (Figure 2).



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Figure 1 Abdominal ultrasound showed a 7-cm ovoidal lesion with a mixed echo pattern. It was possible to distinguish fluid and solid components (including diffuse calcifications).



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Figure 2 Computed tomography image revealed an 8 cm × 6.5 cm × 7 cm, highly inhomogeneous mass composed by multiple calcifications at the periphery. A: Axial view; B: Sagittal view.

FINAL DIAGNOSIS

The imaging features were strongly suspicious for a malignancy originating from mesenchymal cells. Based on these findings, a surgical exploration was performed.

TREATMENT

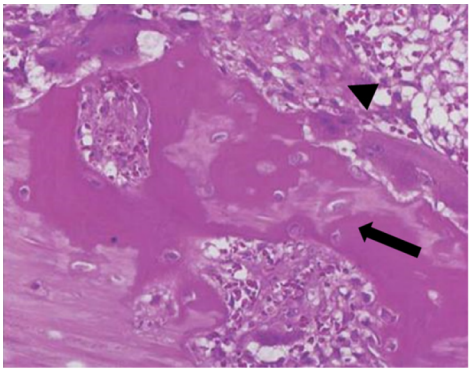
A bulky tumor with dense adhesions to the left iliac bone was found and the intraoperative histological examination was consistent with osteosarcoma. A radical excision of the mass was then carried out.

Gross examination of the surgical specimen revealed a partially capsulated, 8.5 cm × 8 cm × 6 cm mass with hemorrhagic and calcified areas. The lesion presented trabecular architecture characterized by a central area consisting of fiber cells and by a peripheral area consisting of osteoblasts, producing osteoid and bone matrix. Histopathological findings were compatible with IMO (Figure 3).

OUTCOME AND FOLLOW-UP

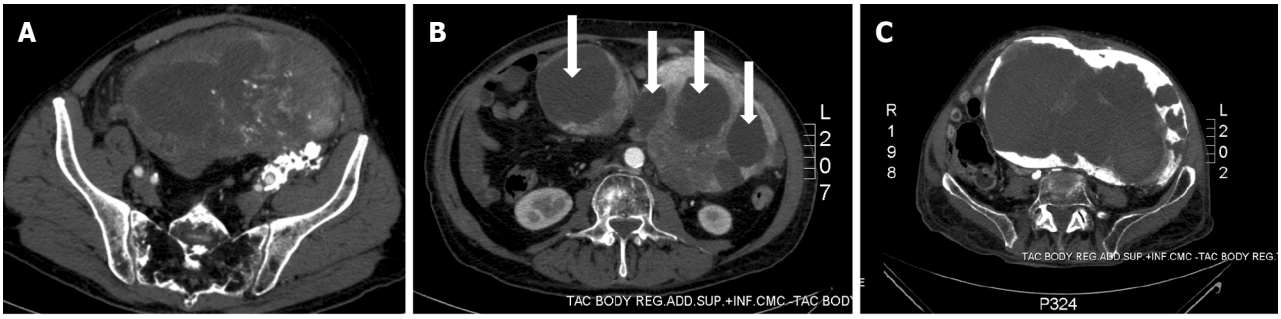
The post-operative course was complicated by a chylous fistula that was managed conservatively. Additionally, a complete thrombosis of the left femoral vein was diagnosed. The patient was then discharged with anticoagulant therapy.

Five months later, the patient returned to the Emergency Department complaining rapidly worsening abdominal pain, nausea, and vomiting. The radiological examinations showed disease recurrence with an inhomogeneous pelvic mass measuring approximately 20 cm in diameter and causing compression of the sigmoid colon (Figures 4A and 5). Because of the bowel obstruction, an explorative laparotomy was planned. At surgery, a hard, hyper vascular lesion strongly adherent to the anterior abdominal wall and to the deep posterior planes was found. Thus, due to the high risk of bleeding, only a biopsy of the mass was performed and the histopathological diagnosis confirmed an IMO. During the postoperative course the patient developed a hemorrhagic shock caused by multiple intralesional bleedings (Figure 4B). An angiography, with embolization of vessels originating from the left iliac artery, was performed with cessation of the bleeding. The lesion, however, continued to grow rapidly, infiltrating



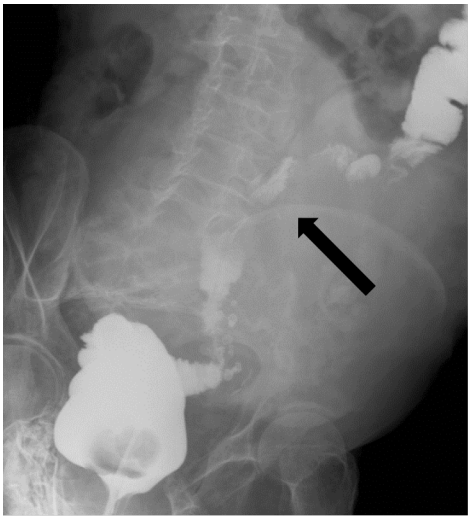
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Figure 3 Microscopic findings of myositis ossificans. Haematoxylin and eosin staining showing a mature lamellar bone neo-formation (arrow) and fibroblasts with elongated nuclei (arrowhead) arranged in short irregular fascicles with the typical "zonation pattern" placed in loose myxoid or collagenous stroma. Occasional mitoses can be observed, in the absence of cellular atypia.



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Figure 4 The computed tomography scan. A: An inhomogeneous pelvic mass measuring almost 20 cm in diameter; B: A mass with multiple haemorrhagic areas (arrows); C: A huge mass filling almost all the abdominal cavity and infiltrating the aortic plane and both ureters.



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Figure 5 Barium enema showing compression of the sigmoid colon (arrow).

the aortic plane and both ureters (Figure 4C). Eventually, the patient dramatically died eight months after the first diagnosis.

DISCUSSION

MO is an infrequent and non-malignant disease distinguished by abnormal heterotopic bone formation within soft tissues[1]. Two different clinical entities of MO have been reported in the literature: Progressive or genetic MO and acquired MO[2,3].

Progressive MO (PMO), also known as Munchmeyer disease, is a rare genetic autosomic dominant disorder characterized by congenital malformation of big toes and progressive heterotopic ossification of connective tissue. It usually begins in the spine and proceeds in a proximal to distal, cranial to caudal or axial to appendicular direction[4]. PMO normally develops in the first decade of life and the evidence of malformed great toes may lead to the correct diagnosis[5].

Acquired MO can be classified into neurogenic (associated with paraplegia) and non-neurogenic; the latter group can be divided into post-traumatic and idiopathic/pseudo malignant[2,3]. The case described in our report was reasonably a PTMO and, in the present article, we will discuss this clinical entity, which represents the most frequent form of MO, accounting for almost 70% of cases[6].

PTMO usually presents within the second and third decade of life, but lesions can arise at any age, as showed in our patient. PTMO typically originates in the context of the large skeletal muscles of the limbs. Quadriceps and brachialis muscles are the two most affected regions because of the high risk of traumas and injuries. However, PTMO can occur in almost every site of the body and even cases of PTMO in the hand have been described in the literature[7].

Abdominal PTMO mostly arises from a midline surgical incision or a trauma site[8], while IMO is an extremely rare condition associated with neoplasms of gastrointestinal tract or previous intra-abdominal surgery[9]. In the few IMO cases reported in literature[10,11], lesions developed inside the mesentery or the omentum after a surgical procedure and tended to grow rapidly, often resulting in bowel obstruction. Interestingly, in our patient the IMO lesion was located next to the previously fractured iliac bone and the mechanical trauma was likely the primum movens for the development of the lesion. The following surgical stress was probably responsible for disease recurrence and especially for the rapid growth evolution.

The clinical presentation of PTMO is highly variable, depending also on the site of origin. In case of PTMO of the limbs, it may range from an incidental finding to a rapidly enlarging painful mass with reduced range of movement. Otherwise, as mentioned before, patients with IMO can present with bowel obstruction. In some cases, clinical symptoms can mimic those of an aggressive malignant sarcoma, representing a diagnostic challenge[12,13].

The diagnosis of PTMO depends strictly on radiological and histological features since symptoms can be vague and clinical history is often silent (the only relevant element may be a trauma in the affected area). CT is the preferred imaging technique for PTMO as it best demonstrates the typical "zonal pattern". This feature is represented by a low-attenuating center with a well-circumscribed, high-attenuating, peripheral rim of calcification. CT may also show the classical "string sign", a thin radiolucent cleft which separates MO from adjacent bone. In our case, imaging revealed an inhomogeneous and hyper vascularized lesion with calcifications located only in one third of the circumference. These features were highly suspicious for a malignant lesion[14,15].

The "zone phenomenon" is also observed on histological tissue samples with a well-organized mature lamellar bone at the periphery, an intermediate osteoid region, and a central immature non-ossified fibroblastic focus[16]. The evidence of that histological feature makes MO diagnosis certain, since malignant neoplasms as osteosarcomas usually have a disorderly growth with a "reverse zoning effect". However, in some cases, a biopsy from the central zone that represents the least organized portion can be histologically suggestive of malignancies, leading to incorrect diagnoses[17]. This is what happened in our case, with an intraoperative histological exam positive for osteosarcoma that led to a surgical excision. Immunohistochemistry is not strictly essential for a correct diagnosis, but it helps to differentiate MO from malignant lesions, especially in atypical cases. MO samples generally include a large number of osteoblasts, which are positive for the marker SATB2. On other hand, osteosarcomas may be characterized by MDM2 and CDK4 overexpression[18,19]. The surgical specimen of our patient demonstrated organized mature lamellar bone at the periphery of the lesion, with a great amount of SATB2 positive cells, thus confirming MO diagnosis.

The management of PTMO is controversial and depends on the severity of patient's symptoms. PTMO is generally self-limiting and lesions often decreases in volume within two years. For this reason, most patients can be treated conservatively with nonsteroidal anti-inflammatory drugs, acetic acid therapy, iontophoresis treatment, magnesium therapy, and etidronate disodium[20,21]. In case of severe and persistent symptoms, surgery is the definitive treatment even if it is associated with local recurrence [22,23]. Particularly, IMO tends to recur and, since this condition is clearly exacerbated by surgery, surgical procedures should be reserved for selected patient[11]. The highest risk of recurrence is reached when surgical excision is performed within 6 mo of previous trauma. Therefore, it is preferable to perform a surgical procedure at least six months after the trauma when the lesion is completely mature and ossified[24]. As discussed before, we decided to proceed with a surgical excision based on pre-operative and intra-operative data and the disease recurrence was dramatically extraordinary in term of growing time. To the best of our knowledge, such aggressive behavior was only described in the literature for genetic forms of MO[25] that usually present in the first decade of life and have a life

expectancy of forty years[26].

CONCLUSION

MO is an uncommon and benign condition that can develop in any part of the body. The diagnosis may be difficult even with multiple imaging modalities, especially when MO develops in atypical locations. Biopsy is the gold standard, but in some case it can be misleading. Surgical treatment should be reserved for symptomatic patients because of the risk of recurrence. The present case emphasizes the challenges and pitfalls a clinician has to face to ensure a correct diagnosis and an appropriate management of this disease.

FOOTNOTES

Author contributions: Carbone G and De Nardi P contributed to manuscript writing and editing, and data collection; Andreasi V contributed to data collection and conceptualization; all authors have read and approved the final manuscript.

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MINIREVIEWS

Minimally invasive surgeries for insertional Achilles tendinopathy: A commentary review

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Abstract

Studies of minimally invasive surgery for insertional Achilles tendinopathy are limited. To establish this surgery, the following techniques must be minimally invasive: Exostosis resection at the Achilles tendon insertion, debridement of degenerated Achilles tendon, reattachment using anchors or augmentation using flexor hallucis longus (FHL) tendon transfer, and excision of the posterosuperior calcaneal prominence. Studies on these four perspectives were reviewed to establish minimally invasive surgery for insertional Achilles tendinopathy. Techniques for exostosis resection were demonstrated in one case study, where blunt dissection around the exostosis was performed, and the exostosis was resected using an abrasion burr under fluoroscopic guidance. Techniques for debridement of degenerated Achilles tendon were demonstrated in the same case study, where the space left after resection of the exostosis was used as an endoscopic working space, and the degenerated Achilles tendon and intra-tendinous calcification were debrided endoscopically. Achilles tendon reattachment techniques using suture anchors have been demonstrated in several studies. However, there are no studies on FHL tendon transfer techniques for Achilles tendon reattachment. In contrast, endoscopic posterosuperior calcaneal prominence resection is already established. Additionally, studies on ultrasound-guided surgeries and percutaneous dorsal wedge calcaneal osteotomy as minimally invasive surgery were reviewed.

Key Words: Achilles tendon; Endoscopy; Fluoroscopy; Osteotomy; Ultrasonography; Tendinopathy; Surgery

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Core Tip: Studies of minimally invasive surgery for insertional Achilles tendinopathy are limited. Therefore, to establish this surgery, the following techniques must be minimally invasive: (1) Exostosis resection at the Achilles tendon insertion; (2) Debridement of degenerated Achilles tendon; (3) Reattachment using anchors or augmentation using flexor hallucis longus tendon transfer; and (4) Excision of the posterosuperior calcaneal prominence. This article reviewed studies from these four perspectives to establish minimally invasive surgery for insertional Achilles tendinopathy. In addition, studies on ultrasound-guided surgeries and dorsal percutaneous dorsal wedge calcaneal osteotomy as minimally invasive surgery were reviewed.

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INTRODUCTION

Insertional Achilles tendinopathy is characterized by exostosis and intra-tendon calcification at the insertion site of the Achilles tendon into the calcaneus[1]. After failing to respond to exhaustive conservative therapy for 3-6 mo, surgery is considered[2,3]. Standard surgical procedures include posterior midline skin incision, calcaneal exostosis resection, partial or total detachment and debridement of the Achilles tendon at its insertion, resection of the posterosuperior calcaneal prominence and retrocalcaneal bursa, and reattachment using anchors or augmentation using flexor hallucis longus (FHL) tendon transfer[4,5]. The surgery's outcomes have been good[6-29]; nonetheless, the recovery was slow due to the invasiveness and the high complication rate due to the large skin incision[6,29-31]. McGarvey *et al*[6] reported a case series of 21 patients where 40% had residual pain for over two years postoperatively[6]. Hörterer *et al*[29] surveyed 118 people who underwent midline incision, partial release and debridement of the Achilles tendon, resection of the posterosuperior calcaneal prominence, and reattachment using anchors. They found that despite the high satisfaction rate, 41% had shoe limitations, and 14% had mild infections[29]. A systematic review by Highlander and Greenhagen[30] reported a 7.0% complication rate for midline incision, and another by Thompson *et al*[31] reported a significantly higher complication rate for midline incision than other incision techniques. Considering these, minimally invasive surgery is preferable. However, studies on minimally invasive surgery for insertional Achilles tendinopathy are scarce[32].

Therefore, to establish minimally invasive surgery for insertional Achilles tendinopathy, all four steps described below must be performed with minimally invasive surgery (Table 1).

This article reviewed studies on the above four techniques, including case reports, cadaver experiments, technical notes, and case series, to establish minimally invasive surgery for insertional Achilles tendinopathy. In addition, reports regarding ultrasound-guided surgeries and percutaneous dorsal wedge calcaneal osteotomy as minimally invasive surgery were also reviewed. In this article, the terms "Haglund disease" and "Haglund syndrome" were avoided because such eponymous terms are unclear[33,34].

ENDOSCOPIC SURGERY FOR INSERTIONAL ACHILLES TENDINOPATHY

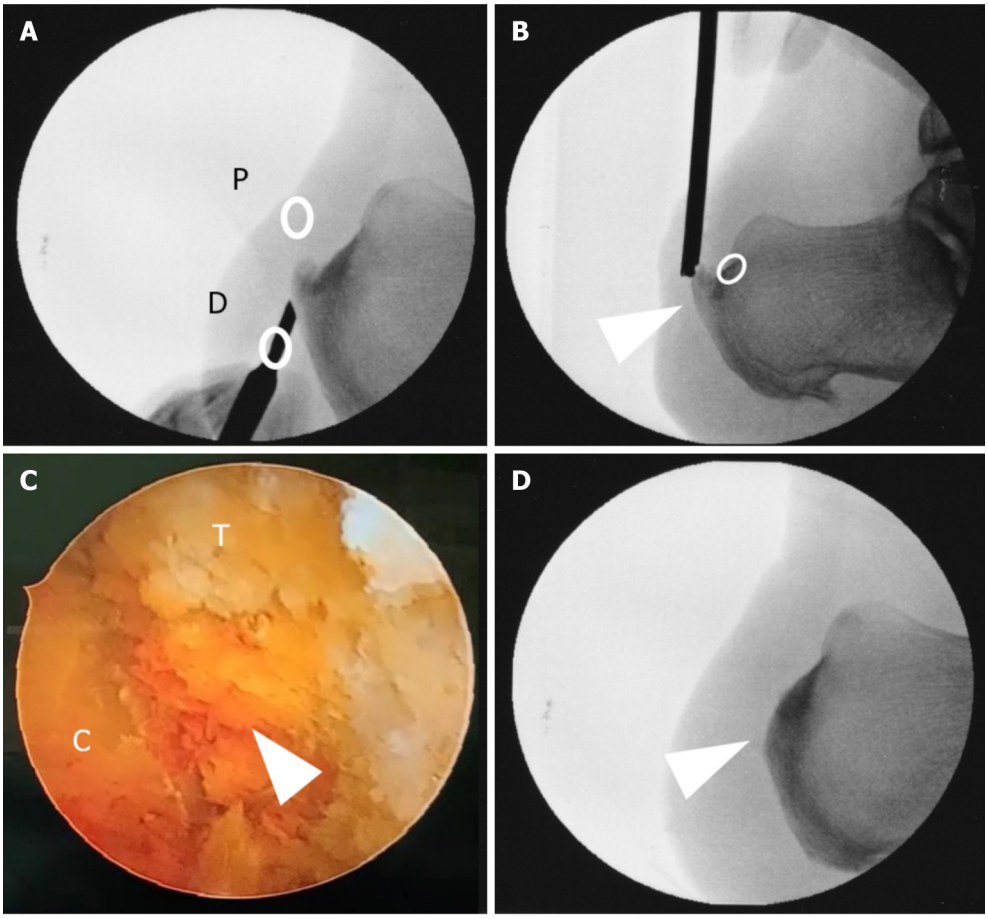
Fluoroscopic calcaneal exostosis resection and endoscopic Achilles tendon debridement

In 2022, Nakajima[32] published a case series of 44 patients who underwent minimally invasive surgeries for insertional Achilles tendinopathy involving techniques of exostosis resection at the Achilles tendon insertion and debridement of degenerated Achilles tendon (Table 1)[32]. The outline of this technique included the following: (1) Blunt dissection was performed around the exostosis with fluoroscopic guidance; (2) An abrasion bur was inserted into the space created by the dissection, and the exostosis was resected fluoroscopically; (3) The space left after resecting the exostosis was used as endoscopy working space; and (4) Debridement of the degenerated Achilles tendon was performed endoscopically (Figure 1). The outcome improved based on the median visual analog scale (VAS) and the Japanese society for surgery of the foot scores from 64.5 mm to 6.5 mm and from 67.0 points to 100 points, respectively. The median time to return to sports was 4.5 mo. Furthermore, postoperative magnetic resonance imaging (MRI) revealed that the space left after resecting the exostosis was filled with soft tissue similar to the Achilles tendon, suggesting natural repair of the attachment site (Figure 2)[32]. The novelty of this study is that it allowed exostosis resection at the Achilles tendon insertion and debridement of the degenerative Achilles tendon to be performed with minimal invasiveness. Besides,

Table 1 Techniques required in minimally invasive surgery for insertional achilles tendinopathy

No.	Techniques
1	Exostosis resection at the Achilles tendon insertion
2	Debridement of degenerated Achilles tendon
3	Reattachment using anchors or augmentation using FHL tendon transfer
4	Excision of the posterosuperior calcaneal prominence

FHL: Flexor hallucis longus.



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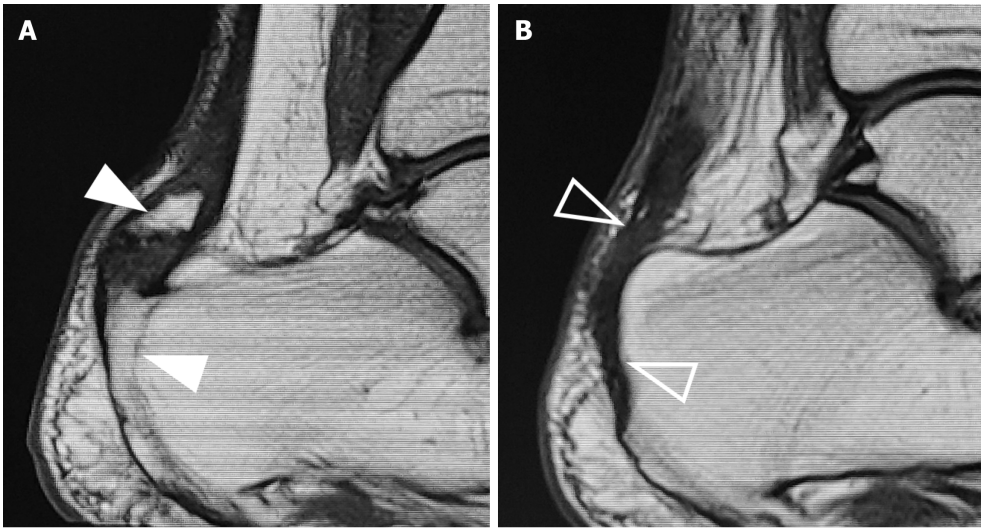
Figure 1 Fluoroscopic and endoscopic calcaneal exostosis resection and Achilles tendon debridement for insertional achilles tendinopathy[32]. A: Blunt dissection around the exostosis. Two portals were created 1 cm proximal and distal from the exostosis (circles), and blunt dissection around the exostosis was performed using a raspatorium; B: Exostosis resection using an abrasion burr under fluoroscopic guidance (arrowhead). Care was taken not to damage the normal insertion of the achilles tendon (circle). The space left after resection of the exostosis was a working space for endoscopy; C: Endoscopic view from the distal portal. The portion of the achilles tendon that had attached to the exostosis was visible as a free end (T). The unresected exostosis was attached to the tendon (arrowhead). The degenerated Achilles tendon was debrided endoscopically; D: Postoperative fluoroscopic view. The exostosis was totally resected (arrowhead). P: Proximal portal; D: Distal portal; C: The calcaneus; T: Free end.

this case series did not require reattachment or augmentation of the Achilles tendon, as natural repair of the Achilles tendon insertion site was observed. In addition, since there was no preoperative retrocalcaneal bursitis in the cases, resection of the posterior superior eminence was not performed.

Endoscopic Achilles tendon reattachment

Several studies have reported techniques for endoscopic reattachment of the Achilles tendon insertion.

Xu *et al*[35] published a case series that described a technique for endoscopically repairing partial Achilles tendon tear at the Achilles tendon insertion caused by endoscopic posterosuperior calcaneal prominence resection[35]. A suture anchor was placed at the center of the bone-resected surface after the posterosuperior prominence resection, and two stab wounds were made on the medial and lateral



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Figure 2 Pre- and postoperative magnetic resonance imaging of the left calcaneus of a patient with insertional achilles tendinopathy who underwent Fluoroscopic and endoscopic calcaneal exostosis resection and achilles tendon debridement[32]. A: Preoperative magnetic resonance imaging (MRI). Exostosis and intra-tendon ossification were visible (white arrows); B: Postoperative MRI at 9 mo postoperatively. The void space left after resection of the exostosis and intra-tendon ossification was filled with soft tissue providing the same signal as the Achilles tendon, suggesting a natural repair.

margins of the Achilles tendon, respectively. Afterward, the Achilles tendon was sutured using the modified Bunnel technique through these four stab wounds. They performed this procedure in seven patients with insertional Achilles tendinopathy; five reported excellent results [American orthopedic foot and ankle society (AOFAS) score, 90-100], and two reported good results (AOFAS score, 80-89).

Vega *et al*[36] also reported a technique similar to that of Xu *et al*[35] in their case series[36]. An anchor with two sutures (four limbs) was placed at the center of the bone-resected surface after the endoscopic resection of the posterosuperior calcaneal prominence. Two limbs were passed through the medial portion of the Achilles tendon and sutured subcutaneously at the medial portal. The remaining two limbs were similarly sutured at the lateral portal. Twelve patients underwent this surgery, improving their AOFAS score from 70 to 92 and their Victorian institute of sports assessment-Achilles (VISA-A) score from 34 to 92.

Michel *et al*[37] published a case report of a patient undergoing endoscopic posterosuperior prominence resection and endoscopic Achilles tendon repair for retrocalcaneal bursitis with partial Achilles tendon rupture[37]. First, the posterosuperior prominence was resected endoscopically, then a suture anchor with 2 limbs was placed on the bone-resected site. Next, sutures were passed through the Achilles tendon using the shuttle relay technique and sutured subcutaneously at the stab wound.

Maquirriain[38] reported in a technical note that after the posterosuperior prominence resection, the partially detached Achilles tendon insertion was reattached to the surface of bone-resected calcaneus using a percutaneous absorbable screw[38].

Hegewald *et al*[39] reported in a technical note that they made three stab wounds on the medial margin of the Achilles tendon and three stab wounds on the lateral margin, sutured the Achilles tendon using a modified Bunnell technique, and finally fixed the sutures to the calcaneus with interference screws[39].

The following three technical notes demonstrated the sequence of exostosis resection at the Achilles tendon insertion, excision of the posterosuperior calcaneal prominence, and reattachment using anchors [40-42]. Debridement of the degenerated Achilles tendon was not performed. Boniface and Vervoort[40] presented the following procedure. First, two proximal portals (medial and lateral) for posterosuperior prominence resection and three distal portals (medial, lateral, and median) for exostosis resection were created. Next, a working space was created between the skin and the Achilles tendon, and exostosis resection, detachment of the middle portion of the Achilles tendon insertion, and posterosuperior prominence resection were performed endoscopically. Finally, the detached middle portion of the Achilles tendon was then reattached to the bone-resected surface with two rows of speed bridges. When this technique was performed with 10 cadavers, it required 120 min the first time and 70 min the last time. The method presented by Miller *et al*[41] is almost identical to that of Boniface and Vervoort, except that the Achilles insertion was totally detached in the former method[41]. Lopes *et al*'s method differs from that of the two previous studies in that the sutures were placed in the tendon[42]. Six portals were created on the medial and lateral margins of the Achilles tendon. After the posterosuperior prominence was resected endoscopically, the Achilles tendon was fixed with two rows of suture anchors that placed the two sutures in the tendon in S-shapes using the six portals.

Endoscopic augmentation using FHL tendon transfer

Hunt *et al*[17] reported a prospective comparative study that revealed no difference in clinical outcomes between procedures with and without FHL tendon transfer[18]; however, FHL tendon transfer was traditionally performed in cases where more than 50% of Achilles tendon insertion was released[7,10,11,15,17,18,27,43]. The advantage of the FHL transfer for Achilles tendon augmentation is that both tendons act in the same walking cycle phase[44]. In addition, studies have reported no loss of function of the hallux due to FHL transfer. Coull *et al*[45] reported that the patients' hallux after FHL tendon transfer achieved the highest AOFAS score and that functional weakness of the hallux was not observed in daily living[45]. Hahn *et al*[46] observed that the FHL tendon was well integrated with the Achilles tendon on postoperative MRI, with ≥ 15% hypertrophy of the FHL muscle in 8 of 13 patients[46]. Other reported donors for augmentation include plantar tendon[6], sural triceps aponeurosis[47], and bone-patellar tendon[48].

A method for endoscopic FHL tendon harvest was published by Lui *et al*[49]. In this method, the FHL tendon was cut below the hallux's interphalangeal joint, the interconnection tendon between the FHL and the flexor digitorum longus was dissociated using a tendon stripper, and the tendon was pulled out through a small skin incision at the Achilles tendon.

To the best of the current author's knowledge, there are no reports of endoscopic Achilles tendon augmentation using the FHL transfer. However, if a technique to integrate the Achilles and harvested FHL tendons is developed, endoscopic FHL transfer will become possible.

Endoscopic posterosuperior calcaneal prominence resection

Several studies reported that posterosuperior prominence resection only for treating insertional Achilles tendinopathy had poor results[50-54]. Watson *et al*[50] reported that endoscopic posterosuperior prominence resection had a poor outcome in patients with calcaneal exostosis and recognized insertional Achilles tendinopathy and retrocalcaneal bursitis as different etiologies of posterior heel pain [50]. Leitze *et al*[51], Ortmann and McBryde[52], Jerosch[53], and Cusumano *et al*[54] excluded cases with severe insertional calcific Achilles tendinopathy for this endoscopic surgery[51-54]. Natarajan and Narayanan[55] reported that 8 out of 40 people with calcaneal exostosis who underwent endoscopic posterosuperior prominence resection would not recommend this procedure[55]. Kondreddi *et al*[56] reported that patients with Achilles tendon degeneration who underwent this surgery had lower subjective satisfaction[56]. However, Sundararajan and Wilde[57] reported that 5 of 20 patients with insertional Achilles tendinopathy presented with retrocalcaneal bursitis based on clinical and MRI findings[57]. Furthermore, a study by Rufai *et al*[58] observed that the periosteum of the posterosuperior prominence was replaced with fibrocartilage in cadavers with calcaneal exostosis[58], suggesting that insertional Achilles tendinopathy and posterior superior prominence pathology are not totally independent. Therefore, posterosuperior prominence resection should not be used alone for insertional Achilles tendinopathy but can be considered an option when needed.

Endoscopic posterosuperior prominence resection has been performed using two portals (medial and lateral)[59-62]. Wu *et al*[63] reported a case series of 27 patients whose three portals were effective. Van Sterkenburg *et al*[64] reported that the optimal endoscopic portal location varied with the shape of the posterosuperior prominence; thus, no index could be established. Lohrer *et al*[65] compared endoscopic and open osteotomy procedures using cadavers and reported similar rates of peroneal nerve injury and more bone fragments in the open osteotomy[65]. Roth *et al*[66] reported that endoscopic surgery resulted in less bone resection than open surgery, which they speculated may contribute to faster recovery[66]. Lui[67] reported that endoscopy in the supine position allowed for easier identification of anatomical structures than in the prone position[67]. Ferranti *et al*[68] reported that in 27 patients who underwent percutaneous posterosuperior prominence resection, the mean VISA-A score improved from 20 preoperatively to 75 postoperatively, and 84% experienced complete satisfaction[68].

Endoscopic gastrocnemius recession

To the best of the author's knowledge, there is only one report on endoscopic gastrocnemius recession for treating insertional Achilles tendinopathy. Tallerico *et al*[69] followed up on 11 patients who underwent endoscopic gastrocnemius recession for an average of 13.8 mo. Ten of the 11 patients were highly satisfied, and the mean postoperative AOFAS score improved from 52.0 preoperatively to 94.8 postoperatively. Six of the 11 patients had calcaneal exostosis, and their AOFAS scores improved from 51.1 preoperatively to 91.9 postoperatively[69]. Gastrocnemius recession can also be a technique for reattaching the Achilles tendon. Gould reported 49 patients with insertional Achilles tendinopathy who underwent J-shaped skin incision, complete Achilles tendon detachment and debridement, posterosuperior prominence resection, and V-Y lengthening and reattachment[70]. Staggers *et al*[71] compared 25 patients who underwent V-Y lengthening of gastrocnemius and 21 who underwent FHL transplantation during open surgery for insertional Achilles tendinopathy and reported no significant difference in subjective satisfaction, VISA-A scores, and VAS scores between both groups[71].

ULTRASOUND-GUIDED SURGERY FOR INSERTIONAL ACHILLES TENDINOPATHY

Ultrasound-guided surgery also has the potential for minimally invasive surgery. However, Khan *et al* [72] reported that although MRI is effective in diagnosing insertional Achilles tendinopathy, ultrasound does not improve diagnostic accuracy[72]; thus, this surgery may be technically demanding for insertional Achilles tendinopathy.

Chimenti *et al*[73] reviewed 34 patients who underwent ultrasound-guided posterosuperior prominence resection, debridement of the Achilles tendon insertion and intra-tendinous calcifications, and retrocalcaneal bursectomy[73]. At 6-12 wk of follow-up, baseline pain decreased from 68% preoperatively to 5% postoperatively, with a satisfaction rate of 70%. In addition, four patients who were followed up for more than 11 mo were free of pain.

Wang *et al*[74] compared outcomes in 10 patients who underwent ultrasound-guided posterosuperior prominence resection and retrocalcaneal bursectomy and 12 who underwent open surgery[74]. The AOFAS scores at two years postoperatively were 95 in the open group and 94 in the minimally invasive group, with no significant difference.

Freed *et al*[75] performed ultrasound-guided Achilles fasciotomy and tenotomy in 26 people with insertional Achilles tendinopathy, with a mean operating time of 4 min and 32 s, a mean follow-up of 16 mo, and a success rate of 85%[75].

PERCUTANEOUS DORSAL WEDGE CALCANEAL OSTEOTOMY FOR INSERTIONAL ACHILLES TENDINOPATHY

Dorsal wedge calcaneal osteotomy for insertional Achilles tendinopathy has been frequently reported since 2010[76-85]. A closing wedge osteotomy of the calcaneus moves the Achilles tendon insertion upward and forward, loosening the Achilles tendon and widening the gap between the Achilles tendon and the posterosuperior prominence. In 1939, Zadek[86] first published a case series of three patients who underwent this osteotomy. Keck and Kelly[87] also published a 3-patient case series of similar osteotomy in 1965. Therefore, this osteotomy is sometimes called the Zadek osteotomy or the Keck and Kelly[87] osteotomy.

Good surgical results have been reported. Georgiannos *et al*[78] reviewed the outcomes of 52 athletes who underwent this osteotomy, with AOFAS scores improving from 59 to 95 and VISA-A scores improving from 65 to 90 at a minimum of three years of follow-up[78]. Maffulli *et al*[82] reported that in 25 patients who underwent this osteotomy, the median VISA-A score improved from 25 to 86, and 3 of 4 patients reported a return to the pre-injury state[82]. Cengiz and Karaoglu[85] followed up on 14 patients who underwent this surgery for more than three years. They reported that the AOFAS score improved from 56 preoperatively to 89 postoperatively, and the VAS score improved from 86 preoperatively to 41 postoperatively[85]. Ge *et al*[80] followed up on 12 patients who underwent this osteotomy for an average of 86 mo, with AOFAS scores improving from 52 to 98 and VISA-A scores improving from 37 to 98. They also reported that these postoperative scores were significantly higher than those of 32 patients who underwent posterosuperior prominence resection[80]. A description of this osteotomy technique was detailed in a review by Syed and Perera[77].

Recently, minimally invasive surgery for this osteotomy has been reported. Vernois *et al*[88] detailed this minimally invasive osteotomy technique using a 3-mm wide and 20-mm long Shannon bur[88]. Nordio *et al*[89] reported that in 26 patients who underwent percutaneous surgery, the Foot function index score improved from 65 to 8. The VAS score improved from 9 to 1, with a mean follow-up of 12 mo, and pain relief was achieved at a mean of 12 wk[89]. Choi and Suh[90] compared the outcomes of 11 patients who underwent minimally invasive osteotomy using a 2.2 mm Shannon bar and 14 patients who underwent open posterosuperior prominence resection. The VISA-A score of this osteotomy improved from 36 to 88, and the VAS score improved from 89 to 36. They also reported that minimally invasive surgery was significantly better than posterosuperior prominence resection at 6 mo postoperatively; however, the outcomes were similar at the final follow-up[90].

CONCLUSION

To establish minimally invasive surgery for insertional Achilles tendinopathy, the following four techniques must be minimally invasive: (1) Exostosis resection at the Achilles tendon insertion; (2) Debridement of degenerated Achilles tendon; (3) Reattachment using anchors or augmentation using FHL tendon transfer; and (4) Excision of the posterosuperior calcaneal prominence. This article reviewed studies from these four perspectives.

Exostosis resection at the Achilles tendon insertion was demonstrated in one case study, where blunt dissection around the exostosis was performed under fluoroscopy, an abrasion bur was introduced into the space created, and the exostosis was resected under fluoroscopic guidance.

Debridement of degenerated Achilles tendon was demonstrated in the same case study, where the space left after resection of the exostosis was an endoscopic working space, and the degenerated Achilles tendon and intra-tendinous calcification were debrided endoscopically.

Achilles tendon reattachment techniques have been demonstrated in several studies, where anchors were placed on the calcaneal surface after the posterosuperior prominence resection, and sutures were passed through the Achilles tendon using several stab wounds and fixated to the anchors.

In contrast, FHL tendon transfer techniques have not yet been published. The minimally invasive FHL harvest was reported in a technical note. Therefore, if a technique to integrate the Achilles tendon and the harvested FHL tendon is developed, endoscopic FHL transfer will become possible.

Endoscopic posterior superior prominence resection has already been established.

As with other minimally invasive surgeries for insertional Achilles tendinopathy, several studies on ultrasound-guided surgery and percutaneous dorsal wedge calcaneal osteotomy have been published.

FOOTNOTES

Author contributions: Nakajima K was the only author and performed everything regarding this study.

Conflict-of-interest statement: The author declares no conflict of interest.

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MINIREVIEWS

Subtalar dislocations: Mechanisms, clinical presentation and methods of reduction

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Abstract

Subtalar joint is a complex joint in hindfoot formed by the talus superiorly and the calcaneus and navicular inferiorly. Subtalar dislocations are high-mechanism injuries, which are caused by simultaneous dislocation of both talonavicular and talocalcaneal joints, without major fracture of the talus. They are usually classified as medial (most common), lateral, anterior and posterior dislocations, based on the position of foot in relation to talus and the indirect forces that have been applied to cause this significant injury. They are usually diagnosed by X rays, but computed tomography and magnetic resonance imaging can be used to identify associated intra-articular fractures and peri-talar soft tissue injuries respectively. Majority being closed injuries, can be managed in ED by closed reduction and cast immobilisation, but if they are open, have poor outcomes. Complications that ensue open dislocations are post-traumatic arthritis, instability and avascular necrosis.

Key Words: Joint; Subtalar; Joint dislocations; Flatfoot; Clubfoot; Talus

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Core Tip: Subtalar dislocations are rare, high mechanism injuries. Comprehensive trauma assessment, along with limb specific assessment is the key approach to deal with these injuries. Lateral dislocations constitute for open injuries commonly, and must be managed according to the BOAST-Open fracture guidelines. Avascular necrosis of the talus due to injury to the canalis tarsi artery, are troublesome complication. Thus, one needs to have high index of suspicion when the dislocation is open or associated with talus fracture.

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INTRODUCTION

Subtalar dislocation is defined as the simultaneous dislocation of both talonavicular and talocalcaneal joints without major fracture of the talus[1]. The first cases of subtalar dislocations were described by Dufaurest[2] and Judey[3] in 1811, yet there followed a considerable period of senescence in exploring this injury. It was not till 1853 that Broca[4] delivered the first classification of subtalar dislocation, which Malgaigne and Buerguer[5] subsequently amended in 1856.

The classifications are founded on the four anatomical positions into which the foot dislocates in relation to talus[5]. The dislocations of the articulations of the talus include talocalcaneal, talonavicular or talo-crural joint. Subtalar dislocations account for approximately 1% of all dislocations[6]. This is a rare injury due to the anatomical and biomechanical stability afforded by the talo-calcaneal and talo-navicular joints, such that it is predominantly as a result of trauma and high-energy mechanisms[7,8]. One must be cognisant to deliver care as per suitable trauma protocols, and there must be a high degree of suspicion for attendant injuries to the talus, ankle, foot, soft tissue compromise, open fracture or dislocation and trauma to alternate body systems[9-11].

The aim of this review is to provide a concise overview of subtalar dislocations including anatomy, classification of injury, clinical presentation, diagnosis, treatment options, outcomes and complications. As a result of this article, we aim to improve the reader's understanding of this topic.

ANATOMY OF SUBTALAR JOINT

The subtalar joint is a complex joint in the hindfoot with many normal anatomic variations[12]. Considered a synovial joint structurally and a plane joint functionally, it is formed by the talus superiorly and the calcaneus and navicular inferiorly[13], it is comprised of three articulating surfaces, the anterior facet is a small articulation between the talus head and the anterior calcaneus facet, the middle facet between medial facet of talus and the middle facet of the calcaneus and a large posterior facet between the posterior facet of talus and the posterior facet of the calcaneus[14].

Anatomically it is considered as two separate chambers; an anterior chamber also known as the talocalcaneal navicular joint is formed by the often congruent anterior and middle facets[14], the floor is formed by the plantar calcaneo-navicular ligament (spring ligament) which has a cartilaginous articular surface[13]. This ligament complex plays a key role in stabilising the talus head, insufficiency can lead to acquired flat foot deformity[12]. The posterior chamber also referred to as the talocalcaneal joint or the anatomical subtalar joint formed by the posterior facet.

The differentiation of the subtalar joint into two distinct joints is only really preferred by anatomists [13]. From a functional point of view the two joints have a common single axis of motion and neither joint has movement independent of the other, therefore many orthopaedic surgeons consider the talocalcaneonavicular joint and the talocalcaneal joint to be one functional unit[15].

EPIDEMIOLOGY

Subtalar dislocations account for 1%-2% of all dislocations and 15% of all peri-talar injuries. Most frequent age of presentation is in the third decade. It occurs 6-10 times more frequently in men than in women and also dislocations were found to be more common on the right foot than the left[16]. Open injuries are present in 20%-25% of cases, where lateral dislocations are open in 41.8% of cases, while medial dislocations are open in 21.9% of cases[17]. These are typically as a result of high-energy injuries, 50% motor vehicle accidents, 20%-30% fall from heights and 14% from sport injuries[16].

CLASSIFICATION OF INJURY

In 1853, Broca[4] then classified the injury according to the direction of dislocation: Medial, lateral and posterior. Subsequently in 1855 and 1856 that Henke *et al*[17], and Malgaigne and Buerguer[5] modified the Broca classification to include anterior subtalar dislocations. The foundation of classification is the anatomy of the foot in relation to the talus (Table 1)[18-21]. It is intriguing that the same system has continued for over a century and this may reflect the uncommon nature of the injury as well as the limited number of studies undertaken.

MECHANISM OF INJURY

This is often associated with high energy trauma, usually, motor vehicle accidents, or falls from a height [6]. However, patients may get these injuries from lower energy mechanisms such as sports injuries, twisting injuries of the foot or fall from standing, especially if the patient is elderly or obese[6]. Subtalar dislocation involves disruption of the surrounding ligaments: Interosseous talocalcaneal ligament (most important), anterior, posterior, lateral and medial talocalcaneal ligament[22]. Typically to cause this dislocation, an axial load is applied, when the patient has plantar flexed foot. The position of the foot in relation to the talus and the indirect forces that have been applied to cause significant and progressive ligamentous and capsular injury determine the type of dislocation, which can be either medial, lateral, anterior, posterior or total[22].

Medial dislocation (acquired clubfoot)

There is a forced inversion of a plantarflexed foot followed by external rotation of the talus with the lateral malleolus acting as a buttress which result in initial rupture of the talonavicular ligament followed by tearing of the interosseous ligament from anterior to posterior. The sustentaculum tali also act as fulcrum for the neck of the talus to pivot around. The reduction might be difficult and blocked by peroneal tendons, EDB (Extensor Digitorum Brevis) or talonavicular joint capsule, with the foot locked into supination[23].

Lateral dislocation (acquired flatfoot)

There is a forced eversion of a dorsiflexed foot followed by external rotation of the talus which leads to initial rupture of the deltoid ligament followed by the interosseous ligament and the talocalcaneal joint, then dorsal talonavicular ligament rupture. Here, the anterior process of the calcaneus acts as fulcrum for the anterolateral corner of the talus to pivot around. The reduction might be difficult and blocked by peroneus tertius (PT) tendon, flexor hallucis longus (FHL), or flexor digitorum longus (FDL), with the foot locked into pronation[6].

Posterior dislocation (shortened foot)

There is a heavy forced plantarflexion of the foot followed by a talocalcaneal joint slip[6]. This is an exceedingly rare entity. It is important to recognize that not all posterior subtalar dislocations are true posterior dislocations. Inokuchi *et al*[1] suggest that the position of the foot is important to define the type of subtalar dislocation: Supination or pronation of the foot at the time of injury leads to medial or lateral displacement. Usually, subtalar dislocation occurs with an associated rotational component. Few reports of posterior subtalar dislocation have been described to date, and all of these describe medial or lateral displacement[24].

Anterior dislocation (elongated foot)

There is an anterior traction of the foot on a fixed lower leg followed by a talocalcaneal joint slip[6]. Pure anterior subtalar dislocation is very rare, with few cases being reported in the past[8]. The first reported case of anterior subtalar dislocation was described by Malgaigne and Burger[5]. Zimmer *et al*[25] summarised eight series of 115 cases of subtalar dislocation-only about 1% of them were anterior dislocations.

Various mechanisms of injury have been proposed. Kanda *et al*[20] believe that anterior subtalar dislocation can be caused by forceful foot supination and ankle dorsiflexion when a patient falls from a height. Tabib *et al*[21] reported that the dislocation followed a direct rear impact over the posterior aspect of heel after a fall injury. Chuo *et al*[26] reported that anterior subtalar dislocation occurred when the patient withdrew the trapped foot.

CLINICAL PRESENTATION WITH ASSOCIATED TALAR INJURIES

One of the commonest presenting complaints in patients with subtalar dislocations is of pain and swelling of the ankle and/or midfoot. On examination, there may be bruising, an obvious gross swelling

Table 1 Classification of subtalar dislocation and associated mechanism of injury

Direction of dislocation	Percentage of all subtalar dislocations (%)	Position of foot at time of injury	Mechanism of injury
Medial (Calcaneus is medial to talus)	65-85[10]	Plantarflexion	"Acquired club foot", forceful inversion of forefoot[10], foot locked in supination
Lateral (Calcaneus is lateral to talus)	15-35[18]	Plantarflexion	"Acquired flat foot", forceful eversion of forefoot[10], foot locked in pronation
Posterior	0.8-2.5[7]	Hyper-plantarflexion	"Shortened foot", force applied to dorsum of foot leading to hyperplantarflexion[10]
Anterior	1[19]	Hyper-dorsiflexion	"Elongated foot", forceful foot supination and ankle dorsiflexion [20] or direct rear impact to posterior heel[21]

which might mask the bony deformity. Surrounding soft tissue involvement depends on the amount of energy involved and on the elapsed time from the injury[27]. There will be reduced range of motion as well as the foot may be locked in a position depending on the type of subtalar dislocation. Often subtalar dislocations as a result of the particular pattern and mechanism of injury will have adjacent bone fractures and injuries including the talus, cuboid, navicular and fibula (Table 2).

Medial subtalar dislocations are characterized by medial displacement of the foot and calcaneus[27]. The talar head is often palpable on the dorsum of the foot between the extensor digitorum longus and extensor hallucis longus tendons, usually locked in supination with inversion of the foot. It is sometimes called "basketball foot" as this is a common mechanism and another term for this injury is "acquired clubfoot"[28]. This type of dislocation is usually associated with fractures of the posterior process of talus, dorsomedial talar head, and navicular bone[29].

Lateral subtalar dislocations are most likely to result in an open dislocation (in upto 25% of the cases [30]) due to the high-energy mechanism leading to injury. Clinically lateral subtalar dislocations can be locked in pronation with eversion of the foot[28]. This type of dislocation is often associated with fractures of the lateral process of talus, anterior calcaneus, cuboid, and fibula[29]. The reduction might be blocked by PT tendon, FHL or FDL, and so the foot becomes locked in pronation.

Posterior subtalar dislocations are commonly accompanied by fractures of the malleoli, talus, or fifth metatarsal[31] and anterior subtalar dislocations are extremely rare and highly unstable injuries involving talus, calcaneal and navicular injuries[26].

DIAGNOSIS

Subtalar dislocations are almost always associated with bony injuries including fractures of the ankle, talar (lateral process and sustentaculum tali), calcaneal and navicular bones carrying the highest risk. The cuneiforms, cuboid and metatarsals might be injured as well[6]. Therefore, all parts of the foot which are at risk of being injured as a result of a subtalar dislocation have to be examined radiographically[9]. Radiographs and computed tomography (CT) are the mainstay of investigations and here we explore the appropriate techniques and findings.

Plain radiographs

The diagnosis of subtalar dislocation is usually made on AP, lateral, and oblique radiographs of the foot or ankle. Some special views might be also useful in diagnosis, *e.g.*, Canale view for evaluating talar neck fractures, which are often oblique to the transverse or sagittal plane of the foot, and are commonly associated with subtalar dislocation, and Harris view of the calcaneus, which allows visualization of the posterior and middle talocalcaneal joints[32]. The nature of the deformity often limits radiographic positioning. Remembering that the talar head and navicular should be congruent on all views can help overcome this limitation. Medial subtalar dislocation results in medial and plantar displacement of the navicular relative to the talar head and medial displacement of the calcaneus relative to the talus. Lateral subtalar dislocation results in lateral and dorsal displacement of the navicular relative to the talar head and lateral displacement of the calcaneus relative to the talus. Talonavicular impaction may prevent successful closed reduction and should therefore be recognized[32]. After reduction, AP and lateral radiographs of the foot as well as AP and mortise views of the ankle are obtained to confirm optimal results. In the absence of deformity, post-reduction radiographs are usually of better quality than those obtained at the time of injury and associated fractures become more apparent[6].

CT scan

Associated intra-articular fractures are difficult to identify at plain radiography and their presence can hinder anatomic reduction and worsen the overall prognosis. Therefore, routine post-reduction CT has

Table 2 Associated bony injuries with each type of dislocation

Bony involvement	Medial dislocation[28]	Lateral dislocation[28]	Posterior dislocation[29]	Anterior dislocation[30]
Talus	+	+	+	+
Navicular	+	-	-	+
Cuboid	-	+	-	-
Fibula	-	+	+	-
Calcaneum	-	+	-	+

been recommended to detect these fractures more accurately[32] and to look for subtalar debris[9].

Magnetic resonance imaging scan

Given the sensitivity of CT in diagnosis, further imaging is not typically indicated; however, magnetic resonance imaging has proven useful for persistent pain after trauma to aid in diagnosis of peri-talar soft tissue injuries and osteochondral injuries such as those in the talar head or dome[33].

TREATMENT

Taking into account that the majority of subtalar dislocations result from high energy mechanisms, there is the potential for adjacent attendant injuries. Following Advanced Trauma Life Support protocols[34], to start with Airway including cervical spine protection, Breathing, Circulation, Disability and Exposure (ABCDE) assessment of the patient, and then limb specific management, necessitating assessment of the neurovascular status and soft tissue.

Majority of these dislocations could be treated by closed reduction and cast immobilisation or by operative stabilisation with an external fixator or if necessary percutaneous K-wire arthrodesis of subtalar and talonavicular joint as a temporizing measure[35].

Early treatment with closed reduction under sedation or more commonly general anaesthetic is required to avoid progressive soft tissue and neurovascular damage[9]. Closed reduction is best achieved through relaxation of the gastrocnemius and soleus which may act as a significant deforming force at the calcaneus, by knee flexion and subsequent traction-countertraction manoeuvre. Once reduction achieved, it is important to reassess the limb neurovascular status, and a plaster backslab offers a simple yet effective method of immobilisation and splintage. Circumferential casting and constrictive bandages should be avoided as this may exacerbate residual swelling and lead to increased compartment pressures, whereas limb elevation will help counteract this process[23]. The table below shows treatment modalities for different dislocations (Table 3).

Open dislocations depict the more severe spectrum of injuries with poor outcomes. Common challenges including infection, post-traumatic arthrosis, and higher chance of talus avascular necrosis [36,37]. These injuries must be treated urgently, with initial broad-spectrum antibiotics in line with local antimicrobial stewardship and tetanus prophylaxis and managed with the same respect as open fractures. Although not directly related, we can utilise the principles through comparative guidance on the management of open fractures, one example is the British Orthopaedic Standards for Trauma-open fractures[38]. Coordinated care with plastic surgical specialists may help with timely preparations for reconstructive care if required. Acute treatment requires wound debridement and extensive irrigation of the injury zone, as well as reduction to an anatomical position. Immobilisation with plaster slab may be sufficient in some cases, yet where there is greater instability and loss of soft tissue coverage, Kirschner wires or even an external fixator may be required as alternative methods of stabilisation[39,40].

COMPLICATIONS + OUTCOMES

The sequelae of subtalar dislocations are grossly described through three key areas: Avascular necrosis of the talus (following injury to canalis tarsi artery), posttraumatic osteoarthritis and instability[41].

Avascular necrosis (AVN) also known as osteonecrosis, is defined as bone death due to ischemia, characterised by stereotypical pattern of cell death and complex repair process of bone resorption and formation[42]. The unique extra and intraosseous vascular anatomy of the talus predisposes for compromised healing potential and AVN as severe sequelae[43]. Avascular necrosis of the talus is a troublesome complication, which is more common in open subtalar dislocations or with talus fractures with rates of up to 50%[40].

Table 3 Reduction methods as per dislocation anatomy

Direction of Dislocation	Reduction manoeuvre (in addition to traction)	Structures that commonly obstruct reduction	Open reduction approach
Medial	Dorsiflexion and eversion of foot	Talar head, extensor digitorum brevis	Ollier's approach or antero-lateral approach
Lateral	Plantarflexion and inversion of foot	Flexor digitorum longus and tibialis posterior	Direct incision atop of talar head
Posterior	Plantarflexion of foot and once talar head disengages from navicular, the foot is dorsiflexed and tractioned distally		
Anterior	Posterior translation of foot whilst under traction		

Post-traumatic arthritis is of variable incidence, however high energy mechanism of injury, evidence of intra-articular talar and calcaneus fractures with osteochondral defects and open fractures are associated with a worse prognosis[36,19]. This can be a cause of significant pain and disability in the longterm[23]. Management is dependent on the pain and functional impact to the patient. For those with more advanced disease and poorly managed pain, physiotherapy and analgesia are unlikely to be adequate. In the presence of adjacent talonavicular and calcaneocuboid arthritis a triple fusion may be considered. Yet subtalar fusion may be reserved for those patients without adjacent arthrosis[39].

Instability is present as a result of ligamentous disruption following dislocation.

CONCLUSION

Subtalar dislocations are rare, high mechanism injuries. Comprehensive trauma assessment, along with limb specific assessment is the key approach to deal with these injuries. Lateral dislocations constitute for open injuries commonly, and must be managed according to the BOAST-Open fracture guidelines. Avascular necrosis of the talus due to injury to the canalis tarsi artery, are troublesome complication. Thus, one needs to have high index of suspicion when the dislocation is open or associated with talus fracture.

FOOTNOTES

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Basic Study

Automated patellar height assessment on high-resolution radiographs with a novel deep learning-based approach

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Abstract

BACKGROUND

Artificial intelligence and deep learning have shown promising results in medical imaging and interpreting radiographs. Moreover, medical community shows a gaining interest in automating routine diagnostics issues and orthopedic measurements.

AIM

To verify the accuracy of automated patellar height assessment using deep learning-based bone segmentation and detection approach on high resolution radiographs.

METHODS

218 Lateral knee radiographs were included in the analysis. 82 radiographs were utilized for training and 10 other radiographs for validation of a U-Net neural network to achieve required Dice score. 92 other radiographs were used for automatic (U-Net) and manual measurements of the patellar height, quantified by Caton-Deschamps (CD) and Blackburne-Peel (BP) indexes. The detection of required bones regions on high-resolution images was done using a You Only Look Once (YOLO) neural network. The agreement between manual and automatic measurements was calculated using the interclass correlation coefficient (ICC) and the standard error for single measurement (SEM). To check U-Net's

generalization the segmentation accuracy on the test set was also calculated.

RESULTS

Proximal tibia and patella was segmented with accuracy 95.9% (Dice score) by U-Net neural network on lateral knee subimages automatically detected by the YOLO network (mean Average Precision mAP greater than 0.96). The mean values of CD and BP indexes calculated by orthopedic surgeons (R#1 and R#2) was 0.93 (± 0.19) and 0.89 (± 0.19) for CD and 0.80 (± 0.17) and 0.78 (± 0.17) for BP. Automatic measurements performed by our algorithm for CD and BP indexes were 0.92 (± 0.21) and 0.75 (± 0.19), respectively. Excellent agreement between the orthopedic surgeons' measurements and results of the algorithm has been achieved (ICC > 0.75, SEM < 0.014).

CONCLUSION

Automatic patellar height assessment can be achieved on high-resolution radiographs with the required accuracy. Determining patellar end-points and the joint line-fitting to the proximal tibia joint surface allows for accurate CD and BP index calculations. The obtained results indicate that this approach can be valuable tool in a medical practice.

Key Words: Medical imaging; Artificial intelligence in orthopedics; Patellar index; Deep learning; Bone segmentation; Region of interest detection

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Core Tip: This study presents an accurate method for automatic assessment of patellar height on high-resolution lateral knee radiographs. First, You Only Look Once neural network is used to detect patellar and proximal tibial region. Next, U-Net neural network is utilized to segment bones of the detected region. Then, the Caton-Deschamps and Blackburne-Peel indexes are calculated upon patellar end-points and joint line fitted to proximal tibia joint surface. Experimental results show that our approach has the potential to be used as a pre- and postoperative assessment tool.

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INTRODUCTION

Patellofemoral joint (PFJ) disorders are common structural and functional problems that may cause pain and instability leading to joint degeneration. The knee osteoarthritis (OA) is one of the most common diseases and its incidence is increasing due to the aging and obesity[1]. Overall, the treatment costs related to knee OA are substantial. Recent developments in medical informatics and artificial intelligence have led to an increasing number of studies on medical imaging of knee OA, but most of the research is focused on the tibiofemoral joint[2]. However PFJ, a third articulation has received insufficient attention. The assessment of patellar height (PH) is a fundamental parameter in diagnosing PFJ pathologies, selection of appropriate treatment and postoperative evaluation[3]. The standard approach for PH assessment is achieved by measuring ratios on X-ray images in the lateral view[4]. PH abnormalities can be recognized using Insall-Salvati, Blackburne-Peel (BP), and Caton-Deschamps (CD) indexes measured on lateral knee radiographs[5]. Patella Baja (PB) and pseudo-Patella Baja are common complications after total knee replacement (TKR) and related to poor outcomes[6]. From a therapeutic point of view, pseudo-Patella Baja with the elevated femorotibial joint line without shortening the patellar tendon can be recognized with the lower BP and CD indexes. The CD and BP ratios are also more important in the diagnosis of PB after TKR[6].

Recently, a substantial attention to reliability of these parameters have been devoted, among others, due to increasing importance of PH in knee replacement surgery, tibial osteotomy, and anterior cruciate ligament reconstruction[3,7,8]. However, such routine tasks are tedious, time-consuming, and prone to considerable inter-observer and intraobserver variability[9]. In recent years, deep-learning (DL) algorithms have gained popularity in medicine, particularly in different aspects of orthopedics[10-12]. They have been used for image classification[13], fracture detection[14] or osteoarthritis diagnosis[15]. Moreover, DL algorithms have also been developed for automatic segmentation of bones on X-ray images to estimate hallux-valgus angles, axial alignment[16,17] and skeletal metastases[18]. Bone

segmentation on X-ray images enables calculation of critical radiological parameters. It is a very difficult task[19], but some work has been done in this area[20,21].

To the best of our knowledge, there are no papers describing the application of neural networks for segmentation of lateral knee radiographs and measurements of patellar indexes on high-resolution radiographs. The method is automatic as it detects the region of interest (ROI) with the patella and proximal tibia region on a high-resolution radiograph, performs bone segmentation on the cropped ROI and then calculates the patellar indexes. The rest of the article is organized as follows. In the next Section we present our dataset for training You Only Look Once (YOLO) neural network, our dataset for training U-Net neural network, training procedure to achieve assumed Dice score and our algorithm for automated calculation of patellar indexes using segmented bones. In the following Section we present experimental results. The last part is devoted to discussion and conclusions.

MATERIALS AND METHODS

The overall pipeline of our method is shown in Figure 1. In order to detect ROI on radiographs we trained a YOLO neural network[22]. We have trained a U-Net model for automatic segmentation of bones of interest. The U-Net segmented the patella and tibia bones. On the segmented patella we extracted two landmark points and then fitted a patellar articular joint line to them. A second line has been fitted to the segmented proximal tibial articular surface. These lines have been used to calculate the CD and the BP indexes. The CD and BP indexes estimated in such a way have been compared with indexes calculated by medical doctors. The YOLO and U-Net networks have been trained on data collected and labelled by us. Radiological images were acquired using Shimadzu BR120 X-Ray Stand (Shimadzu Medical Systems, United States) and CDXI Software (Canon, United States).

Data

In this research, retrospective analysis of prospectively collected images was conducted on radiographs from an electronic database acquired in our institution. Patients whose radiographs were included in this study were examined in the authors' institution from January 2019 to April 2021. We collected a dataset for ROI detection and a dataset for bone segmentation. A dataset used for training the YOLO neural network is described below. The flowchart of data collection and methodology of training a U-Net neural network for bone segmentation is depicted in Figure 2 and described in more detail in subsequent paragraphs.

Dataset for training YOLO

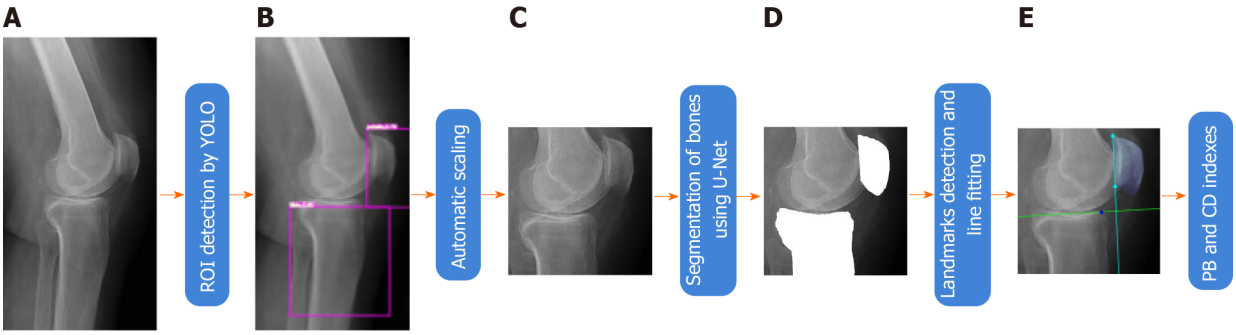
The images in our database are high-resolution images, and only a portion of the radiographs contains pixels belonging to the knee and patella, which are required for calculation of BP and CD indexes. Thus, a YOLO neural network has been used to automatically detect the area of interest[23], *i.e.*, the patella and the proximal tibial artricular surface. One thousand radiographs from our database were selected, anonymized and then manually labeled. On each image we manually determined a rectangle surrounding the patella and a second rectangle surrounding the proximal tibial artricular surface. The YOLO neural network has been trained on 900 images and evaluated on 20 images.

Dataset for U-Net training

For training a U-Net neural network we randomly selected semiflexed lateral knee radiographs from the electronic database of our institution (stage A in Figure 1 and in Figure 2). The exclusion criteria were: Radiographs performed with improper rotational positioning, grade III or more osteoarthritis in Kellgren-Lawrence scale[24] and/or severe axial knee deformations, visible growth plate, artificial elements distorting the image of the bone outline (*e.g.*, osteosynthesis material or knee prosthesis implant), and heterotopic ossifications around the knee joint. The exported input X-ray images have been anonymized and stored in the lossless .png image format (stage B in Figure 2). Afterward, the bones on radiographs were manually labelled by an orthopedic surgeon (tibia and patella) in Adobe Photoshop ver. 22.0 (Adobe Systems, United States). The labelled images were included in the training and validation set (stage C in Figure 2).

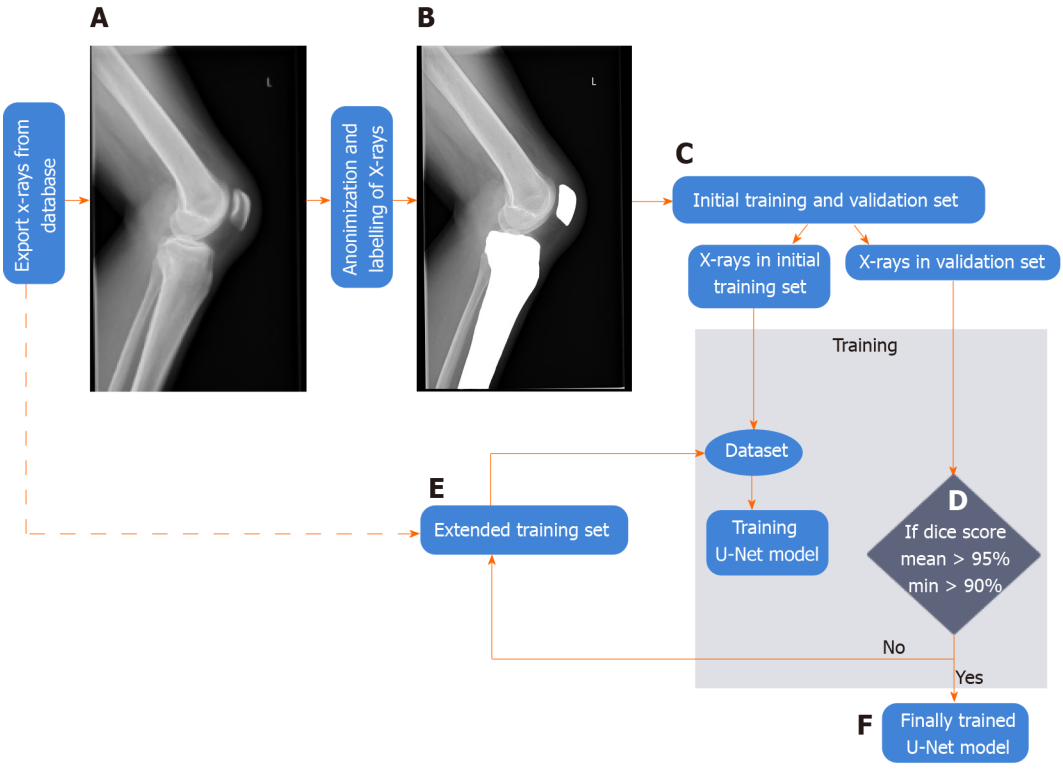
Training and validation of U-Net

Bone segmentation has been performed using a U-Net[25]. The U-Net has been trained on the training set with verification of the accuracy of automatic segmentation (on validation set). The input images with knee area were automatically cropped on the basis of YOLO detections and then scaled to size 512 × 512 (stage B and C in Figure 1). During training, the resized radiographs were fed to the input of the U-Net, whereas corresponding labeled images were fed to the output of the U-Net. Initially, we manually labelled 50 X-rays of which 10 X-rays were included in the validation set to verify the accuracy of bone segmentation, (stage C in Figure 2). The accuracy was assessed using the Dice score[26] (Figure 3).



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Figure 1 Flowchart of the proposed method. A: Input radiograph; B: Bones detected by the You Only Look Once; C: Detected region of interest, resized to size 512 × 512; D: Segmented bones by the U-Net; E: Landmarks detected on the patella and line fitted to them (cyan), and line fitted to tibial surface (green). YOLO: You Only Look Once; CD: Caton-Deschamps; ROI: Region of interest.

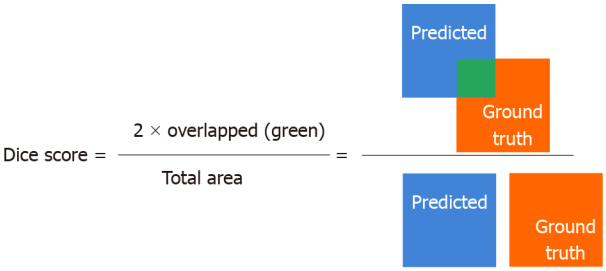


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Figure 2 Flow diagram of the methodology of data collection and training of the U-Net for bone segmentation. A: Radiograms from database; B: Labeled radiograms for training and validation; C: Split of radiograms into training and validation subsets; D: Conditional block for stop the training; E: Extended training set; F: Trained U-Net model.

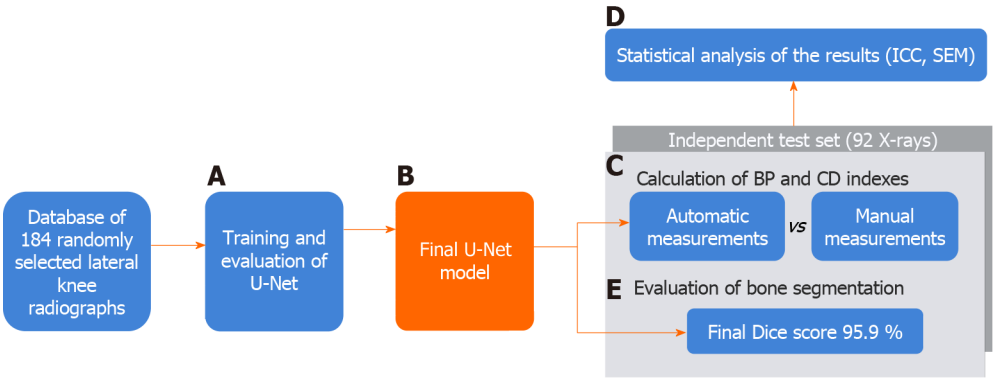
Training procedure to achieve assumed Dice score

The validation set did not change during the training[27]. The U-Net was initially trained on a dataset consisting of 40 X-rays, which was then extended by 10 subjects to achieve the assumed segmentation quality (stage D in Figure 2). After every extension (by 10 radiographs), the U-Net was trained on the extended data from scratch, and the Dice score was calculated (on the validation set). If it was lower than 90%, the extension of the dataset and training of the network were repeated. If Dice score ≥ 90% was achieved, single radiographs were added to the training subset to gain a Dice score ≥ 95% (with minimal Dice score ≥ 90% for each subject (stage E in Figure 2). After the training, we obtained the final U-Net model and final training set (stage F in Figure 2, stage B in Figure 4). The final U-Net model was utilized to segment bones on the test subset. On the segmented bones we determined the characteristic points as well as necessary lines in order to calculate the patellar height and the indexes (stage D and E in Figure 1, stage C in Figure 4). The person responsible for training and evaluating the neural network has not participated in the manual calculation of the patellar indexes and has not seen the results before the final analysis.



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Figure 3 Dice score calculation used to asses bone segmentation performance.



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Figure 4 Flow diagram of patient selection and attaining the required segmentation score. A: Training and evaluation of U-Net; B: Final U-Net model; C: Calculation of blackburne-peel and Caton-Deschamps indexes; D: Statistical analysis; E: Final Dice score. CD: Caton-Deschamps; BP: Blackburne-peel; ICC: Interclass correlation coefficient; SEM: Single measurement.

Algorithm for automated calculation of patellar indexes using segmented bones

The outcomes of the U-Net model (output images with segmented bones - tibia and patella) were used to determine characteristic points and lines (stage E in Figure 1). Articular surface of proximal tibia was automatically determined. Firstly, the anterior corner of the tibial plateau and posterior end-point were determined. Given such boundaries, a line to the points of the proximal tibia joint surface has been fitted. This way the joint line was determined on the basis of many boundary points. An alternative approach would be to determine some landmark points representing articular surface of proximal tibia and then using them to determine the joint line. In contrast to the approach mentioned above, in our approach the joint line is determined more robustly, *i.e.*, on the basis of large number of boundary points segmented by the U-Net. Afterwards, the superior and inferior patellar articular surface endpoints have been determined through simple image analysis, and then used to determine the second line. Finally, these characteristic points and joint lines were automatically used to calculate the CD and the BP[28]. The calculation of the characteristic points and joint lines was done on images with height/ with ratio equal to ROI ratio. The novelty of this research is an innovative approach to estimating joint lines based on the line fitting using automatic bone segmentation (more accurate than method based on the characteristic points, c.f. Discussion Section).

Automatic and manual measurements

We used 92 randomly selected another lateral knee radiographs, collected from the authors' institutional electronic database for the automatic and manual calculations of patellar indexes (stage F in Figure 1; stage C in Figure 4). We carefully examined if there is no overlap of patients (or images) in train/valid and test datasets. Like Lee *et al*[27], we did not create a test set until we had developed the final U-Net model (stage F in Figure 2; stage from B to C in Figure 4). According to Zou *et al*[29], we assumed a minimal number of subjects to estimate the agreement of the measurements between the two methods as 46.

Comparison of measurements

Automatic and manual measurements were performed on 92 X-rays. The computer-generated results were compared with manual measurements performed independently by two orthopedic surgeons (6 and 38 years of experience, stage C in Figure 4). According to the guidelines[30,31], two orthopedic surgeons performed manual measurements of the CD and BP patellar height indexes. They used

Carestream Software ver.12.0 (Carestream Health, United States).

Statistical analysis

Statistical analysis was performed using Statistica 13.1 Software (Tibco Software, United States) and Microsoft Excel 2019 (Microsoft, United States). The intraclass correlation coefficient (ICC) and the standard error for a single measurement (SEM) were calculated for statistical assessment of reliability and compliance of the measurements stage (D in Figure 4). The ICC of 0.4 demonstrates poor, between 0.4 and 0.75 good, and more than 0.75 indicates excellent reliability of the measurements[32].

Accuracy of the bone segmentation of the final U-Net model

The accuracy of bone segmentation (of the final U-Net model) was assessed on the test set to check if the neural network had sufficient generalization capability (whether U-Net could achieve satisfactory results on unknown radiographs). For this evaluation, the X-rays in the test set were manually labelled by the orthopedic surgeon. We compared the Dice scores between the automatically and manually segmented bones (stage E in Figure 4).

Details of image pre-processing, architecture of neural network, and training

Image pre-processing: The labelled images were used for training a U-Net neural network. We designed a U-Net neural network that operates on input images of size 512 × 512 and output images of 512 × 512 with segmented bones. Small holes in automatically segmented bones that can arise from imperfect segmentation were automatically filed.

The architecture and training of neural network

Each U-Net encoder and decoder contained four layers. It has been trained by optimizing Dice loss in 60 epochs using Adam optimizer, learning rate equal to 0.0001, batch size set to 2. During the training a data augmentation consisting of vertical mirroring of images and scaling of images have been executed. The neural network has been trained on the notebook's GPU (RTX3070 GPU, 6GB RAM). Phyton language was utilized to implement the whole algorithm, the U-Net as well as the YOLO (using Keras API).

RESULTS

At the beginning we evaluated the performance of the trained YOLO in detecting the ROI. We determined mean Average Precision (mAP) on 20 test images. The mAP was equal to 0.962. Figure 5 depicts the detected areas on high-resolution radiographs using YOLO. The rectangles representing the bones of interest were then used to calculate the ROIs.

Finally, 184 randomly selected lateral knee radiographs of the 218 (initially prepared database) were included for the analysis. The mean age of patients was 61.9 (± 17.8) years. There were 65 males (35%) and 119 females (65%). The demographic data of the subgroups of patients are presented in Table 1.

Training and validation of the U-Net

The final training set consisted of 82 X-ray images, as well as 10 X-rays in the validation set (which did not change during the training). To compare the reliability of automatic and manual measurements, 92 randomly selected lateral radiographs of the knee in the test set were used.

Comparison of automated and manual measurements

The mean value of CD indexes calculated by orthopedic surgeon (R#1 and R#2) was 0.93 (± 0.19) and 0.89 (± 0.19). For BP indexes it was 0.80 (± 0.17) and 0.78 (± 0.17). Automatic measurements performed by the artificial intelligence (AI) for CD index was 0.92 (± 0.21) and for BP index was 0.75 (± 0.19) (Table 2).

The accuracy of image segmentation performed on the test set was 95.9% (± 1.26). The range of Dice score for individual X-ray images varied from 90% to 97.8% (Figure 6). This result demonstrates that even on a small amount of training data, it is possible to achieve a satisfactory segmentation quality with good generalization on unknown test radiographs that can be used in everyday clinical practice. Our research findings align with Ronneberger *et al*'s conclusions, which pointed out that it is possible to train the U-Net model on very few annotated images[25]. On Google Colab (using CPU) the time needed for the measurement of the patella height on 20 radiographs was equal to about 240 s.

DISCUSSION

This proposed method uses a U-Net to segment bones making the patellofemoral joint and subsequently measures the Caton-Deshamps and Blackburne-Peel patellar height indexes. Our study revealed that

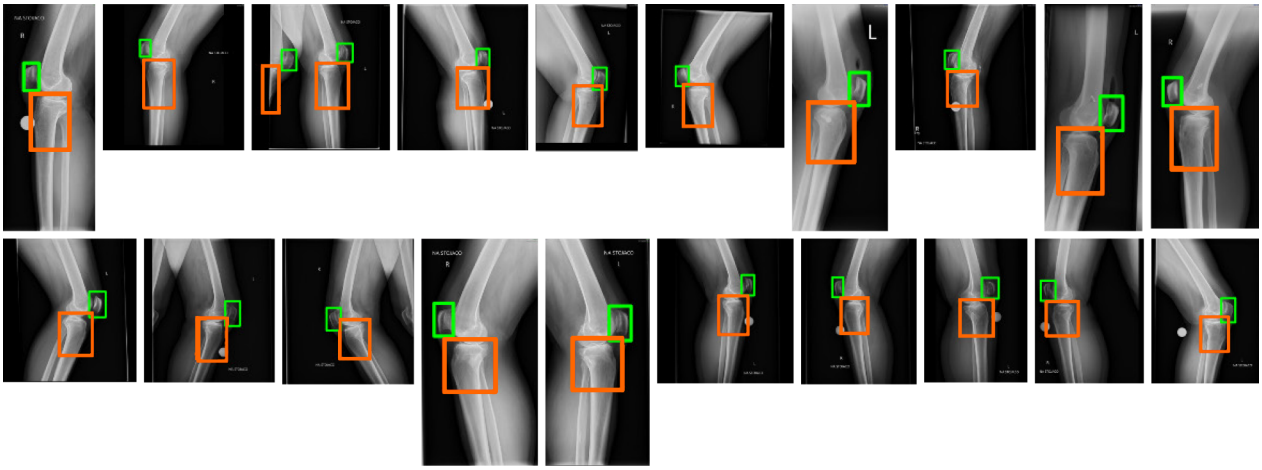
Table 1 Demographic information among the training and testing groups

	Total (*n* = 184)	Training group (*n* = 82)	Validation group (*n* = 10)	Testing group (*n* = 92)
Males/Females	65/119	26/56	4/6	35/57
Left/Right knee	99/85	47/35	3/7	49/43
Age (yr)	61.9 ± 17.83	64.0 ± 17.62	53.7 ± 11.21	61.1 ± 18.37

Table 2 The results of patellar height indexes calculated by two orthopedic surgeons and those achieved by artificial intelligence (based on a deep learning algorithm and neural network)

	CD index	BP index
Orthopedic surgeon (R#1)	0.93 ± 0.19	0.80 ± 0.17
Orthopedic surgeon (R#2)	0.89 ± 0.19	0.78 ± 0.17
Artificial intelligence	0.92 ± 0.21	0.75 ± 0.19

R#1: Senior specialist; R#2: Younger specialist; CD: Caton-deschamps; BP: Blackburne-Peel. Results of indexes are presented as means ± SD.



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Figure 5 Detected bones (patella and proximal tibia) on high-resolution radiographs using You Only Look Once.

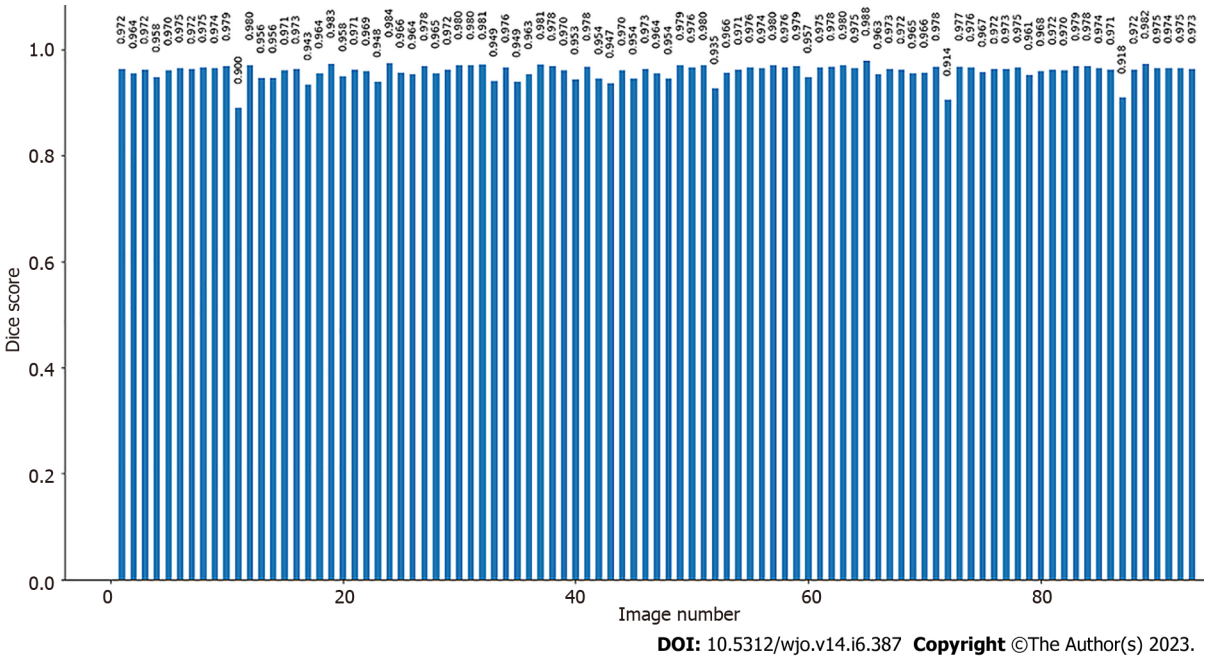
automatic bone segmentation of lateral knee radiographs can be performed with the Dice score of 95.9% (± 1.26). Additionally, a novel approach to automatic estimation of patellar indexes has been proposed. The key points and lines needed for measuring the patellar height indexes were automatically determined based on automatically segmented patella and tibia. Excellent reliability between AI calculations and those performed by orthopedic surgeons for CD [R#1 *vs* AI: ICC = 0.86 (± 0.38), SEM = 0.015; R#2 *vs* AI: ICC = 0.80 (± 0.33), SEM = 0.013] and BP [R#1 *vs* AI: ICC = 0.88 (± 0.38), SEM = 0.015; R#2 *vs* AI: ICC = 0.79 (± 0.32), SEM = 0.014] were obtained (Table 3, Figure 7).

For comparison, a method for patella segmentation[20] uses the principal component analysis to construct a patella shape model and a dual-optimization approach with genetic algorithm and Active Shape Model to fit the model to the patella boundary. The method has been tested on 20 images. However, this method segments only the patella and requires manually cropped images in which the patella occupies considerable part of the images. In a recently proposed method[21], a convolutional neural network was used to detect landmark points to measure patellar indexes. The detection was performed by a pretrained VGG-16 neural network. It has been trained and evaluated on 916 and 102 images, respectively, with manually annotated landmarks. The method has been evaluated on 400 radiographs. The ICC, Pearson correlation coefficient, mean absolute difference, Root Mean Square and Bland-Altman plots have been calculated to compare this method with manual measurements. However, the method operates on images with the patella and the proximal tibial articular occupying considerable part of the images, *i.e.* it is not fully automatic as the ROI was manually cropped from the high-resolution x-ray images. Moreover, only radiographs with clear patellar height landmarks have been utilized in experiments.

Table 3 Reliability assessed with the use of interclass correlation coefficient (± SD) and single measurement among the interobserver measurements

	ICC	SEM
CD index		
R#1 *vs* AI	0.86 ± 0.38	0.015
R#2 *vs* AI	0.88 ± 0.38	0.015
BP index		
R#1 *vs* AI	0.80 ± 0.33	0.013
R#2 *vs* AI	0.79 ± 0.32	0.014

R#1: Senior specialist; R#2: Younger specialist; AI: Artificial intelligence; SEM: Single measurement; CD: Caton-deschamps.



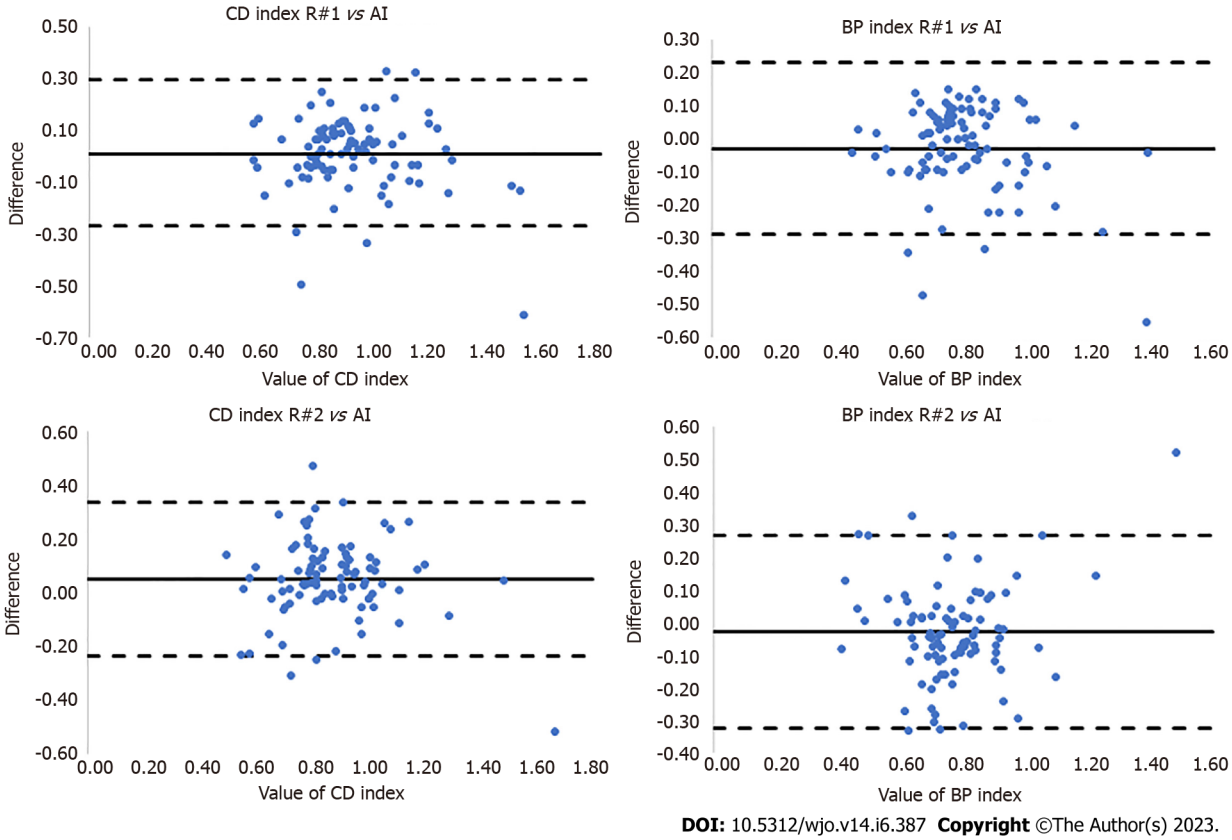
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Figure 6 Distribution of dice score results for test images (92 subjects).

The method of Ye *et al*[21] relies on keypoints, which needs far bigger number of annotated radiographs for training the network. In contrast, our work is in line with recent research direction which focuses on training deep models on small datasets. It is worth noting that this is an important aspect as acquiring and labeling medical data is expensive, among others due to privacy concerns. In contrast to keypoint-based methods, our method relies on a large number of boundary points, making it more resistant to outliers and errors (through boundary-aware analysis). Our initial experimental results show that even in the case of training a neural network for keypoints regression on several times larger number of labeled images, the errors are much larger in comparison to the errors of our method. The method is fully automatic as the YOLO detects bones making the patellofemoral joint on high-resolution images, U-Net segments the bones, a line is fitted to the segmented proximal tibial articular surface, and a second line passing through two landmarks detected on the segmented patella are determined. Then they are used to calculate the patellar height indexes. However, good technical execution and sufficient quality of the input images are mandatory to obtain reliable results for automatic measurements. In some specific cases, additional hardware (screws, plates), heterotopic ossifications, large osteophytes that distort the bone outline and oblique view (instead of proper lateral), may slightly reduce quality of bone segmentation, which is the main limitation of this method. We agree with Zheng *et al*[33], who emphasized that absolute errors may be reduced by increasing the number of subjects in the training group.

Strengths, limitations and future work

Our algorithm for automatic measurements of patellar indexes permits the evaluation of indexes on



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Figure 7 Bland-Altman plots illustrating the differences between R#1 *vs* artificial intelligence (AI) and R#2 *vs* AI for Caton-Deschamps and Blackburne-Peel indexes. Continuous lines represent a mean (bias), dashed lines represent +2 and -2 SD values. BP: Blackburne-peel; CD: Caton-deschamps; AI: Artificial intelligence.

high data volume. Taking into account that the proposed algorithm allows measurements on high-resolution radiographs, low effort is needed to get patellar indexes, *i.e.* no manual cropping of knee region is required in contrast to the previous methods. One of the advantage of the proposed method is that relatively small amount of manually labelled bones on images is needed to achieve reliable bone segmentation. Although, higher number of manual annotations for training YOLO responsible for knee detection is needed, the labelling of knee regions can be done in relatively short time. This study has some limitations. Firstly, in the current study, the ROIs that were determined on the basis of YOLO detections were resized to size required by the U-Net, *i.e.*, 512 × 512. This means that the keypoints and lines were determined on images with somewhat smaller resolution than the original radiographs. Secondly, the accuracy of the results depends on: The manual segmentation performed by the researcher during the training phase; the amount and quality of training data, and the architecture of the applied neural network. In current work, the training of neural networks and evaluation of the algorithm was performed on images acquired in a single institution, *i.e.* our hospital. Thus, further work is needed to collect radiographs from various hospitals to train networks and asses accuracy of the algorithm on radiograms acquired by different devices. Moreover, the input images may have different levels of intensity and quality. These technical aspects should be emphasized and resolved in medical centers that will implement the algorithm for automatic measurement of patellar indexes. In future work we are planning to combine boundary-aware analysis with landmark-based DL measurements. We also plan to extend the U-Net and compare it with recent networks for image segmentation. Additionally images from different hospitals will be used in the research.

CONCLUSION

The aim of this study was to investigate the reliability of automated patellar height estimation using DL-based bone segmentation and detection on high-resolution images. It showed that reliable automatic patellar height measurements can be achieved on lateral knee radiographs with the accuracy required for the clinical practice. We demonstrated that proximal tibia and patella bones can be segmented precisely (Dice score greater than 95%) by U-Net neural network on knee regions automatically detected by the YOLO network (mean Average Precision mAP greater than 0.96). Determining patellar end-points and the joint line by fitting to points of the proximal tibia joint surface enables calculating the

Caton-Deschamps and Blackburne-Peel indexes with very good reliability. Automated measurements are comparable to measurements performed by orthopedic surgeons (SEM greater than 0.75). Experimental results indicate that our approach can be valuable as a pre-operative and potentially as a postoperative assessment tool for big volume data analysis in medical practice.

ARTICLE HIGHLIGHTS

Research background

Recent advancements in artificial intelligence and deep learning have contributed to the development of medical imaging techniques, leading to better interpretation of radiographs. Moreover, there is an increasing interest in automating routine diagnostic activities and orthopedic measurements.

Research motivation

The automation of patellar height assessment using deep learning-based bone segmentation and detection on high-resolution radiographs could provide a valuable tool in medical practice.

Research objectives

The aim of this study was to verify the accuracy of automated patellar height assessment using a U-Net neural network and to determine the agreement between manual and automatic measurements.

Research methods

Proximal tibia and patella was segmented by U-Net neural network on lateral knee subimages automatically detected by the You Only Look Once (YOLO) network. The patellar height was quantified by Caton-Deschamps and Blackburne-Peel indexes. The interclass correlation coefficient and standard error for single measurement were used to calculate agreement between manual and automatic measurements.

Research results

Proximal tibia and patella were segmented with 95.9% accuracy by the U-Net neural network on lateral knee subimages automatically detected by the YOLO network (mean Average Precision mAP greater than 0.96). Excellent agreement achieved between manual and automatic measurements for both indexes (interclass correlation coefficient > 0.75, SEM < 0.014).

Research conclusions

Automatic patellar height assessment can be achieved with high accuracy on high-resolution radiographs. Proximal tibia and patella can be segmented precisely by U-Net neural network on lateral knee subimages automatically detected by the YOLO network. Determining patellar endpoints and fitting the line to the proximal tibia joint surface enables accurate Caton-Deschamps and BP index calculations, making it a valuable tool in medical practice.

Research perspectives

Future research can focus on the clinical implementation of this automated method, which has the potential to enhance diagnostic accuracy, reduce human error, and improve patient outcomes.

FOOTNOTES

Author contributions: Kwolek Ka, Grzelecki D, Tyrakowski M designed research; Kwolek Ka, Kwolek Ko performed research; Kwolek Ka, Kwolek Ko elaborated analytic tools, Kwolek Ka, Tyrakowski M, Kowalczewski J, Marczak D analyzed data; Kwolek Ka, Dariusz G, Kwolek Ko, Tyrakowski M wrote the paper.

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Conflict-of-interest statement: The authors have no conflict of interest concerning the materials or methods used in this study or the findings specified in this article.

Data sharing statement: No additional data are available.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

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ORIGINAL ARTICLE

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Two surgical pathways for isolated hip fractures: A comparative study

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Abstract

BACKGROUND

Hip fractures (HF) are common among the aging population, and surgery within 48 h is recommended. Patients can be hospitalized for surgery through different pathways, either trauma or medicine admitting services.

AIM

To compare management and outcomes among patients admitted through the trauma pathway (TP) *vs* medical pathway (MP).

METHODS

This Institutional Review Board-approved retrospective study included 2094 patients with proximal femur fractures (AO/Orthopedic Trauma Association Type 31) who underwent surgery at a level 1 trauma center between 2016-2021. There were 69 patients admitted through the TP and 2025 admitted through the MP. To ensure comparability between groups, 66 of the 2025 MP patients were

propensity matched to 66 TP patients by age, sex, HF type, HF surgery, and American Society of Anesthesiology score. The statistical analyses included multivariable analysis, group characteristics, and bivariate correlation comparisons with the χ^2 test and *t*-test.

RESULTS

After propensity matching, the mean age in both groups was 75-years-old, 62% of both groups were females, the main HF type was intertrochanteric (TP 52% *vs* MP 62%), open reduction internal fixation was the most common surgery (TP 68% *vs* MP 71%), and the mean American Society of Anesthesiology score was 2.8 for TP and 2.7 for MP. The majority of patients in TP and MP (71% *vs* 74%) were geriatric (≥ 65-years-old). Falls were the main mechanism of injury in both groups (77% *vs* 97%, $P = 0.001$). There were no significant differences in pre-surgery anticoagulation use (49% *vs* 41%), admission day of the week, or insurance status. The incidence of comorbidities was equal (94% for both) with cardiac comorbidities being dominant in both groups (71% *vs* 73%). The number of preoperative consultations was similar for TP and MP, with the most common consultation being cardiology in both (44% and 36%). HF displacement occurred more among TP patients (76% *vs* 39%, $P = 0.000$). Time to surgery was not statistically different (23 h in both), but length of surgery was significantly longer for TP (59 min *vs* 41 min, $P = 0.000$). Intensive care unit and hospital length of stay were not statistically different (5 d *vs* 8 d and 6 d for both). There were no statistical differences in discharge disposition and mortality (3% *vs* 0%).

CONCLUSION

There were no differences in outcomes of surgeries between admission through TP *vs* MP. The focus should be on the patient's health condition and on prompt surgical intervention.

Key Words: Isolated hip fractures; Admitting service; Trauma center; Time to surgery; American Society of Anesthesiologists score; Preoperative consultations

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Core Tip: We evaluated 2094 hip fracture patients admitted for surgery to a level 1 trauma center over a 5-year period. Patients were stratified based on the admitting service, either trauma or medical. After a propensity score matching comparison of 66 patients in each group it was revealed that there was no difference in outcomes. Predictors of a prolonged hospital length of stay were increased American Society of Anesthesiology score and delayed time to surgery. Predictors of mortality were increased American Society of Anesthesiology score and increased age. The health condition of the patient, but not the admitting service, was the defining factor for management and outcomes.

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INTRODUCTION

As life expectancy rises around the world along with the number of elderly individuals, the incidence of hip fractures (HF) is estimated to reach 6.3 million in 2050[1]. Each year in the United States alone over 300000 people aged 65 and older are hospitalized for HF[2-4].

Patients can be hospitalized for operative fixation of HF through different pathways, including trauma, orthopedic, and medicine admitting services[5-8]. In the studies comparing surgical *vs* nonsurgical pathways it has been reported that the admitting service can affect the management patterns and outcomes of patients with HF[5,6,9].

For example, in one study by Greenberg *et al*[5], the authors determined that patients with HF admitted to the medicine service had longer hospital stays than patients admitted to the orthopedic service, even after controlling for demographics and preoperative comorbidities. A 2018 study by Lott *et al*[6] also concluded that patients with HF admitted to the medicine service had longer lengths of stay (LOS) and more complications compared to patients admitted to the trauma/orthopedic service. In contradiction to these conclusions, other studies determined that there were no differences in complication rates or LOS between the admitting services[8,10].

The impact of preoperative pathways on the outcomes was previously addressed in diverse cohorts of patients, which differed in inclusion/exclusion criteria such as age, hospital settings, mechanism of injury, preoperative medication, or surgical management[7,8,10-12]. The rationale for our study was the existing controversy over which hospital service is best suited for the optimal admission process for patients with HF and associated with the best outcomes.

At our institution patients with HF can be admitted through the Emergency Department or through the Trauma Department depending on how they are transported to the hospital by the first responders. If the patient is admitted through the Emergency Department, the hospitalist or internal medicine physician will admit the patient to the Medical Service. If the patient is admitted through the Trauma Department, the trauma surgeon will admit the patient to the Trauma Service. After a radiographic confirmation of a HF, a consultation of the orthopedic surgeon is requested by the admitting service. After admission to either service, the internal medicine physician or the trauma surgeon may request additional consultations if necessary for preoperative clearance.

We analyzed the clinical characteristics and outcomes of patients admitted for HF surgery through trauma services and compared to those admitted through medical services.

MATERIALS AND METHODS

This Institutional Review Board-approved retrospective cohort study was granted a waiver of informed consent and included 2094 adult patients (≥ 18-years-old) with HF who underwent operative fixation at an urban level 1 trauma center between January 1, 2016 and May 31, 2021. All patients presented with AO/Orthopedic Trauma Association fracture Type 31A-C[13]. Patients with other traumatic, non-orthopedic injuries requiring surgical intervention, including head, thoracic, or abdominal injuries were excluded. Additional exclusion criteria were: In-hospital HF; patients with pathologic fractures; periprosthetic fractures; open fractures; previous fracture; or surgery at the current fracture site.

Patients were stratified in two groups based on the admitting service: Those who were admitted through the trauma pathway (TP) of the level 1 trauma center (n = 69); and those who were admitted through the medical pathway (MP) (n = 2025).

To ensure comparability between groups, propensity matching by age, sex, type of HF, type of HF surgery, and American Society of Anesthesiology (ASA) score was performed, which resulted in 66 patients in each group for comparison (Figure 1). In the propensity matching process there were 3 TP patients who did not match and therefore were excluded from the comparison.

Analyzed variables included age, sex, body mass index, mechanism of injury, Glasgow Coma Score, comorbidities, pre-injury anticoagulation use, ASA score, insurance status, admission day of the week, number of preoperative consultations, type of HF, presence of fracture displacement, time to surgery, time of surgery, type of HF surgery, intensive care unit and hospital lengths of stay (ICULOS, HLOS), discharge disposition, and mortality. We also analyzed the weekend effect of admissions in the propensity matched groups.

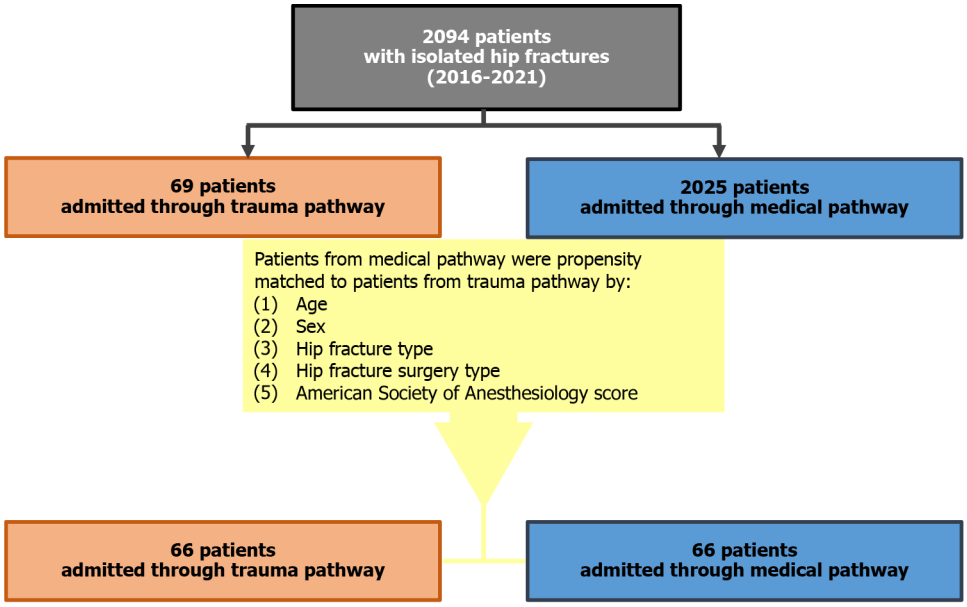
Variables were identified *via* the International Classification of Diseases 9th and 10th edition and extracted from patient's electronic medical records. Geriatric age was defined as 65 years or older[14]. Weekend effect was defined as any of the following due to admission from Friday to Sunday: A longer time to surgery; longer HLOS; or higher mortality[12,15-17]. Extended HLOS was defined as more than 6 d. This number was based on our data and the commonly reported HLOS for patients with HF[3,18-20].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software version 23.0 (IBM, Armonk, NY, Untied States). Propensity score matching was completed without replacement, with a 0.2 caliper and with a randomized order of patients while drawing matches, which resulted in a one-to-one paired selection. The analyses included group characteristics and bivariate correlation comparisons. Categorical variables were analyzed with the χ^2 test. Variable means were analyzed using independent samples t-test and Mann Whitney U test. Multivariable analysis for the predictors of extended LOS and mortality was performed in the total population. Receiver operating characteristic (ROC) area under the curve analysis was used to determine threshold values for extended length of stay and mortality prediction variables. One way analysis of variance was used for the analysis of age and HLOS by ASA score. Statistical significance was assumed when the calculated P value was below 0.05.

RESULTS

Over the duration of 65 mo, 2094 patients with HF were admitted for surgical repair: 69 (3.3%) patients through TP; and 2025 (96.7%) through MP.



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Figure 1 Study design and flow chart of all patients with hip fractures.

General comparison

The general comparison between all TP and MP patients is presented in Table 1. MP patients were older and included more geriatric patients; however, geriatric patients comprised more than two-thirds of each group. Falls were the prevailing mechanism of injury in both groups, comprising at least 74% in each group. The analyzed cohorts had slightly different types of HF. There were no differences in sex, admission day, ASA score distribution, time to surgery, type of HF surgery, HLOS, discharge disposition, and mortality.

Multivariable analysis and ROC analysis showed that increased ASA score and extended time from admission to surgery were two statistically significant predictors for the extended HLOS. The significant predictors for mortality were age > 83 (P = 0.000, odds ratio: 6.0) and ASA score ≥ 4 (P = 0.000, odds ratio: 5.1). The threshold values were based on the ROC curve with area under the curve or concordance index of 0.697 (95% confidence interval: 0.640-0.755) and 0.698 (95% confidence interval: 0.630-0.765).

Propensity matched comparison

The comparison of propensity matched patients, 66 TP and 66 MP, is presented in Table 2. Propensity matched TP patients had statistically higher motor vehicle collisions as a mechanism of injury (falls were still the prevailing mechanism of injury in more than three-quarters of patients in both groups), a higher presence of HF displacement, more requests for neurological consultation, and a longer duration of surgery.

There were no differences between the groups in body mass index, comorbidities, anticoagulation use, admission day, number of consultations before surgery, insurance status, and mean time from admission to HF surgery. An additional analysis of the time from admission to surgery through TP and MP divided in 12-h increments is presented in Figure 2. At any 12 h interval, the number of patients in the TP and MP groups was similar, with two-thirds (63.6% in TP and 66.7% in MP) having surgery within 24 h and over 90% (95.5% in TP and 93.9% in MP) having surgery within 48 h of admission.

The two groups had comparable ICULOS and HLOS. The similar distribution of HLOS in propensity matched TP and MP is shown in Figure 3. The discharge disposition and mortality were also comparable. The 2 expired patients in the TP group were 87-years-old and 96-years-old. One patient had renal failure and was discharged to hospice. The other patient had a cardiac arrest during surgery.

Within the propensity matched TP group there were 41 patients admitted on a weekday and 25 patients admitted on a weekend. The two sub-groups had comparable time to surgery (22.8 h *vs* 22.5 h, P = 0.926), HLOS (5.6 d *vs* 7.6 d, P = 0.130), and mortality (2.4% *vs* 4.0%, P = 0.720). Within the propensity matched MP group there were 37 patients admitted on a weekday and 29 patients admitted on a weekend. The two sub-groups had comparable time to surgery (21.7 h *vs* 24.7 h, P = 0.490) and HLOS (5.3 d *vs* 6.9 d, P = 0.239). There was no mortality in the MP sub-groups.

Mean age and HLOS stratified by ASA score in the different patient groups is presented in Table 3. One way analysis of variance demonstrated that in the total population, age and HLOS both increased significantly (both P = 0.000) as ASA increased. In the propensity matched TP population, age increased significantly (P = 0.001) as ASA increased from 2 to 4. Higher ASA was associated with older age and longer HLOS.

Table 1 General comparison between all trauma pathway and medical pathway patients, *n* (%)

Variable	Trauma, *n* = 69	Medicine, *n* = 2025	*P* value
Age in yr	72.9 (17.5)	83.2 (9.2)	0.000[a]
Geriatric	47 (68.1)	1928 (95.2)	0.000[a]
Sex, female/male	44 (63.8)/25 (36.2)	1367 (67.5)/658 (32.5)	0.515
Mechanism of injury	-	-	0.000[a]
Fall	51 (73.9)	2005 (99.0)	-
MVC	18 (26.1)	11 (0.5)	-
Stress fracture	0 (0.0)	9 (0.4)	-
Admission day	-	-	0.171
Monday	10 (14.5)	317 (15.7)	-
Tuesday	12 (17.4)	281 (13.9)	-
Wednesday	16 (23.2)	268 (13.2)	-
Thursday	5 (7.2)	311 (15.4)	-
Friday	10 (14.5)	297 (14.7)	-
Saturday	7 (10.1)	276 (13.6)	-
Sunday	9 (13.0)	275 (13.6)	
Hip fracture type	-	-	0.000[a]
Femoral neck/head	28 (40.6)	972 (48.0)	-
Intertrochanteric	35 (50.7)	1020 (50.4)	-
Intertrochanteric with subtrochanteric	6 (8.7)	33 (1.6)	-
Hip surgery type	-	-	0.205
Total arthroplasty	4 (5.8)	177 (8.7)	-
Hemi arthroplasty	15 (21.7)	613 (30.3)	-
Open reduction and internal fixation	47 (68.1)	1116 (55.1)	-
Pinning	3 (4.3)	119 (5.9)	-
ASA score before hip surgery	2.8 (0.6)	2.9 (0.6)	0.044[a]
ASA score before hip surgery	-	-	0.079
I	1 (1.4)	9 (0.4)	-
II	21 (30.4)	393 (19.4)	-
III	41 (59.4)	1393 (68.8)	-
IV	6 (8.7)	230 (11.4)	-
No. of consultations before hip surgery	0.9 (0.9)	0.9 (0.8)	0.620
Time: Admission to hip surgery in h	23.0 (13.4)	27.0 (28.5)	0.255
Hospital length of stay in d	6.3 (4.4)	5.7 (4.9)	0.347
Mortality	2 (2.9)	62 (3.1)	0.938
Hospital disposition	-	-	0.068
Skilled nursing facility	28 (40.6)	1147 (56.6)	-
Rehabilitation	25 (36.2)	589 (29.1)	-
Home	13 (18.8)	212 (10.5)	-
Hospice	1 (1.4)	51 (2.5)	-
Expired in hospital	1 (1.4)	11 (0.5)	-
Long-term acute care facility	1 (1.4)	15 (0.7)	-

[a]*P* < 0.005 denotes significant difference.
ASA: American Society of Anesthesiologists; MVC: Motor vehicle collision; SD: Standard deviation.

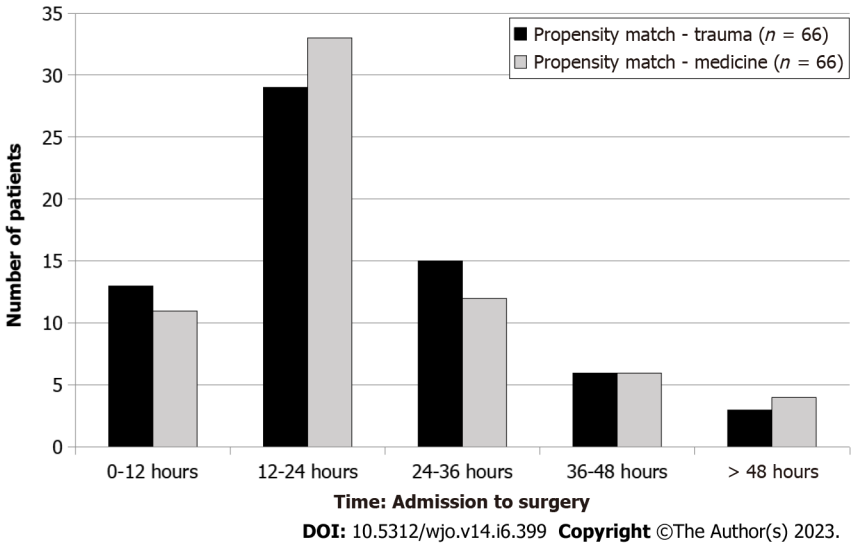


Figure 2 Time from admission to surgery in propensity matched trauma and medical pathway groups in 12 h increments.

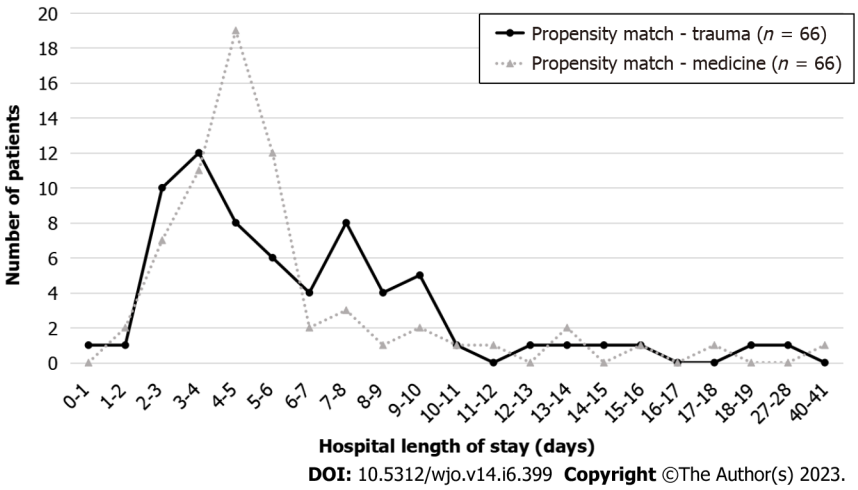


Figure 3 Number of patients in propensity matched trauma and medical pathway groups stratified by hospital length of stay.

DISCUSSION

In studies that relate to different admission pathways and how the admission pathway affects the outcomes in patients with HF, there is a noticeable difference in the age of included patients, ranging from 50-years-old to 75-years-old[7,9-11]. Other inclusion/exclusion criteria also differ significantly, as some HF studies exclude patients undergoing total hip replacement, patients who expired before hospital discharge, patients who were not admitted to a surgical ICU, or include only patients with mechanism of injury as fall or only patients with presurgical transthoracic echocardiography[7,12,17,19,21]. There is also a broad array of different settings ranging from level 1 trauma centers to safety-net and tertiary hospitals[8,19,22,23].

In our study, we utilized propensity score matching to address the imbalance in the characteristics of TP and MP patients, as was recommended by Chuang *et al*[10] in their comparison of medicine *vs* orthopedic service for management of HF. There are only two published studies on patients with HF that utilized the propensity score matching methodology. However, they were conducted to evaluate the impact of preoperative echocardiography[24,25].

Our results indicated that ASA score as a measure of patient's condition is a predictor of a longer HLOS and mortality. Our findings support the conclusions reported by Garcia *et al*[26] that an increase

Table 2 Characteristics of propensity matched patients admitted through the trauma pathway and medical pathways, *n* (%)

Variable	Trauma, *n* = 66	Medicine, *n* = 66	*P* value
Age	75.0 (14.5)	75.0 (13.3)	0.990
Sex, female/male	41 (62.1)/25 (37.9)	41 (62.1)/25 (37.9)	1.000
ASA Score before hip surgery	-	-	0.498
II	19 (28.8)	23 (34.8)	-
III	41 (62.1)	40 (60.6)	-
IV	6 (9.1)	3 (4.5)	-
Hip fracture type	-	-	0.057
Femoral neck/head	27 (40.9)	25 (37.9)	-
Intertrochanteric	34 (51.5)	41 (62.1)	-
Intertrochanteric with subtrochanteric	5 (7.6)	0 (0.0)	-
Hip surgery type	-	-	0.650
Total arthroplasty	4 (6.1)	6 (9.1)	-
Hemi arthroplasty	15 (22.7)	10 (15.2)	-
Open reduction and internal fixation	45 (68.2)	47 (71.2)	-
Pinning	2 (3.0)	3 (4.5)	-
Geriatric	47 (71.2)	49 (74.2)	0.696
BMI	24.9 (6.6)	24.9 (5.0)	0.988
Comorbidities	62 (93.9)	62 (93.9)	1.000
Cardiac comorbidities	47 (71.2)	48 (72.7)	0.846
Anticoagulation	32 (48.5)	27 (40.9)	0.381
Mechanism of injury, Fall/MVC	51 (77.3)/15 (22.7)	64 (97.0)/2 (3.0)	0.001[a]
Admission day	-	-	0.401
Monday	9 (13.6)	7 (10.6)	-
Tuesday	11 (16.7)	8 (12.1)	-
Wednesday	16 (24.2)	10 (15.2)	-
Thursday	5 (7.6)	12 (18.2)	-
Friday	10 (15.2)	13 (19.7)	-
Saturday	7 (10.6)	10 (15.2)	-
Sunday	8 (12.1)	6 (9.1)	-
Glasgow coma score	14.6 (0.8)	15.0 (0.2)	0.000[a]
Hip fracture displacement	50 (75.8)	26 (39.4)	0.000[a]
No. of consultations before hip surgery	1.8 (0.9)	1.7 (0.9)	0.198
Consultations before surgery	-	-	-
Cardiology	29 (43.9)	24 (36.4)	0.375
Neurology/neurosurgery	12 (18.2)	1 (1.5)	0.001[a]
Pulmonology	2 (3.0)	5 (7.6)	0.244
Time: Admission to hip surgery in h	22.7 (12.7)	23.0 (16.9)	0.892
Orthopedic surgery length in h	1.0 (0.6)	0.7 (0.3)	0.000[a]
ICULOS in d	4.5 (4.3)	8.0 (4.6)	0.066
HLOS in d	6.3 (4.5)	6.0 (5.4)	0.709
Mortality	2 (3.0)	0 (0.0)	0.154

Hospital disposition	-	-	0.507
Skilled nursing facility	29 (43.9)	31 (47.0)	-
Rehabilitation	29 (43.9)	26 (39.4)	-
Home	6 (9.1)	9 (13.6)	-
Expired in hospital/hospice	2 (3.0)	0 (0.0)	-
Insurance status	-	-	0.060
Public	48 (72.7)	47 (71.2)	-
Private	10 (15.2)	17 (25.8)	-
Uninsured	8 (12.1)	2 (3.0)	-

[a]$P < 0.005$ denotes significant difference.

ASA: American Society of Anesthesiologists; BMI: Body mass index; HLOS: Hospital length of stay; ICULOS: Intensive care unit length of stay; MVC: Motor vehicle collision; SD: Standard deviation.

Table 3 Mean age and hospital length of stay stratified by American Society of Anesthesiologists score, *n* (%)

ASA, score	All patients, *n* = 2094			Propensity matched trauma group, *n* = 66			Propensity matched medicine group, *n* = 66		
	n %	Age, mean	HLOS, mean	*n*	Age, mean	HLOS, mean	*n*	Age, mean	HLOS, mean
1	10 (0.5)	65.0	5.3	-	-	-	-	-	-
2	414 (19.8)	77.1	4.7	19	65.6	5.8	23	74.0	5.7
3	1434 (68.5)	84.1	5.7	41	77.5	6.5	40	76.4	6.3
4	236 (11.3)	85.8	7.5	6	87.7	6.9	3	64.0	4.4

ASA: American Society of Anesthesiologists; HLOS: Hospital length of stay.

in ASA score has a strong association with an increased LOS in elderly patients with HF. Our observations are also in compliance with reports that the ASA score is associated with mortality, LOS, and time to surgery[17,27,28]. Mok *et al*[28] correspondingly recommended that ASA score be added as a criterion for allocation of high-risk patients with HF and for indicating the appropriate admitting service.

In our study, the average number of consultations per patient was similar in all groups. Cardiology was the most common consultation in the TP and MP cohorts. While cardiac comorbidities were registered in approximately 70% of patients, cardiology consultations were implemented in only around 40% of patients. Our data are remarkably similar to that recently reported by Hoehmann *et al*[19], with a 44.4% rate of cardiology consultations in patients with HF in a geriatric population of 65 years and older. Neurology was the second most common consultation in TP patients, while pulmonology was the second most common in MP patients. Having a similar Glasgow Coma Score in both groups and having excluded traumatic brain injury patients, the higher rate of neurological consultations in TP patients may be a result of precaution, attributed to the higher number of motor vehicle collisions as a mechanism of injury.

Surgical intervention for HF is recommended within 48 h[29,30]. Recent studies indicate that surgery within 24 h of admission is associated with shorter HLOS or mortality[31-33]. Delaveau *et al*[11] also recommended "early" surgery within 24 h of admission in orthogeriatrics. Two-thirds of our patients underwent hip surgery within 24 h of admission, and the majority of patients were geriatric. In our study, less than 5% of patients had surgery later than the recommended 48 h benchmark, compared to 9.5% in the report from level I and II trauma centers by deMeireles *et al*[7] and compared to 16.3% in the review of the National Trauma Data Bank by Bhatti *et al*[2] that included level I-IV trauma centers and other hospitals. Our findings support the notion that a longer time to surgery is correlated with extended HLOS. The longer time of orthopedic surgery in our TP patients can be attributed to displaced HF occurring more often.

Elkbuli *et al*[9] in his comparison conducted in a similar setting to ours found that patients with isolated HF admitted to a surgical service had shorter ICULOS and that mortality did not differ from the nonsurgical admission pathway. However, nonsurgical admission patients were younger. In our propensity matched comparison study, mortality was also not statistically different. ICULOS tended to be shorter in TP patients, but the difference did not reach statistical significance. However, our patients

were propensity matched by age.

Our data did not show the weekend effect reported by others, as there was no delay of surgery, longer HLOS, or higher mortality[15,16,34,35]. Our observations were in line with reports by Nijland *et al*[12] and Yeo *et al*[22] who also did not find the weekend effect.

The distribution of insurance types between TP and MP patients did not show statistical significance. However, it seems that there was a trend towards less insured patients in TP. In the study by Bhatti *et al* [2] there was no difference in repair times for patients with public insurance or no insurance when compared to patients with private insurance.

The main conclusion of our study was that the health condition of the patient, but not the admitting service, was the defining factor in the management and outcomes of patients with HF. Our conclusion was similar to a recent report by Bauman *et al*[8] concluding that the severity of illness impacts the outcomes more than the admitting service.

In an analysis of geriatric patients with isolated HF as a result of a fall surgically treated at 35 level 1 or level 2 trauma centers, deMeireles *et al*[7] did not find an association between the admitting service and mortality or hospice discharge. However, they found that it was the comorbidity burden that correlated with an increased risk of mortality.

Limitations

This study had limitations that must be considered when interpreting the results. The retrospective nature of this study brings up deficiencies in prerecorded data and the assessments available for extraction and analysis. Although collection of data was completed for a considerable amount of time, the records of only one hospital were analyzed.

CONCLUSION

There were no notable differences in the management and outcomes between patients who underwent HF surgery but were admitted through two different pathways (trauma *vs* medicine). Prolonged LOS was associated with an increased ASA score and longer time to surgery, while mortality was associated with an increased ASA score and age. The admission pathway was not the defining factor in the management of patients with HF. The focus should be on the patient's health condition upon admission and a prompt surgical intervention.

ARTICLE HIGHLIGHTS

Research background

Isolated hip fractures (HF) are common, especially among the elderly population, and falls are the main mechanism of injury. Depending on the hospital settings and institutional policies, patients can be admitted for surgery through different pathways (medicine or trauma). There is a scarcity of studies utilizing the propensity score matching methodology in the analysis of the data on this subject.

Research motivation

It has been reported that the admitting service may influence the outcomes of patients with HF. The motivation behind this study were the conflicting conclusions and ongoing debates over which admitting service is associated with better results. We hypothesized that it is necessary to contribute new data and a new outlook to help achieve improvements in the treatment of patients with HF.

Research objectives

To analyze the characteristics and compare the outcomes of similarly injured patients with HF admitted through trauma *vs* medicine service at an urban level 1 trauma center.

Research methods

This was a retrospective cohort study. Patients with HF were divided into two groups based on the admitting service: Trauma *vs* medicine. Propensity score matching was utilized to ensure comparability between the groups. Patients were propensity matched by age, sex, HF type and surgery, and the American Society of Anesthesiology score. The statistical analyses included group characteristics, bivariate correlation comparisons, multivariable analysis, and one way analysis of variance.

Research results

Time to surgery, time in the intensive care unit, hospital length of stay, discharge disposition, and mortality were not statistically different between the two groups. The average number of preoperative consultations was similar in both groups with cardiology consultation being the most common. Higher

American Society of Anesthesiology score was associated with a longer hospital stay and mortality.

Research conclusions

The health condition of the patient, but not the admission pathway, is the defining factor in the management and outcomes of patients with HF.

Research perspectives

Research should be conducted across multiple medical centers to include larger cohorts with more focus on predictors of adverse outcomes as well as the potential cost differences between the admission pathways.

FOOTNOTES

Author contributions: Fokin AA and Weisz RD conceptualized the research study; Fokin AA, Wycech Knight J, Puente I, and Weisz RD designed the methodology; Fokin AA, Puente I, and Weisz RD were the project administrators and supervisors; Wycech Knight J, Darya M, and Stalder R performed the research; Wycech Knight J performed the software analysis; Fokin AA, Wycech Knight J, Darya M, Stalder R, Puente I, and Weisz RD performed formal data analysis and validation; Fokin AA, Wycech Knight J, Darya M, and Stalder R wrote the original draft of the manuscript; Fokin AA, Wycech Knight J, Darya M, Stalder R, Puente I, and Weisz RD performed manuscript review and editing; and all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Surgical and long-term functional outcomes of patients with Duchenne muscular dystrophy following spinal deformity correction

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Abstract

BACKGROUND

Life expectancy in patients with Duchenne muscular dystrophy (DMD) has improved due to advances in medical care. DMD patients develop progressive spinal deformity after loss of ambulatory function and onset of wheelchair dependence for mobility. There is limited published data on the effect of spinal deformity correction on long-term functional outcomes, quality of life (QoL), and satisfaction in DMD patients.

AIM

To investigate the long-term functional outcomes following spinal deformity correction in DMD patients.

METHODS

This was a retrospective cohort study from 2000-2022. Data was collected from hospital records and radiographs. At follow-up, patients completed the muscular dystrophy spine questionnaire (MDSQ). Statistical analysis was performed by linear regression analysis and ANOVA to analyse clinical and radiographic factors significantly associated with MDSQ scores.

RESULTS

Forty-three patients were included with mean age 14.4 years at surgery. Spino-pelvic fusion was performed in 41.9% of patients. Mean surgical time was 352.1 min and mean blood loss was 36% of estimated total blood volume. Mean hospital stay was 14.1 d. Postoperative complications occurred in 25.6% of patients. Mean preoperative scoliosis was 58°, pelvic obliquity 16.4°, thoracic kyphosis 55.8°, lumbar lordosis 11.1°, coronal balance 3.8 cm, and sagittal balance + 6.1 cm. Mean

surgical correction of scoliosis was 79.2% and of pelvic obliquity was 80.8%. Mean follow-up was 10.9 years (range: 2-22.5). Twenty-four patients had died at follow-up. Sixteen patients completed the MDSQ at mean age 25.4 years (range 15.2-37.3). Two patients were bed-ridden and 7 were on ventilatory support. Mean MDSQ total score was 38.1. All 16 patients were satisfied with the results of spinal surgery and would choose surgery again if offered. Most patients (87.5%) reported no severe back pain at follow-up. Factors significantly associated with functional outcomes (MDSQ total score) included greater duration of post-operative follow-up, age, scoliosis postoperatively, correction of scoliosis, increased lumbar lordosis postoperatively, and greater age at loss of independent ambulation.

CONCLUSION

Spinal deformity correction in DMD patients leads to positive long-term effects on QoL and high patient satisfaction. These results support spinal deformity correction to improve long-term QoL in DMD patients.

Key Words: Duchenne muscular dystrophy; Scoliosis; Surgical; Functional; Outcomes

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Core Tip: Duchenne muscular dystrophy (DMD) patients develop progressive spinal deformity after loss of independent ambulation. There is limited data on the effect of spinal deformity correction on long-term functional outcomes or satisfaction in DMD patients. This retrospective cohort study investigated long-term functional outcomes following spinal deformity correction in DMD patients, reporting clinical, surgical, radiographic and functional outcomes. All patients were satisfied with surgical outcomes at long-term follow-up. Surgical correction of spinal deformity can have favourable long-term effects on quality of life (QoL) in DMD patients. These results support surgical correction of spinal deformity to improve long-term QoL in DMD patients with spinal deformity.

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INTRODUCTION

Duchenne muscular dystrophy (DMD) is an inherited X-linked disease. Mutations in the Xp21 region of the X chromosome leads to absence of dystrophin resulting in skeletal, respiratory, and cardiac muscle weakness[1,2]. The natural history of untreated DMD is progressive muscle weakness with loss of independent ambulation by 9-10 years of age, as well as progressive cardiomyopathy and respiratory failure[3]. The mean survival in the absence of ventilatory support is 19.5 years[4]. Advances in medical therapy have improved the life expectancy for patients with DMD into their third and fourth decades of life[5]. Patients with DMD develop scoliosis after loss of ambulatory capacity and onset of wheelchair dependence for mobility[6]. The scoliosis is typically a long thoracolumbar C-shaped curve, with at least 85% of DMD patients experiencing a progression of deformity at a mean rate of 2.1° per month[7,8]. Respiratory function, measured by forced vital capacity (FVC), declines after loss of ambulation, and the rate of decline increases with progression of scoliosis[9]. Progressive spinal deformity also results in pelvic obliquity which impairs wheelchair sitting ability[10].

Bracing is ineffective in controlling progression of scoliosis in patients with DMD[10]. Surgical correction of scoliosis is indicated when scoliosis develops; surgical correction of scoliosis aims to correct spinal deformity, pelvic obliquity, and to prevent further curve progression with the aim to improve sitting balance, wheelchair mobility, and quality of life (QoL)[6,10-12]. DMD patients undergoing surgical correction of spinal deformity are at high risk of perioperative morbidity and mortality due to cardiomyopathy, respiratory dysfunction, reactions to anaesthetic agents, soft tissue compromise, osteoporosis, risk of instrumentation failure and prolonged intensive care unit (ICU) admission[6].

There is limited published data on the effect of surgical correction of spinal deformity on long-term functional outcomes, QoL and satisfaction in patients with DMD[13-15]. The aim of this study was to investigate the clinical, surgical and long-term functional results following surgical correction of scoliosis in patients with DMD, and to investigate clinical and radiological factors that predict long-term

functional outcomes following surgery.

MATERIALS AND METHODS

Study population and data collection

We retrospectively reviewed prospectively-collected data of 113 consecutive patients with DMD who were seen in a National Spinal Deformity Service (NSDS) between January 2000 and August 2022; forty-three of these patients (38%) who were wheelchair-dependent underwent correction of spinal deformity by posterior instrumented spinal fusion. All patients had an established diagnosis of DMD prior to referral to the NSDS and were receiving treatment. Indications for surgical correction of spinal deformity included progressive spinal deformity associated with deteriorating pain, sitting ability, function, and ability to provide nursing care. All patients had minimum data available including pre-operative clinical and demographic details, comorbidities, operative details including complications, pre- and post-operative radiographic parameters, and minimum post-surgical follow-up of two years. Exclusion criteria were patients diagnosed with a non-DMD myopathy, patients managed non-operatively, and patients without clinical, demographic, or operative details available for minimum follow-up of two years. Functional outcomes were assessed by the Muscular Dystrophy Spine Questionnaire (MDSQ)[16]. Cause of death was recorded for patients deceased at follow-up. This study was approved by the institutional review board and the requirement for a signed informed consent was waived.

Preoperative assessments

All patients were regularly reviewed in multidisciplinary medical clinics at our institution before and after surgery and assessed in dedicated multidisciplinary pre-assessment anaesthetic-led clinics to optimise their co-morbidities and provide preparation for spinal surgery. Preoperative assessments included overnight sleep studies, as well as anaesthetic, cardiology, dietician, gastroenterology, neurology, physiotherapy, and respiratory team reviews. All patients were wheelchair dependent at the time of referral to the NSDS.

Operative technique

All patients underwent correction of spinal deformity with posterior instrumented spinal fusion with use of hybrid (pedicle hooks/screws, sublaminar wires) or all pedicle screw instrumentation with local autograft and supplemental allograft bone. Pelvic fixation was performed with use of bilateral iliac screws. Intraoperative spinal cord monitoring was performed recording cortical/cervical somatosensory evoked potentials, which remained stable in all patients; transcranial motor evoked potentials were not recorded as none of the patients in the cohort were able to ambulate. Surgical technique also included use of arterial and central venous lines, prophylactic IV antibiotics, cell salvage, urinary catheter, and placement of a nasogastric tube.

Postoperative care

Patients were transferred to the ICU for postoperative care, including haemodynamic support, non-invasive ventilation (NIV), chest physiotherapy, early mobilisation into their wheelchair, and administration of nasogastric feeds. Patients were transferred to a normal ward when medically stable, and discharged to home when oral nutrition, pain control, pulmonary function and wound healing were stable and well-established.

Radiographic measurements

The radiological parameters of scoliosis were measured on spinal radiographs by two authors using digital software (Vue PACS, Carestream Health, United Kingdom) based on consensus agreement on the anatomical landmarks; the mean of the two values was used in the data set for analyses. The same landmarks were used for measurement of the curves on consecutive radiographs. Spinal radiographs were performed including posteroanterior and lateral sitting scoliosis views, and preoperative supine traction views. The following parameters were measured preoperatively and at follow-up: Scoliosis (Cobb angle), scoliosis flexibility index (%): [(Preoperative Cobb angle – supine traction Cobb angle)/(preoperative Cobb angle) × 100], pelvic obliquity (°), pelvic obliquity flexibility index (%): [(Preoperative pelvic obliquity angle – supine traction pelvic obliquity angle)/(preoperative pelvic obliquity angle) × 100], pre- and post-operative lumbar lordosis (T12-S1, °), pre- and post-operative thoracic kyphosis (T1-T12, °), pre- and postoperative sagittal balance (C7 plumb line, cm), pre- and post-operative coronal balance (C7 plumb line, cm), correction of scoliosis (%): [(Preoperative Cobb angle – postoperative Cobb angle)/(preoperative Cobb angle) × 100)], and correction of pelvic obliquity (%): [(Preoperative pelvic obliquity angle – postoperative pelvic obliquity angle)/(preoperative pelvic obliquity angle) × 100)].

Statistical analysis

All data were entered into Microsoft Excel and analysed using XLSTAT (Microsoft Corporation, Washington, United States). Clinical, operative, and both preoperative and postoperative radiographic variables for the patient cohort were analysed for their correlation with MDSQ total scores. Stepwise multiple linear regression analysis was performed to determine which individual quantitative variables correlated with MDSQ total scores. Quantitative variables included postoperative follow-up (years), age at final follow-up (years), age at loss of independent ambulation (years), age at surgery (years), duration of surgery (minutes), intraoperative blood loss (mLs), length of ICU stay postoperatively, total length of hospital stay (days) and radiographic measurements. Qualitative variables were analysed for their association with MDSQ total scores using ANOVA; qualitative variables included preoperative gastrostomy for nutrition, preoperative NIV, instrumented fusion to the pelvis, and occurrence of postoperative complications.

RESULTS

Characteristics of patients and surgical outcomes

A total of 43 patients with DMD underwent posterior correction of scoliosis with use of instrumentation and bone graft. The mean age at surgery was 14.4 years (SD: ± 1.6; range: 10.8-18.2). The clinical, operative, and pre- and post-operative radiographic details of the patient cohort are shown in Table 1. Four patients (9.3%) required gastrostomy placement for nutrition preoperatively, five patients (11.6%) required NIV preoperatively, and five patients had moderate left ventricular systolic dysfunction. The distal extent of spinal fusion was L4 in four patients (9.3%, Figure 1), L5 in 21 patients (48.8%), and the pelvis in 18 patients (41.9%, Figure 2).

The mean length of stay in ICU and in hospital are shown in Table 1. Patients requiring hospital stay greater than two weeks after surgery had ongoing nutritional or respiratory difficulties, including the establishment of NIV which required patient familiarisation and carer training before discharge. Postoperative complications included early deep wound infection treated by debridement, antibiotics and retention of instrumentation (four patients; 9.3%), removal of prominent pelvic screws and lateral connectors with trimming of the distal end of the rods while the spine was fused (one patient; 2.3%), pneumonia (two patients, 4.6%), and hepatotoxicity related to paracetamol administration (four patients; 9.3%). During the postoperative follow-up period, 24 patients (55.8%) died; the cause of death for these patients is shown in Table 2. The mean time between surgical correction of spinal deformity and death for these patients was 8.9 years (SD: ± 3.8 years; range 3.9-16.1 years). The incidence of surgical correction of scoliosis in patients with DMD has reduced over the two decades of the study period (32 patients underwent surgical correction of scoliosis from 2000-2010; 11 patients underwent surgical correction from 2011-2022).

Radiographic outcomes

Preoperative and postoperative radiographic parameters of spinal deformity for the cohort are shown in Table 1. The mean preoperative scoliosis was 57.5° (SD: ± 31.4°; range: 10°-120°), which was corrected to mean 15.9° postoperatively (SD: ± 16.6°; range: 0°-60°); resulting in mean scoliosis correction of 79.2% (SD: ± 18.7%; range: 40%-100%). The mean preoperative pelvic obliquity was 16.3° (SD: ± 13.2°; range: 0°-46°), which was corrected to mean 4.6° postoperatively (SD: ± 6.4°; range: 0°-23°), resulting in mean pelvic obliquity correction of 80.8% (SD: ± 25.2%; range: 19%-100%).

Thoracic kyphosis improved from mean 55.8° (SD: ± 28.7°; range: 0°-98°) preoperatively to mean 33.3° (SD: ± 7.7°; range: 20°-55°) postoperatively. Lumbar lordosis improved from mean 11.1° (SD: ± 20.7°; range: 0°-79°) preoperatively to mean 35.6° (SD: ± 8.9°; range: 20°-55°) postoperatively. Coronal balance was 3.8 cm (SD: ± 2.7 cm; range: 0-12 cm) preoperatively, improving to mean 0.68 cm (SD: ± 1.1 cm; range: 0-4.5 cm) postoperatively. Sagittal balance was 6.1 cm (SD: ± 6.4 cm; range: -11.4 to 1 cm) preoperatively, improving to mean -0.18 cm (SD: ± 1.6 cm; range -4 to 5.4 cm) postoperatively (Table 1).

Long-term functional status

Nineteen patients were alive and invited to complete the MDSQ to assess their functional outcome at long-term follow-up; two patients refused, and one patient was unable to report their outcomes. Sixteen patients completed the MDSQ at a mean postoperative follow-up of 10.9 years (SD: ± 4.7; range: 2-22.5 years); their mean age at completion of the MDSQ was 25.4 years (SD: ± 5.4; range: 15.2-37.3 years). Two (12.5%) of these patients were bed-ridden and 7 (43.75%) were on home ventilatory support. The mean MDSQ total score for these 16 patients was 38.1 (SD: ± 25.9; range: 1-100). All 16 patients were satisfied with the results of scoliosis surgery and reported that they would choose surgical correction of scoliosis again if offered. Fourteen patients (87.5%) reported no significant back or hip pain at long-term follow-up (Table 3).

Table 1 Summary demographics, and radiographic and operative details for patients with Duchenne muscular dystrophy and spinal deformity treated by posterior instrumented spinal fusion (mean ± SD)

Parameter (units)	Patient cohort
Number of patients (*n*)	43
Clinical/operative	
Age at surgery (yr)	14.4 (± 1.6; 10.8-18.2)
Spinal deformity, *n* (%)	
Scoliosis	33 (76.7)
Kyphoscoliosis	10 (23.3)
Single thoracolumbar curve	40 (93)
Double thoracic and lumbar curve	3 (7)
Gastrostomy for nutrition pre-operatively, *n* (%)	4 (9.3)
NIV pre-operatively, *n* (%)	5 (11.6)
Moderate left ventricular systolic dysfunction, *n* (%)	2 (4.6)
Operative time (minutes)	352.1 (± 72.7; 150-490)
Intraoperative blood loss (%; TBV)	36 (± 23.5; 12-150)
Distal fusion extent, *n* (%)	
L4	4 (9.3)
L5	21 (48.8)
Pelvis	18 (41.9)
Length of stay in ICU (days)	6.5 (± 3.1; 3-17)
Length of stay in hospital (days)	14.1 (± 7.2; 7-30)
Postoperative complications, *n* (%)	11 (25.6)
Early wound infections	4 (9.3)
Removal of instrumentation (pelvic fixation)	1 (2.3)
Hepatotoxicity	4 (9.3)
Pneumonia	2 (4.6)
Preoperative radiographs	
Scoliosis (Cobb angle; °)	57.5 (± 31; 10-120)
Scoliosis on traction radiographs (°)	32 (± 24; 0-92)
Scoliosis flexibility index (%)	52 (± 27.5; 7-100)
Pelvic obliquity (°)	16.3 (± 13.2; 0-46)
Pelvic obliquity on traction radiographs (°)	9.2 (± 9.3; 0-35)
Pelvic obliquity flexibility index (%)	58 (± 31; 0-100)
Thoracic kyphosis (T5-T12; °)	55.8 (± 28.1; 0-98)
Lumbar lordosis (T12-S1; °)	11.1 (± 20.3; 0-79)
Coronal balance (C7PL, cm)	3.8 (± 2.7; 0-12)
Sagittal balance (C7PL, cm)	6.1 (± 6.4; -11.4-1)
Postoperative radiographs	
Scoliosis (Cobb angle; °)	15.6 (± 16.4; 0-60)
Scoliosis correction (%)	79.2 (± 18.6; 40-100)
Pelvic obliquity (°)	4.6 (± 6.4; 0-23)
Pelvic obliquity correction (%)	80.8 (± 25; 19-100)

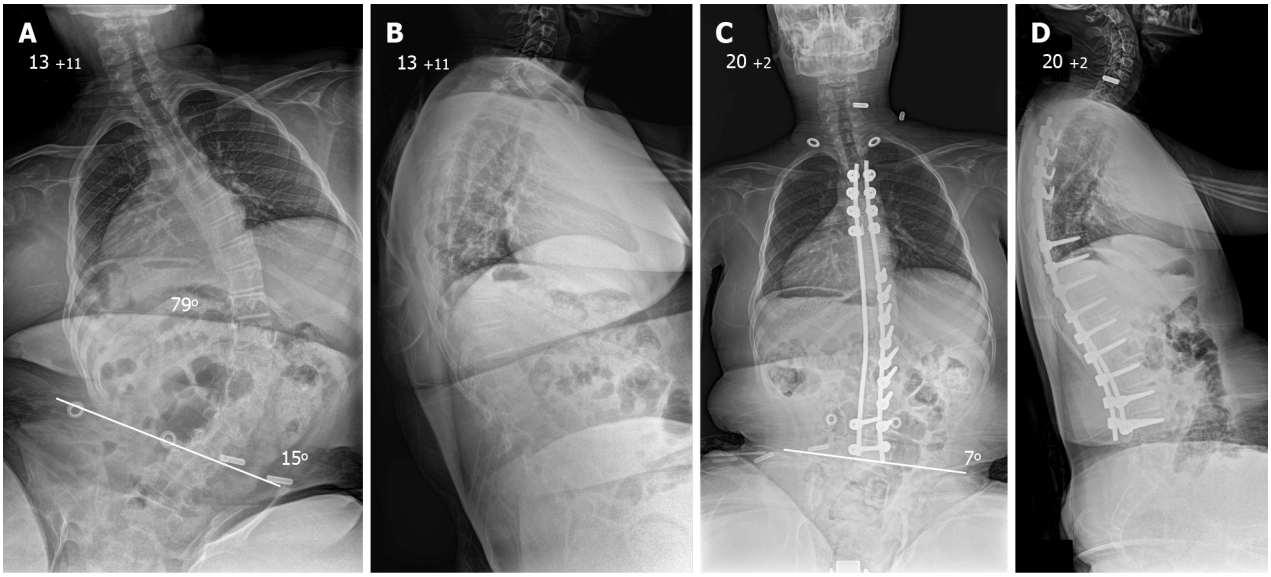
Thoracic kyphosis (T5-T12; °)	33.7 (± 7.3; 20-55)
Lumbar lordosis (T12-S1; °)	35.8 (± 8.7; 20-55)
Coronal balance (C7PL, cm)	0.68 (± 1.1; 0-4.5)
Sagittal balance (C7PL, cm)	-0.18 (± 1.6; -4 to 5.4)

C7PL: C7 plumb line; NIV: Non-invasive ventilation; TBV: Total blood volume; ICU: Intensive care unit; L: Luque sublaminar wires.

Table 2 Aetiology of death during follow-up in patients with Duchenne muscular dystrophy after surgical correction of spinal deformity, *n* (%)

Cause of death	Number of patients
Respiratory failure	10 (41.6)
Pneumonia	7 (29.2)
Severe left ventricular systolic dysfunction	6 (25)
Tracheostomy bleeding	1 (4.2)

In our cohort of 43 patients with Duchenne muscular dystrophy who underwent surgical correction of spinal deformity, 24 patients died during follow-up due to respiratory failure, pneumonia, severe left ventricular systolic dysfunction, or tracheostomy bleeding.



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Figure 1 A patient aged 13 years and 11 months. A and B: With a thoracolumbar collapsing kyphoscoliosis and associated pelvic obliquity; C and D: He underwent a posterior spinal fusion extending from T3-L4 which achieved a balanced spine in the coronal and sagittal planes with good correction of the spinal and pelvic misalignment.

Effect of clinical and radiographic factors with long-term functional status

The relationship between clinical and radiographic parameters and the functional outcomes (MDSQ total score) was assessed (Table 4). Greater duration of postoperative follow-up, increased patient age, higher degree of scoliosis postoperatively, lesser correction of scoliosis, and increased lumbar lordosis postoperatively were significantly associated with lower MDSQ total scores. Greater age at loss of independent ambulation was significantly associated with higher MDSQ total scores.

The demographic details, surgical techniques, radiographic and functional outcomes in our cohort of DMD patients managed by surgical correction of scoliosis are compared with previously published series in Table 5. Our cohort is one of a few published studies reporting both surgical and functional outcomes at long-term follow-up using a validated disease-specific patient-reported outcome measure, the MDSQ. The mean MDSQ total score reported by our cohort at long-term follow-up (completed at mean age 25.4 years) following surgical correction of scoliosis compared favourably with previous published studies, despite greater duration of follow-up (Table 5). The follow-up (mean 10.9 years) for

Table 3 Muscular Dystrophy Spine Questionnaire results

Item	Question	Item mean score	SD	Range
	"Last week how difficult was it to…"			
1	Get dressed	0	0	0
2	Go to the toilet	0	0	0
3	Lean forward and reach out in front of me	1.06	1.34	0-4
4	Move myself around in bed	0.5	0.8	0-2
5	Write (*e.g.*, a short note and sign it)	1.06	1.69	0-4
6	Do up my zipper	0	0	0
7	Sit up in bed	1.93	1.52	0-4
8	Lift my arms to reach	0.8	1.25	0-4
9	Lift my head when lying down	0.9	1.18	0-4
10	Transfer or move from one position to other	0.4	0.89	0-3
11	Use both hands (*e.g.*, put toothpaste on my toothbrush)	0.8	1.16	0-4
12	Use 1 arm and hand for balance while reaching in front with the other hand	0.75	1.12	0-4
13	Hold a spoon or fork by myself as part of a meal	0.8	1.47	0-4
14	Lift a cup/glass to my mouth by myself to drink	0.68	1.25	0-4
15	Sit comfortably in a good position, in my wheelchair all day	2.06	1.61	0-4
16	Shift weight or change my hip position in my wheelchair	0.68	1.01	0-3
17	Use the computer	2	1.46	0-4
18	Finish brushing my teeth	0.56	1.15	0-4
19	Change my arm position in my arm rests	1.18	1.51	0-4
20	Turn to reach for something	0.5	1.09	0-4
21	Bend forwards to eat	1	1.36	0-4
22	Sit in my chair all day without breaks	2	1.86	0-4
23	Sleep comfortably in bed	2.375	1.6	0-4
24	Sit at the table for meals	3	1.3	0-4
25	Bend forward to drink from a straw	1.43	1.67	1-4
26	Keep balance while sitting in my wheelchair	3	1.31	0-4
27	Look good while sitting in my wheelchair	3	1.46	0-4
	"Last week, how bad was…"			
28	Pain in my hips or back last week	3.125	1.2	0-4
29	Me being out of breath last week	2.43	1.8	0-4
	Total score	38.1	25.9	1-100

Items 1-27 are rated 0-4 (0: I can't do it at all; 1: Very difficult; 2: Moderately difficult; 3: A little difficult; 4: Not difficult); items 28 and 29 are rated 0-4 (0: Extremely bad; 1: Very bad; 2: Bad; 3: A little bit bad; 4: Not a problem). Results of the Muscular Dystrophy Spine Questionnaire (16) completed by patients (n = 16) with Duchenne Muscular Dystrophy at long-term follow-up after surgical correction of scoliosis (mean follow-up: 11 years).

the assessment of functional outcomes in our cohort was the longest among published studies. The complications and hospital stay outcomes in our cohort of patients are compared with previously published series in Table 6. In our cohort of DMD patients, there was a low overall incidence of postoperative complications (25.6%), and no perioperative deaths (Table 6).

Table 4 Correlation between clinical, operative, and both preoperative and postoperative radiographic variables with patient-reported Muscular Dystrophy Spine Questionnaire total scores: Quantitative clinical, operative and radiographic variables were assessed for correlation with Muscular Dystrophy Spine Questionnaire total scores by linear regression analysis; standardised coefficients are displayed

Clinical/radiological variable	Value/coefficient estimate (95%CI)	*P* value
Clinical/Operative parameters		
Postoperative follow-up (yr)	-0.766 (-1.138, -0.394)	0.001[a]
Age (yr)	-0.651 (-1.086, -0.216)	0.006[a]
Age at loss of independent ambulation (yr)	0.496 (0.127, 0.865)	0.013[a]
Age at surgery (yr)	-0.146 (-0.519, 0.227)	0.410
Preoperative gastrostomy (Y/N)[1]	-0.036 (-1.072, 1.001)	0.941
Preoperative NIV use (Y/N)[1]	0.110 (-0.731, 0.951)	0.777
Duration of surgery (minutes)	-0.030 (-0.603, 0.543)	0.911
Intraoperative blood loss (%, TBV)	-0.297 (-0.841, 0.247)	0.257
Instrumented fused to pelvis (Y/N)[1]	0.542 (-0.221, 1.306)	0.145
Length of ICU stay (days)	0.123 (-1.010, 1.255)	0.817
Length of stay in hospital (days)	-0.535 (-1.663, 0.593)	0.322
Postoperative complications (Y/N)[1]	0.010 (-0.703, 0.723)	0.975
Preoperative radiographic parameters		
Scoliosis (Cobb angle) (°)	0.268 (-5.330, 5.867)	0.907
Scoliosis on traction radiographs (Cobb angle)	-2.771 (-9.706, 4.164)	0.351
Scoliosis flexibility index (%)	-2.797 (-6.952, 1.359)	0.144
Pelvic obliquity (°)	-0.531 (-4.784, 3.723)	0.761
Pelvic obliquity on traction radiographs (°)	1.036 (-4.511, 6.582)	0.651
Pelvic obliquity flexibility index (%)	1.368 (-2.465, 5.200)	0.401
Lumbar lordosis (T12-S1; °)	0.346 (-1.880, 2.571)	0.706
Thoracic kyphosis (T5-T12; °)	0.153 (-2.283, 2.589)	0.878
Sagittal balance (C7PL, cm)	0.533 (-1.041, 2.106)	0.424
Coronal balance (C7PL, cm)	0.213 (-1.401, 1.828)	0.748
Postoperative radiographic parameters		
Scoliosis (Cobb angle) (°)	-3.005 (-4.718, -1.292)	0.004[a]
Correction of scoliosis (%)	2.167 (1.053, 3.282)	0.002[a]
Pelvic obliquity (°)	0.367 (-0.765, 1.499)	0.468
Correction of pelvic obliquity (%)	0.433 (-0.263, 1.129)	0.185
Lumbar lordosis (T12-S1; °)	-0.642 (-1.184, -0.100)	0.027[a]
Thoracic kyphosis (T5-T12; °)	0.043 (-0.345, 0.430)	0.802
Sagittal balance (C7PL, cm)	-0.190 (-0.768, 0.389)	0.464
Coronal balance (C7PL, cm)	0.886 (-0.215, 1.987)	0.099

[1]Indicates qualitative variable.
[a]Indicates statistically significant result ($P < 0.05$).
L: Luque sublaminar wires; C7PL: C7 plumb line; NIV: Non-invasive ventilation; TBV: Total blood volume; ICU: Intensive care unit.

DISCUSSION

Surgical correction of spinal deformity in patients with DMD aims to prevent curve deterioration, correct spinal balance and pelvic obliquity in order to permit more comfortable positioning, sitting in

Table 5 Clinical and radiographic outcomes of surgical correction of scoliosis in patients with Duchenne muscular dystrophy, the current and previous studies reporting clinical and radiographic outcomes are summarized

Study	Current	Heller	Sengupta		Marsh	Cervellati	Hahn	Mehta	Modi	Takaso	Debnath		Alexander	Duckworth	Suk	Nedelcu	Scannell		Takaso	Yang
Year	2022	2001	2002		2003	2004	2008	2009	2010	2010	2011		2013	2014	2014	2016	2017		2018	2020
Patients (*n*)	43	31	50		30	20	20	36	18	28	22	18	28	26	40	13	47	13	27[1]	99
Instrumentation (*n*)	PH/PS/SL or PS	I	L/G or L-rod	L/G or L-rod	C/HL/USS/S	L/CD	PS/G	PS	PS	PS	SL	PS	L/G and/or PS	SL or PS	CD	UR	L	PS	PS	CD
Distal instrumented level [*n* = (if subset)]	L4 (21), L5 (4), P (18)	SP	P (31)	L5 (19)	P	SP	P	L5 (26); P (10)	L5 (7); SP (11)	L5	P	L5	NA	L4/5 (14); SP (12)	LL (5); P (40)	SP	P	P	L5	LL (5); P (94)
Age at surgery (yr)	14.4	14.1	14	11.7	14.7	13	14	13.5	14.4	13	12.5	11.8	14.2	14.2	14.9	12.7	13	14	13.5	15.1
Pre-op FVC%	NA	54.3	44	58	33	NA	55	NA	NA	NA	57	53	NA	NA	NA	NA	59	48	NA	NA
Post-op FVC%	NA	NA	NA	NA	NA	NA	54	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FVC% at final F/U	NA	52.7	NA	NA	NA	NA	47	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pre-op scoliosis (°)	57.5	48.6	48.4	19.8	61	48	44	71	76.4	74	45.3	42.8	56.4	59	65.5	30	31	43	70	65.8
Scoliosis (initial post-op) (°)	NA	12.5	16.7	3.2	24.2	22	10	25.5	30.1	14	NA	NA	21.6	13	NA	2	16	12	15	NA
Correction of scoliosis (%)	79.2	74.3	66	80	60.3	54.2	77	65	63.3	81	NA	NA	61.7	78	NA	93.3	NA	NA	78.6	50.6
Scoliosis at final F/U (°)	15.6	12.5	22	5.2	NA	28	9	28.5	31.3	17	17.7	7.3	NA	NA	36.2	4.2	21	12	17	32.5
Scoliosis loss of correction (°)	NA	0	5.2	2	NA	6	1	3	1.2	3	NA	NA	NA	NA	NA	2.2	5	0	2	NA
Pre-op pelvic obliquity (°)	16.3	18.2	19.8	8.9	18.1	19.8	14	14.8	18.1	9	14.5	11.2	NA	21	20.7	7.7	7	6	15	21
Pelvic obliquity (initial post-op) (°)	NA	3.8	7.2	2.2	NA	10	3	6.7	8.6	3	NA	NA	NA	3	NA	0.6	5	3	5	NA
Correction of pelvic obliquity (%)	80.8	79.1	63.6	76	NA	49.5	65	54.7	52	66.7	NA	NA	NA	85.7	NA	92.2			66.7	53.8
Pelvic obliquity at final F/U (°)	4.6	5.1	11.6	2.9	NA	NA	3	9.3	8.8	6	5.6	2	NA	NA	11.4	1.5	5	2	6	9.7
Fusion to sacropelvis (%)	41.9	100	100	0	100	100	100	27.8	66.7	0	100	0	NA	46.2	89.9	100	100	100	0	94.9

Duration of surgery (min)	352.1	363	310	240	212	180	307	332	348	282	260	216	NA	260	NA	170	227	332	270	NA
Blood loss (mL or % TBV)	36%	3373	4100	3300	4900	1200	2642	2955	2561	950	3400	2000	NA	1882	NA	2553	1327	1596	910	NA
F/U (yr)	10.9	1.8	4.6	3.5	Until discharge	5	5.2	1.6	1.4	3.3	4.5	2.3	1	2	3.86	6.9	4	4	3	6.6
MDSQ score at F/U	38.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	35.1	NA	NA	NA	NA	NA

[1]This cohort included 20 Duchenne muscular dystrophy patients and 7 patients with spinal muscular atrophy.

C: Colorado; CD: Cotrel-Dubousset; FVC: Forced vital capacity; F/U: Follow-up; G: Galveston technique; H: Harrington; HL: Harrington-Luque; L: Luque sublaminar wires; LL: Lower lumbar; MDSQ: Muscular Dystrophy Spinal Questionnaire; P: Pelvis; PH: Pedicle hooks; PS: Pedicle screws; S: Synergies; SL: Sublaminar instrumentation; SP: Sacropelvis; USS: AO universal spine system; NA: Not available; TBV: Total blood volume; NA: Not available.

wheelchair, day-to-day activities and QoL[10]. There is limited published literature reporting surgical and functional results at long-term follow-up after surgical correction of spinal deformity in patients with DMD. This retrospective cohort study describes validated patient-reported functional outcomes at the longest available follow-up and surgical outcomes following correction of scoliosis in DMD patients.

Posterior instrumented spinal fusion is indicated for treatment of progressive scoliosis in patients with DMD[12,17,18]. Surgical correction of spinal deformity is recommended before respiratory and cardiac function deteriorate to the extent that general anaesthesia and complex major surgery are unsafe and whilst spinal deformity remains flexible[19-21]. Early surgery may lead to potential sitting height loss, but this is not perceived as a problem[22]. Luque instrumentation and sublaminar wiring for spinal stabilisation in patients with DMD resulted in high patient satisfaction[23]. Results of surgical correction with hybrid constructs utilising pedicle-based anchors and/or instrumentation to the pelvis indicated improved radiographic correction of spinal deformity[24]. Subsequent comparison of sublaminar instrumentation, hybrid instrumentation, and pedicle screw constructs demonstrated that pedicle screw constructs provided a marginally better correction and maintained coronal deformity correction better at follow-up[25]. Pedicle screw instrumentation in patients with DMD achieves better correction of both spinal deformity and pelvic obliquity[10,26]. The patients in our cohort were treated by hybrid or all pedicle screw instrumentation. This resulted in a satisfactory correction of scoliosis from 57.5° to 15.6° at final follow-up (mean 79.2% correction), compared to other reported cohorts of DMD patients managed by hybrid and all pedicle screw constructs (Table 5).

The distal extent of spinal instrumentation to correct spinal deformity and pelvic obliquity remains controversial in the published literature. Traditional management principles include fixation to the sacrum or pelvis to correct pelvic obliquity and improve sitting balance[27]. Distal fixation to the lower lumbar spine with Luque instrumentation has been associated with progression of pelvic obliquity postoperatively, whereas no progression occurred after fixation to the pelvis[28]. Distal instrumentation to the lower lumbar spine using pedicle screws may produce satisfactory results when surgery is performed at a younger age and with milder curves without significant pelvic obliquity (< 15°)[27]. Pedicle screw fixation in multiple levels of the thoracic and lumbar spine provides sufficient stability for spinal correction and mild pelvic obliquity correction. In the presence of significant pelvic obliquity, a combination of L5 pedicle screws and iliac screws provides a stable foundation to correct spinal and

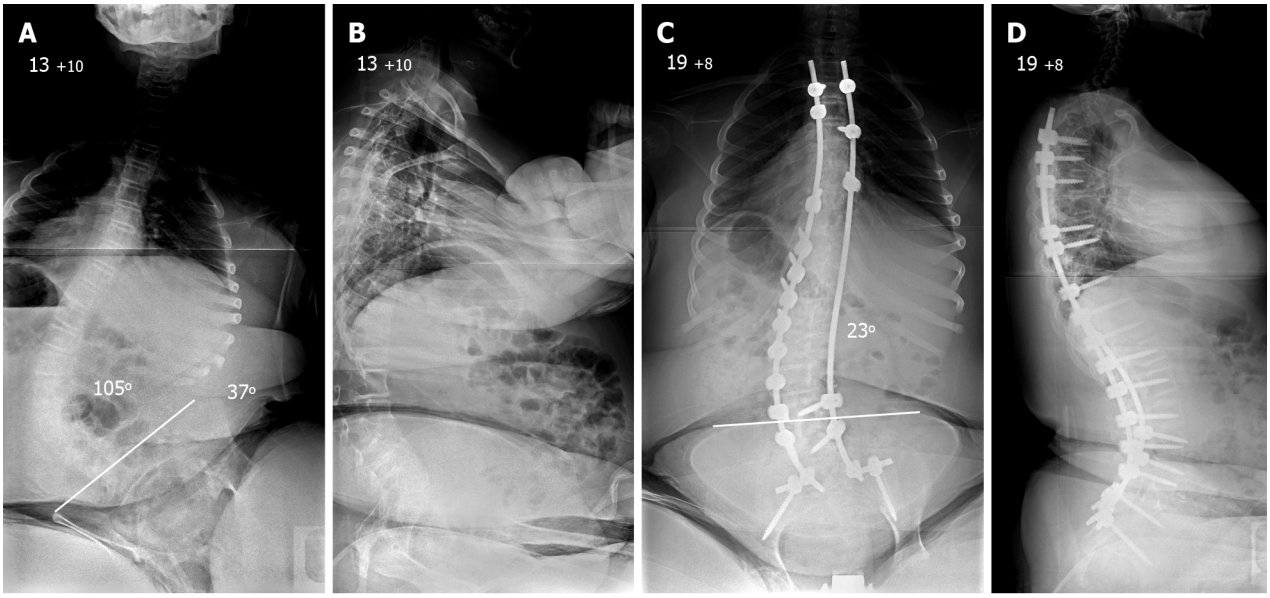
Table 6 Complications and hospital stay outcomes following surgical correction of scoliosis in patients with Duchenne muscular dystrophy; the current and previous studies reporting complications and hospital stay outcomes are summarised

Study	Current	Heller	Sengupta		Marsh	Cervellati	Hahn	Mehta	Modi	Takaso	Debnath		Alexander	Duckworth	Suk	Nedelcu	Scannell	
Year	2022	2001	2002		2003	2004	2008	2009	2010	2010	2011		2013	2014	2014	2016	2017	
Patients (*n*)	43	31	50		30	20	20	36	18	28	22	18	28	26	40	13	47	13
Instrumentation (*n*)	PH/PS/SL or PS	I	L/G or L-rod	L/G or L-rod	C/HL/USS/S	L/CD	PS/G	PS	PS	PS	SL	PS	L/G and/or PS	SL or PS	CD	UR	L	PS
Distal instrumented level (*n*)	L4 (21), L5 (4), P (18)	SP (31)	P (31)	L5 (19)	P (30)	SP (*n* = 20)	P (*n* = 20)	L5 (26), P (10)	L5 (7), SP (11)	L5 (28)	P (22)	L5 (18)	NA	L4/5 (14), SP (12)	LL (5), P (40)	SP (13)	P (47)	P (13)
ICU stay (days) (patient, *n*)	6.5	3	NA	NA	NA	2	3.2	0.4 (*n* = 10)	0.45 (*n* = 4)	NA	2.3	1.8	NA	4.5	NA	NA	2	4
Hospital stay (days)	14.1	21	16.7	7.7	22	NA	19	17.9	19	NA	8.5	7	NA	13	NA	NA	7	7
Complications (%; *n*)	25.6%; WIRI (4), ROPI (1), pn (2), hep (4)	D (5%), pu (24%), instr 10%, WHP (28%), GI (23%), Thr (5%), Bl (5%)	16%; DIAR (1), RI (4)	10.5%; DIARI (1); RI (1)	30%; PE (1), REI (4), CA (1), TR (2), LFT (1), Pn (2), WI (2)	30%; CA (1), NB (1), SPS (1), Instr (3)	20%; D (1), PO (1), WHP (1), DIARI (1)	47%; D (1), Instr (3), Co (7), PI (6)	48.1%; D (CA; 1), UTI (2), Co (6), HT (3), TIL (1), AT (2), CBP (2), Instr (1)	17.9%; I (5)	54.5%; Bl (2), WI (5), PRS (3), Instr (2)	16.7%; WI (2), Instr (1)	17.8%; WI (3), An (2)	38.5%; WI (6), Hep (4), GI (2), Pn (2)	52.5%; Pu (20), WI (1)	53.8%; WHP (3), WI (2), Instr (2),	68%; Instr (12), Inf (2)	54%; PJK (1), WI (3)

C: Colorado; CD: Cotrel-Dubousset; FVC: Forced vital capacity; G: Galveston technique; H: Harrington; HL: Harrington-Luque; L: Luque sublaminar wires; LL: Lower lumbar; P: Pelvis; PS: Pedicle screws; S: Synergies; SL: Sublaminar instrumentation; SP: Sacropelvis; USS: AO universal spine system; NA: Not available. Complications abbreviations: An: Aneamia; AT: Atelectasis; Bl: Bleeding; CA: Cardiac arrest; CBP: Convex back pain; Co: Coccygodynia; D: Death; DIAR: Deep infection and reinstrumentation; DIARI: Deep infection and removal of instrumentation; GI: Gastrointestinal; Hep: Hepatotoxicity; HT: Haemothorax; I: Ileus; Inf: Infections (not categorised); Instr: Instrumentation complication/failure; LFT: Abnormal liver function tests; NB: Neurogenic bladder; PE: Pleural effusion; PI: Prominent instrumentation; PJK: Proximal junction kyphosis; Pn: Pneumonia; PO: Pulmonary oedema; PRS: Prolonged respiratory support; Pu: Pulmonary; REI: Reintubation; RI: Revision of instrumentation; ROPI: Removal of prominent instrumentation; SPS: Sacral pressure sore; Thr: Thrombosis; TIL: Tingling in legs; TR: Tracheostomy; UTI: Urinary tract infection; WHP: Wound healing problems; WI: Wound infection; WIRI: Wound infection and retention of instrumentation; NA: Not available.

pelvic deformity[10]. Segmental pedicle screw instrumentation and fusion to lower lumbar spine may be sufficient if the curve apex is at L2 or higher and if the L5 tilt is less than 15°[29]. It is important to balance this, with avoidance of progression of pelvic obliquity and the potential for further surgery in patients with DMD whose cardiopulmonary health will predictably deteriorate[24]. In our cohort of DMD patients treated with hybrid and all pedicle screw constructs, satisfactory correction of pelvic obliquity was achieved from mean 16.4° preoperatively to 4.6° postoperatively (mean correction of 80.8%) (Table 5).

Hybrid constructs have been associated with a high incidence of instrumentation-related complications (21%), pseudarthrosis (10%), junctional and thoracic kyphosis[30-32]. All pedicle screw constructs provide better maintenance of coronal correction, with loss of correction only 1°-3° over follow-up



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Figure 2 A patient aged 13 years and 10 months. A and B: With a thoracolumbar collapsing kyphoscoliosis and severe associated pelvic obliquity which was rigid on supine traction; C and D: A posterior spinal fusion extending from T3 to the sacrum with pelvic fixation of the rods achieved good correction of the spino-pelvic imbalance in the coronal and sagittal planes.

(Table 5). Rigid pedicle screw instrumentation also allows immediate postoperative mobilisation which is critical for patients with DMD to avoid respiratory complications[10]. Pelvic fixation has been associated with a higher complication rate compared to distal fixation to the lower lumbar spine, including increased blood loss and length of hospital stay[27]. A higher incidence of deep wound infections postoperatively has been reported in patients with DMD, but no increased risk of blood loss, compared to other neuromuscular conditions[33].

Risk factors for prolonged postoperative ICU stay for DMD patients after spinal surgery have been reported, including greater preoperative scoliosis angle, greater estimated blood loss during surgery, and cardiopulmonary complications[34]. Preoperative forced expiratory volume < 40% has been associated with development of respiratory complications postoperatively[34]. DMD patients in our cohort had a low incidence of complications (25.6%), similar total hospital stay (mean 14.1 d) but greater ICU stay (mean 6.5 d) after spinal surgery compared to other cohorts in the published literature (Table 6); this may be due to availability and selection of patients for postoperative care in ICU. All patients in our cohort were routinely transferred to ICU for postoperative care, whereas this was reserved for selected patients in previous cohorts.

Respiratory function declines most rapidly in patients with DMD during the accelerated growth spurt in adolescence[35]. FVC in patients with DMD reduces at a rate of 4% per year after loss of ambulation, and an additional 4% decline is associated with each 10° progression of scoliosis[9]. Spinal surgery improves postoperative respiratory muscle strength; respiratory muscle training can reduce perioperative complications and effectively maintain pulmonary function perioperatively[36]. Following surgical correction of spinal deformity, FVC decline improved from 4% per year preoperatively to 1.75% per year postoperatively[37]. Spinal deformity correction is associated with a lesser rate of decrease in FVC, reduced need for NIV, and patients reporting that they can breathe more easily postoperatively [15]. DMD patients with high-risk pulmonary dysfunction (FVC < 30%) and severe scoliosis can undergo spinal surgery with all pedicle screw instrumentation and general anaesthesia after respiratory muscle training. Surgical correction was maintained at follow-up, while patients and parents were highly satisfied and believed scoliosis surgery improved their function, sitting balance and QoL despite high rates for significant complications[38].

Surgical treatment for DMD patients with scoliosis delays the decline in pulmonary function and is correlated with improved survival[13]. The combination of surgical correction of spinal deformity and provision of home nocturnal ventilation has an additive effect on survival for patients with DMD; the presence of severe cardiomyopathy is also a determining factor in life expectancy in patients with DMD [3]. Surgical management of scoliosis in DMD patients has been associated with a significantly lower mortality rate at 6.4 years follow-up, compared to those managed without surgery (8.1% *vs* 22%)[13].

There is limited evidence in the literature reporting validated patient-reported outcome measures following surgical correction of spinal deformity in patients with DMD. Previous studies have described patients and their carers reporting improved sitting balance, wheelchair mobility, appearance, functional freedom of their arms, nursing care, satisfaction and respiratory function following surgery compared to their preoperative status[39]. The MDSQ is a validated patient-reported questionnaire

assessing symptoms and functional abilities important to children with scoliosis and muscular dystrophy[16]. A single study previously reported MDSQ scores in DMD patients with scoliosis treated surgically or nonoperatively at mean 3.8 years follow-up; significantly higher scores were reported by patients after spinal surgery compared to those managed nonoperatively. Better scores were reported by patients managed surgically regarding sitting in wheelchair or chairs, mobility and positioning in wheelchair, appearance, pain, and respiratory symptoms when sitting, compared to patients treated conservatively[15].

This study is the first to describe functional outcomes for DMD patients following surgical correction of scoliosis at long-term follow-up (mean 10.9 years). The MDSQ total score was 38.1, similar to previously reported postoperative scores at follow-up (Table 5), with higher scores for sitting comfortably in wheelchair, sleeping comfortably in bed, pain in my hips and back, and being out of breath (Table 3). Factors significantly associated with lower MDSQ total score, and therefore predictive of worse long-term function, included greater duration of post-operative follow-up, increased patient age, greater residual scoliosis postoperatively, lesser degree of scoliosis correction, and increased lumbar lordosis postoperatively (Table 5). Greater age at loss of independent ambulation was significantly associated with higher MDSQ total scores. Due to the natural history of progressive muscular weakness causing gradual functional decline in patients with DMD, it follows that greater duration of postoperative follow-up and higher age at last assessment are associated with worse function as indicated by the MDSQ. Greater residual scoliosis and lesser scoliosis correction at follow-up suggest a more severe preoperative spinal deformity probably due to a more severe underlying disease and therefore were also associated with worse function assessed by the MDSQ. Conversely, greater age at loss of independent ambulation may indicate a less severe disease course and be related to higher MDSQ total scores (Table 5).

The relationship between increased lumbar lordosis postoperatively and worse functional scores is unclear. Five patterns of sagittal plane spinal deformity have been described in DMD patients[40]; greater number of patients will need to be assessed with clinical, radiological, and functional outcomes to determine optimal restoration of lumbar lordosis and sagittal profile for non-ambulatory DMD patients. Patients in our cohort reported high satisfaction at long-term follow-up after surgery and all replied that they would choose surgical correction of spinal deformity again if offered. These results indicate that surgical correction of spinal deformity can improve QoL in DMD patients and is, therefore, indicated in the presence of a severe/progressive deformity despite an increased risk of complications compared to patients with no underlying neuro-disability.

This study has strengths and limitations. This is a single-centre retrospective cohort review assessing surgical results and validated patient-reported functional outcomes using the MDSQ following surgical correction of spinal deformity in DMD patients at the longest reported postoperative follow-up (mean 10.9 years). This provided a standardised approach for the treatment and management of these patients. Increased number of patients completing MDSQ at long-term follow-up may help to investigate the relationship between sagittal spinal balance and functional scores. Further tests of function have been reported and may help to provide a comprehensive functional assessment in patients with DMD. The manual muscle test is a quantitative muscle test. The modified Rancho scale and Swinyard scale assess mobility and function in neuromuscular patients. However, these tests of function may not be useful in the evaluation of function in patients with advanced DMD and scoliosis[15].

CONCLUSION

This study reports surgical and validated patient-reported functional outcomes at long-term follow-up after surgical correction of scoliosis in DMD patients. Posterior instrumented spinal fusion is associated with satisfactory correction of spinal deformity and pelvic obliquity which is maintained at follow-up. All patients were satisfied with surgical results at long-term follow-up. Long-term functional outcomes were predicted by patient age, age at loss of ambulation, duration of follow-up, severity of residual scoliosis postoperatively, degree of scoliosis correction and lumbar lordosis. Surgical correction of spinal deformity can have positive long-term effects on QoL and is recommended in DMD patients with spinal deformity.

ARTICLE HIGHLIGHTS

Research background

Life expectancy in patients with Duchenne muscular dystrophy (DMD) has improved due to advances in medical care. DMD patients developed progressive spinal deformity after loss of ambulatory function and onset of wheelchair dependence for mobility. Surgical correction of scoliosis in patients with DMD aims to improve sitting balance, wheelchair mobility and quality of life (QoL). DMD patients undergoing surgical correction of spinal deformity are at high risk of perioperative morbidity and

mortality.

Research motivation

There is limited published data on the effect of spinal deformity correction on long-term functional outcomes, QoL, and satisfaction in DMD patients.

Research objectives

The aim of this study was to investigate the clinical, surgical, and long-term functional results following surgical correction of scoliosis in patients with DMD, and to investigate clinical and radiological factors that predict long-term functional outcomes following surgery.

Research methods

This was a retrospective cohort study, reviewing data from 113 consecutive patients with DMD who were seen in a National Spinal Deformity Service between January 2000 and August 2022. Data were collected from hospital records and radiographs. All patients had minimum data available including pre-operative clinical and demographic details, comorbidities, operative details including complications, pre- and post-operative radiographic parameters, and minimum post-surgical follow-up of two years. Functional outcomes were assessed by the muscular dystrophy spine questionnaire (MDSQ).

Research results

Forty-three patients underwent correction of spinal deformity by posterior instrumented fusion, comprising 38% of the whole cohort (43/113 patients); spinopelvic fusion was performed in 41.9% of patients, the mean surgical time was 351 min, mean blood loss was 36% of estimated total blood volume, mean hospital stay was 14.1 d, and postoperative complications occurred in 25.6% of patients. The mean correction of scoliosis was 79.2%, mean correction of pelvic obliquity was 80.8%, and mean post-surgical follow-up was 10.9 years. Mean MDSQ total score at follow-up was 38.1; all 16 patients completing the MDSQ were satisfied with the results of spinal surgery and would choose surgery again if offered, and most patients (87.5%) reported no severe back pain at follow-up. Factors significantly associated with functional outcomes (MDSQ total score) included greater duration of post-operative follow-up, age, scoliosis postoperatively, correction of scoliosis, increased lumbar lordosis postoperatively, and greater age at loss of independent ambulation.

Research conclusions

Spinal deformity correction in DMD patients leads to positive long-term effects on QoL, and high patient satisfaction. These results support spinal deformity correction to improve long-term QoL in DMD patients.

Research perspectives

Posterior instrumented spinal fusion is indicated for treatment of progressive scoliosis in patients with DMD; surgical correction of spinal deformity is recommended before respiratory and cardiac function deteriorate to the extent that general anaesthesia and complex major surgery are unsafe and whilst spinal deformity remains flexible. DMD patients in our cohort had a low incidence of complications compared to other cohorts in the published literature. Surgical management of scoliosis in DMD patients has been associated with a significantly lower mortality rate at 6.4 years compared to those managed without surgery, and patients and parents were highly satisfied and believed scoliosis surgery improved their function, sitting balance, and QoL. Surgical correction of spinal deformity can improve QoL in DMD patients and is, therefore, indicated in the presence of a severe/progressive deformity despite an increased risk of complications compared to patients with no underlying neurodisability.

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FOOTNOTES

Author contributions: Tsirikos AI was the guarantor, treated the patients, designed the study, participated in acquisition, analysis and interpretation of the data and drafted the manuscript; Arshad A and Roberts S participated in analysis and interpretation of the data and drafted the manuscript.

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Informed consent statement: The requirement for a signed informed consent was waived.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Incidence of sports-related sternoclavicular joint dislocations in the United States over the last two decades

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Abstract

BACKGROUND

Epidemiological understanding of acute sternoclavicular (SC) dislocations secondary to sports across the United States is poorly defined.

AIM

To identify and assess epidemiological trends of SC dislocations occurring secondary to sports-related mechanisms across United States over the past two decades.

METHODS

This cross-sectional, descriptive epidemiological study evaluates epidemiological trends of SC dislocations from sports that present to emergency departments (EDs) across the United States. Data were obtained from the National Electronic Injury Surveillance System database spanning two decades. Data on incidence,

patient demographics, mechanisms of injury, dislocation types, incident locales, and patient dispositions were collected.

RESULTS

1622 SC dislocations occurred nationwide from 2001 to 2020 [incidence = 0.262/1000000 people, confidence interval (CI) = 0.250-0.275], comprising 0.1% of shoulder/upper trunk dislocations. Most patients were male (91%, *n* = 1480) and aged 5-17 (61%, *n* = 982). Football, wrestling, and biking were the most frequently implicated sports, with contact sports responsible for 59% of athletic injuries (*n* = 961). Recreational vehicle-related sports injuries, such as all-terrain vehicles, dirt bikes, and mopeds accounted for 7.8% of all injuries (*n* = 126), with dirt bikes specifically comprising 3.7% (*n* = 61). Ultimately, 82% were discharged from the ED (*n* = 1337), 12% were admitted (*n* = 194), and 6% were transferred (*n* = 90). All recorded posterior dislocations were admitted or transferred from the ED. Patients sustaining SC dislocations from contact sports had a significantly increased risk of hospital admission or transfer rather than discharge from the ED as compared to patients whose injuries were from non-contact sports (incidence rate ratio = 1.46, CI: = 1.32-1.61, $P < 0.001$).

CONCLUSION

SC dislocations from sports continue to be rare with a stably low incidence over the past two decades, likely comprising a smaller proportion of shoulder dislocations than previously thought. Contact sports are a frequent source of injury, especially among school-aged and teenage males. Most patients are discharged directly from the ED; however, a substantial number are hospitalized, many of which had documented posterior dislocations. Ultimately, understanding the epidemiology and mechanism-related trends of acute SC dislocations is important given the potential severity of these injuries, concentration in a specific population, and uncertainty linked to rare presentation.

Key Words: Sternoclavicular dislocation; Sternoclavicular joint; Epidemiology; Football; Contact sports

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Core Tip: Sternoclavicular (SC) dislocations from sports continue to be rare with a stably low incidence over the past two decades, likely comprising a smaller proportion of shoulder dislocations than previously thought. Contact sports are a frequent source of injury, especially among school-aged and teenage males. Most patients are discharged directly from the emergency department; however, a substantial number are hospitalized, many of which had documented posterior dislocations. Ultimately, understanding the epidemiology and mechanism-related trends of acute SC dislocations is important given the potential severity of these injuries, concentration in a specific population, and uncertainty linked to rare presentation.

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INTRODUCTION

Dislocations of the sternoclavicular (SC) are rare: In 1958, Cave *et al*[1] reported that this diarthrodial saddle joint accounts for less than 3% of joint dislocations involving the shoulder[1-3]. The rarity of these injuries imputes why many orthopedic surgeons will not treat an SC dislocation during their career[4]. Even among shoulder and elbow surgeons, SC dislocations are uncommon: An international survey of these pertinent subspecialists reveals only half treat at least one anterior SC dislocation annually[4,5]. Subsequently, there is limited consensus regarding the epidemiology of SC dislocations, which is further exacerbated by how published data is often limited to smaller observational studies given the low SC dislocation volume at individual institutions[6,7].

Despite limited epidemiological data, injury biomechanics are well-defined in the existing literature. Due to the presence of a strong, stabilizing posterior capsule as well as intrinsic and extrinsic ligamentous structures, SC dislocations typically occur in the anterior rather than posterior direction[3,4,

6,8-10]. Injury may occur as a result of direct forces applied to the anteromedial clavicle that cause posterior migration behind the sternum or by indirect forces applied to the anterolateral or posterolateral shoulder[10,11]. Sports and athletic activities are frequent sources of SC dislocations, with contact sports notably increasing an athlete's risk of sustaining direct blows to the medial clavicle or, more commonly, indirect rolling and compression forces on the shoulder[8,10,11]. The potential for posterior dislocation increases the risk of mediastinal penetration that may require emergency operative management with a vascular or cardiothoracic surgeon on standby, increasing the general clinical concern surrounding the acute injury[4,5,9,10,12].

The purpose of the present study is to provide an updated epidemiological analysis of primary, acute SC dislocations secondary to athletic activities that presented to emergency departments (EDs) across the United States over the last two decades. We hypothesize that SC dislocations from sports are rare and comprise less than 1% of estimated shoulder dislocations that present to EDs in general. Given existing concern for injury to structures surrounding the SC joint and the risk that reduction of the SC joint may entail, we further hypothesize that a substantial portion of patients presenting to EDs is admitted or transferred to another facility rather than directly discharged and that patients with injuries secondary to contact sports are more likely to be hospitalized than those from non-contact sports, reflective of greater potential for severe injury.

MATERIALS AND METHODS

This epidemiological study is a cross-sectional, descriptive assessment of SC dislocations from athletic activities presented to EDs across the United States over the past 20 years. Data were sourced from the National Electronic Injury Surveillance System (NEISS) database, a creation of the United States Consumer Product Safety Commission to track and estimate product-related injuries occurring nationwide. NEISS data are collected and deidentified by a hospital coordinator assigned to one of approximately 100 facilities across the United States that are purposefully selected to create a probability sample of EDs across the country. Data is sourced from both clinical information and follow-up telephone communication as needed.

Database query

The NEISS database was queried for all primary and secondary "upper trunk" and "shoulder" dislocations occurring over the twenty years from 2001 to 2020, although secondary injuries were only coded beginning in 2019. All narrative summaries were reviewed. Patients were excluded if the qualitative description did not reflect SC dislocation related to sports participation.

Data collection

National incidences were calculated from census numbers based on the injuries reported in the NEISS. Patient demographics included age and sex, with age-stratified into categories of patients less than five, 5-17, 18-44, 45-64, and over 65 years old. Dislocations were classified as anterior or posterior if this information was explicitly available in the narrative summary. Mechanisms of injury as identified by product involvement, incident locale, hospital size, and disposition from the ED were also collected and reviewed.

Statistical analysis

Weighted descriptive statistics were calculated for included patients based on population estimates. Incidence rates per 1000000 persons at risk and corresponding 95% confidence intervals (CIs) were also calculated based on United States census data population and by demographic-based distribution numbers. Mid-p two-sided P values were calculated for all incidence rate ratios and Poisson approximations to construct incidence rate CIs. Trends regarding injury rates over the two-decade period were assessed with linear regression. χ^2 tests were used to compare dislocation rates in comparable patient cohorts. All analyses were conducted in Stata 17 software[13].

RESULTS

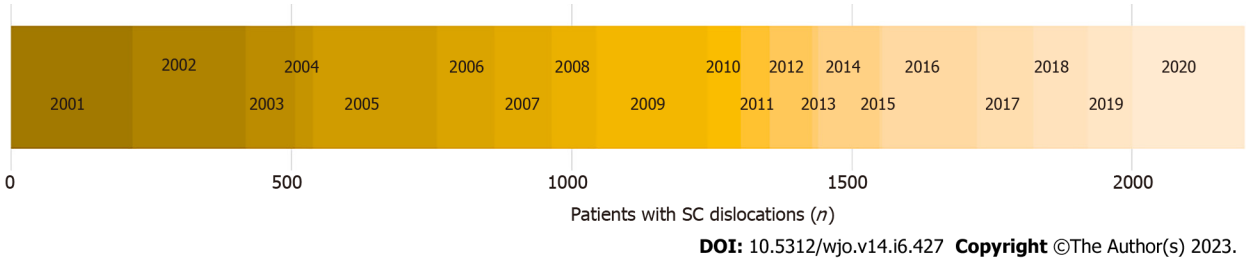
Cumulatively, 1622 SC dislocations occurred nationwide over the twenty-year study period from 2001 to 2020, comprising 0.10% of upper trunk and shoulder dislocations (n = 1616268). In total, there were 0.262 dislocations per 1000000 people (95%CI: 0.250-0.275) from 2001 to 2020 (Figure 1). All SC dislocations were primary injuries. There was no appreciable linear trend among injury incidence compared between relevant years (P = 0.338).

Demographics

A majority of patients with SC dislocations were male (91%, n = 1480) (Table 1). The incidence of sports-

Table 1 Patient demographics, incident locale, and emergency department disposition

	% (Estimated *n*)
Sex	
Male	91% (1480)
Female	9% (142)
Age	
< 5	-
5-17	61% (982)
18-44	28% (456)
45-64	11% (184)
> 65	-
Incident locale	
Home	14% (235)
Street	3% (49)
Other public property	2% (32)
School	5% (82)
Place of recreation/sports	57% (917)
Unspecified	19% (307)
Disposition	
Released	82% (13370)
Transferred	6% (90)
Admitted	12% (194)



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Figure 1 Annual sternoclavicular dislocations over two decades. SC: Sternoclavicular.

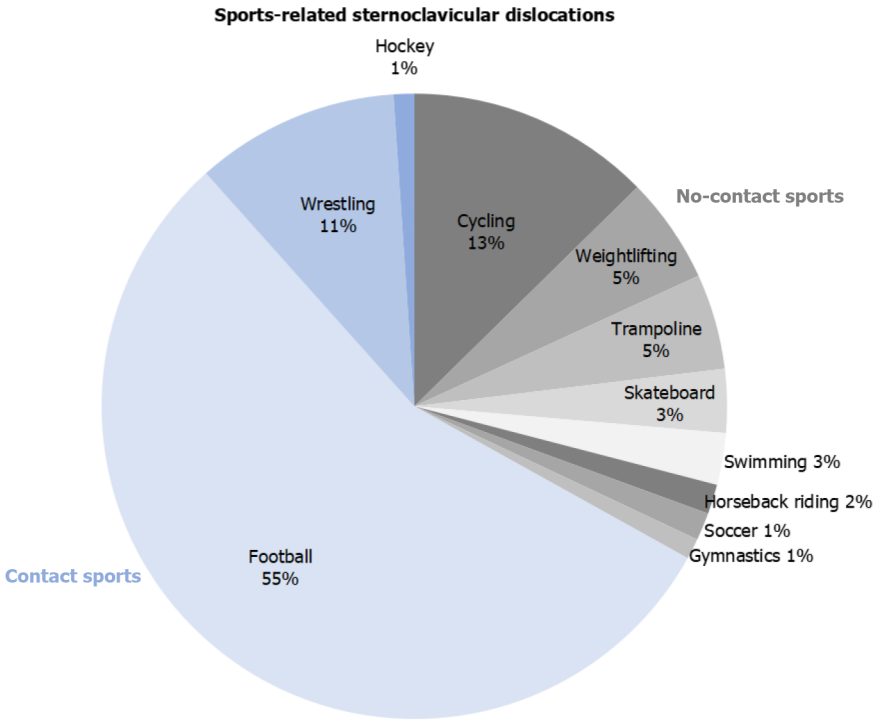
related dislocations in male patients was 0.471 per 1000000 person-years (CI: 0.447-0.496), ultimately tenfold higher than the incidence among female patients (0.046 dislocations per 1000000 person-years, CI: 0.039-0.055) with statistical significance (ratio = 10.1, CI: 8.49-12.1, $P < 0.001$). Trends in age revealed that 61% of dislocations occurred in patients aged 5-17 (n = 982) followed by 28% in patients 18-44 (n = 456). Among patients aged 5-17, the incidence rate was 0.913 dislocations per 1000000 people (95%CI: 0.856-0.971), which represents a substantially higher incidence in this population than both 18-44-year-old patients (0.200 dislocations per 1000000 people, CI: 0.182-0.219) as well as all other age groups combined (0.317 dislocations per 1000000 people).

Mechanism of injury

Football-related injuries were the most common and accounted for 49% of all sport-related SC dislocations (n = 795), followed by wrestling (n = 151) and biking (n = 121) injuries (Figure 2, Table 2). The three contact sports linked to SC dislocations - football, wrestling, and hockey - accounted for two-thirds of all injuries (59%; n = 961). All contact sport-related dislocations occurred in male patients. While SC dislocations from sports were uncommon in women, general exercise-related injuries and horseback riding-related injuries (n = 120; n = 22, respectively) were the most common mechanisms among female patients. Recreational vehicle-related sports injuries, such as all-terrain vehicles, dirt

Table 2 Mechanisms of injury

Sport	% (Estimated *n*)
Football	49% (795)
Wrestling	9% (151)
Bicycle	8% (121)
General exercise	7% (120)
Weightlifting	5% (79)
Trampoline use	4% (71)
Dirt bike	4% (61)
All terrain vehicle	3% (48)
Skateboard	3% (47)
Swimming	2% (39)
Horseback riding	1% (22)
Soccer	1% (21)
Moped	1% (17)
Gymnastics	< 1.0% (15)
Hockey	< 1.0% (15)
Total	1622



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Figure 2 Sports-related sternoclavicular dislocations.

bikes, and mopeds, accounted for 7.8% of all injuries (n = 126), with dirt bikes specifically comprising 3.7% (n = 61).

Dislocation type

Anterior *vs* posterior dislocations were not specified in NEISS data in most patients (71%; n = 1552). Anterior dislocations were specifically reported in 0.26% of cases (n = 6,), while posterior dislocations were reported in 2.9% of cases (n = 64). All posterior dislocations specified in NEISS occurred in 15- to

17-year-old males during athletic activity, with half of the raw reported dislocations sustained in football (n = 28). Other patients sustained posterior SC dislocations during wrestling (n = 16), hockey (n = 5), and skateboarding (n = 15).

Incident locale

SC dislocations were most commonly sustained at places of recreation or sport (57%; n = 917). Injuries in homes were the second most common (14%; n = 235). Of patients whose dislocations occurred at recreational facilities, 85% were male (n = 782) with an average age of 19 SD = 10. This reflects a similarly aged but less predominantly male population as compared to the patients who sustained sports-related SC dislocations in homes, of which all were male (n = 235) with an average age of 18 (SD = 14).

Patient disposition

Overall, disposition for 82% of patients occurred as discharge directly from the ED (n = 1337). Otherwise, 12% of patients were admitted to the facility (n = 194) and 6% underwent transfer to another facility (n = 90). Although very few dislocations were coded as anterior *vs* posterior, all that were coded as posterior were admitted or transferred and all that were coded as anterior were discharged directly from the ED. Patients sustaining SC dislocations from contact sports had a significantly increased risk of hospital admission or transfer rather than discharge from ED as compared to patients whose injuries were from non-contact sports (incidence rate ratio = 1.46, CI: 1.32-1.61, P < 0.001).

DISCUSSION

SC dislocations from sports are rare, with only 1622 cases presenting to United States ED's over the last two decades. A majority of afflicted patients are male and between 5-17 years old. Dislocations are frequently sustained during contact sports and often occur at places of recreation or sporting activity. For the few patients with specified anterior *vs* posterior dislocations, all posterior dislocations occurred in males aged 15-17 and were admitted or transferred upon presentation to the ED. In total, 82% of patients were discharged directly from the ED with the remainder admitted or transferred to another facility.

Given that SC dislocations are consistently reported as rare injuries, much of the published literature can only report small case series, rendering an injury burden across the United States more difficult[10]. However, there is evidence that most patients with concern for SC pathology present to medical care early after injury, with approximately 80% of patients in a case series by Laffosse *et al*[14] receiving a diagnosis and undergoing a closed reduction within the first 48 hours of injury. Because of the rarity of these injuries and the relative promptness after which patients present to medical attention, the larger and nationally representative NEISS database enables a more targeted assessment of the epidemiology of acute and traumatic SC dislocations.

Our epidemiological assessment of acute sports-related SC dislocations suggests that the incidence may be lower than previous literature suggests[1,10,12,15,16]. Estimates by Cave *et al*[1] from 1958 indicate that SC dislocations account for less than 3% of all shoulder-related dislocations and continue to be quoted throughout current literature[4]. Comparatively, our assessment of weighted NEISS data suggests that SC joint injuries comprise approximately a tenth of a percent of shoulder and upper trunk dislocations. A meta-analysis by Tepolt *et al*[16] found that 71% of SC dislocations injuries in existing literature were linked to athletics while Cave *et al*[1] estimated that SC dislocations comprise 3% of shoulder and elbow dislocations overall; subsequently, our findings indicating that SC dislocations from sports comprise 0.1% of overall shoulder dislocations suggest that SC dislocations from athletics are even rarer than previously estimated. In our assessment of sports-related SC dislocations, there is a notably strong tendency for SC injury from contact sports. The link between SC dislocations in football players, rugby players, and wrestlers is well-documented in literature[11,14,17-19], with a 1996 study published in the British Journal of Sports Medicine going so far to title their paper, "Posterior SC dislocation: an American football injury." Football-related injuries are not limited to high-school-aged or recreational athletes, and there are documented accounts of professional football players treated for SC dislocations[19]. The strong link between SC dislocations and American football offers a potential explanation for why American shoulder and elbow surgeons report seeing proportionally more SC dislocations than Canadian or Flemish surgeons, as a small survey of international shoulder and elbow surgeons revealed that 25% of the 53 American shoulder specialists reported at least three anterior dislocations per year compared to 19% of the 28 Flemish surgeons and 5% of the 128 Canadian surgeons [5]. Due to the rarity of these injuries and the frequent lack of obvious physical deformity, early diagnosis of SC dislocations can be challenging[19]. Consequently, establishing specific sports as frequently implicated mechanisms appropriately increases clinical suspicion for this rare injury pattern in these specific patient populations at a greater risk of injury.

Aligning with trends of increased SC dislocations in adolescents identified in prior literature[7,11,16], the majority of SC dislocations in our study occurred in young males between 5-17 years of age. One cause of increased risk in these patient populations may lie in sports participation, as football and wrestling are male-dominated sports often played by high-school or college-aged athletes. However, biomechanical factors may also play a role. The medial clavicular epiphysis may remain unfused up until age 25, rendering younger patients at increased risk for epiphyseal disruption causing posterior displacement[11,14]. Clavicular physeal fractures are radiographically indifferentiable from SC dislocations and present with similar immediate complications[11,14]; subsequently, the role of the late-fusing clavicular physis in predisposing young patients to these injuries may denote other physis-related risk factors. Interestingly, a study by Laffosse *et al*[14] reports that the only statistically significant difference between epiphyseal disruption *vs* SC dislocations was in patient age: The average age for patients presenting with epiphyseal disruption was 16.9 and ranged from 15-20 years *vs* those with SC dislocation was 24.2 and ranged from 17-41. With the knowledge that contact sports are a common mechanism of injury, the tendency for SC dislocations to present in young males raises a question regarding the degree to which increased exposure from contact sport participation *vs* preexisting biomechanical factors drive this increased risk.

Although much of the anterior *vs* posterior dislocation data is unavailable in our study group, there were 64 patients with specified posterior dislocations, confirming that a minimum of 2.9% of the SC dislocations that presented to EDs occurred posteriorly, reflecting an unexpectedly high percentage of posterior SC dislocations in the last 20 years. Historically, posterior dislocations are exceptionally uncommon: the classic epidemiological case series by Cave *et al*[1] of 1603 shoulder girdle injuries included only one posterior SC dislocation; the 50-year case series by Nettles *et al*[15] reports only three posterior injuries out of 60 SC dislocations; and 1996 literature review by Wirth *et al*[10] yielded fewer than 110 cases of posterior dislocations worldwide. Possible explanations include improved imaging techniques leading to fewer missed posterior diagnoses, increased rates of injuries caused by the specific activities that accrue a high risk of posterior dislocations, or increased frequency of presentation of the more severe posterior dislocations to EDs while anterior dislocations present to lower acuity facilities, possibly as chronic injuries. Regardless, future data collection that includes dislocation direction at a multi-institutional level could help better elucidate these trends.

Regarding disposition, most patients presenting to EDs with SC dislocations are discharged directly from the ED. In concordance with our hypothesis, all patients in our study presented with documented posterior dislocations were admitted or transferred. The limited availability of anterior *vs* posterior dislocation data in NEISS renders it difficult to compare the rates of these injury patterns in our data set; however, anterior dislocations are well-documented to be more common and less severe than posterior dislocations, implying that 82% of patients who were discharged from the ED more likely sustained anterior rather than posterior dislocations. Furthermore, patients with contact sports-related mechanisms were significantly more likely to be admitted or transferred compared to those with injuries from non-contact sport mechanisms, suggesting that injuries from sports with physical contact require more resources and may be more severe than those from other athletic activities.

Limitations to the present study stem from the paucity of SC dislocations and the resultant low sample size. While the NEISS database enables a more comprehensive and nationwide pool of acute traumatic injuries, it does not capture patients who present to urgent care or outpatient facilities, which means that the incidence of anterior and/or chronic dislocations may be higher as any severe injuries that presented to those facilities would likely be transferred to an ED. Furthermore, injury details such as anterior *vs* posterior dislocations were rarely present. Regarding population estimates, calculations relied on available census data, which necessitated projection statistics for the 2020 year.

CONCLUSION

SC dislocations from sports continue to be rare with a stably low incidence over the past two decades, likely comprising a smaller proportion of shoulder dislocations than previously thought. Contact sports are a frequent source of injury, especially among school-aged and teenage males. Most patients are discharged directly from the ED; however, a substantial number are hospitalized, many of which had documented posterior dislocations. Ultimately, understanding the epidemiology and mechanism-related trends of acute SC dislocations is important given the potential severity of these injuries, concentration in a specific population, and uncertainty linked to rare presentation.

ARTICLE HIGHLIGHTS

Research background

Epidemiological characterization of acute sternoclavicular (SC) dislocations is sparse, with classic epidemiology of injury dating back to the 1950s.

Research motivation

Characterize the epidemiology of acute SC dislocations over the last two decades.

Research objectives

This study aims to describe the epidemiological trends of SC dislocations that present to United States Emergency Departments (EDs) related to sports participation.

Research methods

Data for this cross-sectional, descriptive epidemiological study were obtained from the National Electronic Injury Surveillance System database spanning two decades.

Research results

The incidence of SC dislocations nationwide was found to be 0.262 per 1000000 people and comprised 0.1% of shoulder and upper trunk dislocations. The majority of patients were male (91%, n = 1480) and between ages 5-17 (61%, n = 982), and most sustained injuries in contact sports (59%, n = 961) with football the most frequently implicated sport. Most patients (82%, n = 1337) were discharged from the ED. Patients with SC dislocations from contact sports had a significantly increased risk of hospital admission or transfer rather than discharge from the ED (incidence rate ratio = 1.46, CI: 1.32-1.61, P < 0.001).

Research conclusions

SC dislocations sustained during sports are rare. Ultimately, contact sports are a frequent source of injury and the majority of patients are discharged directly from the ED.

Research perspectives

Future research will further clarify incidence of anterior *vs* posterior SC dislocations and characterize trends in treatment over time.

FOOTNOTES

Author contributions: Sandler AB contributed to the data collection, statistical analysis, presentation of data, writing of manuscript, presentation of figures and tables, and revisions of manuscript; Baird MD and Scanaliato JP contributed to the statistical analysis, and the writing, editing, and revision of the manuscript; Harris AL contributed to the writing and editing of the manuscript; Raiciulescu S contributed to the statistical analysis and editing of the manuscript; Green CK and Dunn JC contributed to the editing of the manuscript; Parnes N contributed to the conception of the idea for the manuscript, oversight throughout the course of the study, and writing, editing, revisions of the manuscript.

Institutional review board statement: All data used in the above study were obtained from a free, publicly-accessible database: The National Electronic Injury Surveillance System.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Data sharing statement: Data were obtained from the United States Consumer Product Safety Commission at the following website: https://www.cpsc.gov/Research--Statistics/NEISS-Injury-Data.

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ORIGINAL ARTICLE

Observational Study

Achieving high union rates after first metatarsophalangeal joint arthrodesis: Radiographic outcomes and technical pitfalls

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Abstract

BACKGROUND

Fusion of the first metatarsophalangeal (MTP1) joint is a common surgery performed to correct hallux rigidus, hallux rigidus et valgus and other painful degenerative diseases of the MTP1.

AIM

To assess outcomes of our surgical technique including non-union rates, accuracy and aims of correction.

METHODS

Between September 2011 and November 2020 a total 72 of MTP1 fusions were performed using a low profile, pre-contoured dorsal locking plate and a plantar compression screw. Union and revision rates were analyzed with a minimum clinical and radiological follow up of at least 3 mo (range 3-18 mo). The following parameters were evaluated on pre- and postoperative conventional radiographs: Intermetatarsal angle, Hallux-valgus angle, dorsal extension of the proximal phalanx (P1) in relation to the floor and the angle between the Metatarsal 1 and the P1 (MT1-P1 angle). Descriptive statistical analysis was performed. Pearson analysis was used to assess for correlations between radiographic parameters and achievement of fusion.

RESULTS

An overall union rate of 98.6% (71/72) was achieved. Two out of 72 patients did not primarily fuse with one patient suffering from a non-union, whilst the other demonstrating a radiological delayed union without clinical symptoms, with eventually complete fusion after 18 mo. There was no correlation between the measured radiographic parameters and the achievement of fusion. We believe the reason for the non-union was mainly attributed to the patient's incompliance without wearing the therapeutic shoe leading to a fracture of the P1. Furthermore,

we didn`t find any correlation between fusion and the degree of correction.

CONCLUSION
With our surgical technique, high union rates (98%) can be achieved using a compression screw and a dorsal variable-angle locking plate to treat degenerative diseases of the MTP1.

Key Words: Arthrodesis; First metatarsophalangeal joint; Dorsal plate; Arthrodesis

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Core Tip: The most important findings in this study are that metatarsophalangeal joint fusion using a compressions screw and a dorsal plate can achieve union rates close to 100% even in patients that are diabetic or smoke. Furthermore, we didn't find any correlation between the degree of correction and risk of nonunion.

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INTRODUCTION

Arthrodesis of the metatarsophalangeal (MTP1) joint is a common surgery performed to correct hallux rigidus, hallux rigidus et valgus and other painful degenerative diseases of the MTP1. Furthermore, it is a salvage procedure for failed hallux valgus surgery. High patient satisfaction and union rates have been reported in the literature with union rates ranging from 77% to 100%[1-4]. Nevertheless, nonunion of the arthrodesis has been purported as a common complication with unsatisfying results often leading to revision surgery[5,6].

A wide range of fixation methods has been published showing that biomechanically the most stable construct is a combination of a compression screw and a dorsal locking plate[2,7,8]. Commonly a dorsal plate fixation is used as it offers superior strength and sagittal plane rigidity allowing for immediate weight bearing[9,10]. In our own institution we have been using the combination of a compression screw with a dorsal locking plate for more than 10 years. The technique is similar to the technique published by Kumar *et al*[11] with slight variations.

The given literature about radiologic outcomes after arthrodesis of the first ray is limited. Therefore, the aim of this study was to retrospectively assess our own patient collective regarding non-union rate, degree of correction, complications, look for independent risk factors of failure and describe our own surgical technique using a compression screw and a dorsal plate while giving some insightful tips on how to avoid classical pitfalls.

MATERIALS AND METHODS

This retrospective study was approved by the ethics commission board of northwest- and central-Switzerland and was conducted entirely at the authors institution: BASEC Nr 2021-00837. Patients recruited have provided written informed consent.

Study cohort

Out of the institution's database every MTP1 arthrodesis that was executed between September 2011 and November 2020 was identified. The consecutive cohort consisted of 9 male patients and 62 female patients with 34 left and 38 right feet. The average age was (70 years, range 32-90). All patients underwent fusion of the MTP1 by using a compression screw and a low-profile dorsal locking plate. An anatomical, variable-angle dorsal locking plate 2.4/2.7 mm (DePuy-Synthes, Johnson&Johnson) was used. Pre and postoperatively weight bearing radiographs (anterior-posterior, oblique and lateral) were obtained. All Patients with a minimum follow-up of 3 mo and a complete radiographic data set as mentioned above were included in the study.

Surgical technique and postoperative protocol

A single surgeon (SB) performed all surgeries. A classical medial approach is used to expose the medial capsule. A longitudinal incision is used to divide the capsule. After opening the capsule, the capsule is partially released from the metatarsal head. Afterwards the joint is dislocated and a 1.6 mm Kirschner wire is inserted centrally into the first metatarsal head. Now spherical reamers are used to prepare a convex first metatarsal head and a concentric concave proximal phalanx (P1). Afterwards 1 mL demineralized bone matrix is applied (Osteosparx, SeaSpine Carlsbad, CA 92008) into the arthrodesis gap. Now the correct position of the arthrodesis is adjusted under fluoroscopy. The sagittal position is verified using a flat tray simulating a weight-bearing situation. Once the correct position is set, the joint is temporarily fixated with a Kirschner wire inserted from medial to lateral and proximal to distal direction already defining the position of the compression crew. Now the clinical and radiologic position of the arthrodesis is checked again. The reduction is secured with a 4.3 mm cannulated screw (Qwix, Integra) inserted over the wire. Afterwards any dorsal prominences are removed allowing for a good fit of the arthrodesis plate. The plate can be provisionally fixed using olive-Kirschner wires. After assuring the correct position of the plate standard variable-angle locking screws are used. Now, the implant position and length of the screws is checked again, and the correct position of the arthrodesis is verified under fluoroscopy. Subsequently, the wound is closed in layers with non-absorbable suture material for the skin. A sterile wound dressing and a flat operative shoe are applied.

Postoperatively, full weight bearing is allowed with wearing the flat operative shoe day and night for 6 wk[12,13]. At six weeks regular shoes were permitted. Clinical-radiological follow-up takes place after 6 wk and 3 mo.

Radiographic assessment

The following parameters were evaluated on pre- and postoperative conventional radiographs which are widely used and accepted as the standard of care and decision making[14]: Intermetatarsal angle (IMA), Hallux-valgus angle (HVA), dorsal extension of the P1 in relation to the floor and the angle between the Metatarsal 1 and the P1 (MT1-P1 angle) as shown in Figure 1. Measurements were always taken from recordings of the last available follow-up. All conventional radiographs were recorded during weight bearing. Imaging was analyzed in a blinded manner by two independent orthopedic surgeons on the picture archiving and communication system (PACS) using PACS measurement tools. Fusion was defined as patients being pain free at 3 mo and by vanishing of the gap within the arthrodesis in at least three cortices.

IMA: The IMA was measured using the long axis of the first and second Metatarsal. An angle of less than 9° was viewed as normal[15].

HVA: The HVA was assessed by using the long axis of the first Metatarsal in relation to the P1. A value of less than 15 was deemed physiologic[16].

Dorsal extension of P1 in relation to the floor: The Angle between the long axis of the P1 in relation to the floor was measured on lateral radiograph to assess the position of the arthrodesis.

Angle between the first MT1 and the P1 angle: The position of the P1 in relation to the MT1 was measured on a lateral standing weight bearing radiograph.

Statistical analysis

Descriptive analysis of patient characteristics and outcome parameters was performed. For continuous variables the mean and range are reported. Frequencies and percentages were used for dichotomous variables. Union rates are reported as frequencies and exact pearson-clopper 95% confidence intervals (CI) were calculated. The subgroup analyses of diabetics and smokers was done in a descriptive fashion due to the low number of observations. Statistical analyses were computed using Stata/IC 15.1 software (StataCorp LP, College Station, TX, United States).

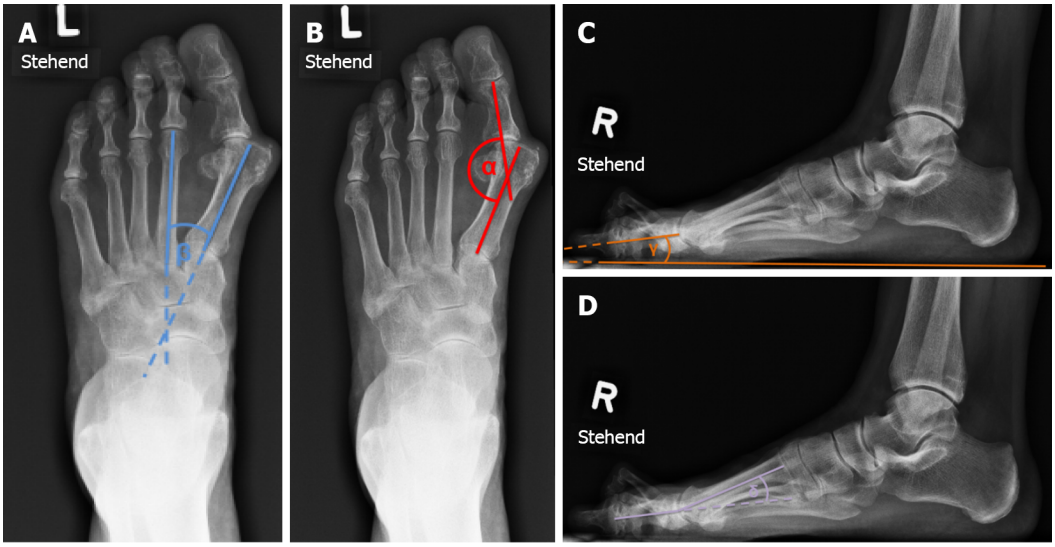
RESULTS

Of 71 patients with 72 feet were included in the study with a minimum follow up of three months. There were 9 male and 62 female patients with an average age of 70.1 years (range 32-90). The body mass index averaged 26.5 kg/m^2 (range 17-38). Further patient characteristics are displayed in Table 1. Out of these, 71 patients showed a fused arthrodesis (98.6%) at the latest follow-up with one patient suffering from malunion. One patient finally fused after 18 mo showing a delayed union while being asymptomatic throughout the whole period. One patient did not stick to the postop rehab protocol due to a rapidly increasing dementia leading to a P1 fracture. In consideration of the patient's underlying disease and freedom from symptoms, revision surgery was not performed. In one case the locking mechanism of the locking screws failed leading to relapse in valgus and pronation of the first toe which eventually fused in that position. In total three patients developed a symptomatic adjacent joint

Table 1 Demographics and comorbidities

Classification	
Age, years (Avg, range)	70.1 (range 32-90)
Gender	9 males; 62 females
BMI, kg/m^2 (Avg, range)	26.5 (range 17-38)
Surgical side	38 right; 34 lefts
Follow-up, months (Avg, range)	3 (60-108)
Previous surgeries	4
Diabetes Mellitus	8
Smoker (Avg PY, range)	13 (28, range 20-40)
Rheumatic disease	12
Immunosuppression	6

Avg: Average; BMI: Body mass index; PY: Pack years.



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Figure 1 The radiographic measurements: α = intermetatarsal angle, β = Hallux-valgus angle, γ = P1-Floor, δ = Mt1-P1 angle. A: The radiographic measurements of the intermetatarsal angle; B: The radiographic measurements of the Hallux-valgus angle; C: The radiographic measurements of P1-Floor angle; D: The radiographic measurements of the Mt1-P1 angle.

degeneration over time (15-37 mo). In one case the first tarsometatarsal joint (TMT I) and in two cases the interphalangeal (IP) joint was affected all requiring a TMT or IP joint arthrodesis over time. The preoperative HVA was in average 25.2 (range 14-64) with a correction down to 12 in average (range 2-27) while the preoperative IMA was 13.48 (range 4.5-24) with a postoperative correction to 9.2 in average (range 3.5-15). The preoperative MT1-P1 angle was 8.7 (range -28.05 to 55) with postoperative values of in average 16.89 (-4.05 to 34.5) which was already shown. All radiographic parameters are in detail displayed in Table 2. All patients with diabetes and smoking fused without showing signs of delayed healing or wound healing disorders. Only one patient developed a postoperative wound infection, which ultimately required a skin graft. Preoperatively the patient had a duplex ultrasound which did not show diminished perfusion. During the wound healing disorder another angiography was performed which showed a long-distance stenosis of the superficial femoral artery and the popliteal artery which was treated by balloon dilatation. Another wound healing disorder appeared that was successfully treated with oral antibiotics

Table 2 Pre- and postoperative radiographic parameters

	Preoperative (Avg, range)	Postoperative (Avg, range)
Hallux-Valgus-angle	25.21 (14-64)	12 (2-27)
Intermetatarsal-angle	13.48 (3.5-15)	9.2 (3.5-15)
P1-floor	3.33 (-38.05-18.55)	1.23 (-15.35-18.9)
MT1-P1	8.37 (-28.05-55)	16.89 (-4.05-34.5)

Avg: Average.

DISCUSSION

Arthrodesis of the MTP1 is a highly successful surgery to treat degenerative diseases of the MTP1. It has already been shown that using a construct of a compression screw and dorsal locking plate offers biomechanically the most stable construct[10]. In our own cohort, union rate was 98.6% (CI: 90.3-99.6) with one nonunion and one delayed union which we counted as a union as it finally fused. One malunion appeared due to failure of the locking mechanism. This patient had a known osteoporosis and suffered over the course of time of insufficiency fractures of the ipsilateral second and third metatarsal as a sign of lowered bone density. The clear nonunion was most likely attributed to a rapidly progressing dementia with incompliance regarding the postop protocol. In a big systemic review with 2656 joint included Roukis found an overall nonunion incidence of 5.4% with a symptomatic nonunion in only 1.8% which is consistent with our own data[17]. Interestingly in our own data, there was no association of nonunion or wound healing disorders with diabetes or smoking[18]. All patients with a nonunion or delayed union were non-diabetic and did not smoke. We used the P1-floor angle to radiologically assess the sagittal position of the great toe as already described[1,19]. A valgus of 5-20 degrees in the ap view has been recommended as a desired result in an earlier publication[16]. In our own cohort we measured an average postoperative valgus of 12 (range 2-27) which is again, consistent with recently published data[20]. The postoperative IMA was 9.2 (3.5-15) which can be deemed as borderline if you apply the cut-off values as mentioned above. Correspondingly McKean *et al*[21] showed that a complete correction of the IMA cannot be achieved in patients undergoing MTP1 fusion for severe HV deformity without an additional first metatarsal osteotomy[21]. We didn`t find any correlation between the amount of correction and risk of nonunion which is most likely attributed to the small numbers as according to Weber *et al*[18] negative influencing factors were the presence of preexisting diseases, higher grades of osteoarthritis, and a relative increased dorsiflexion position of the great toe after surgery[18].

The MT1-P1 angle was used to assess the sagittal position of the first ray. In our opinion this needs to be done intraoperatively using a flat tray as mentioned above and recommended by Drittenbass *et al*[20] simulating a weight-bearing situation as the MT1-P1 is strongly influenced by the position of the first metatarsal which differs in flatfoot, cavo-varus or other foot deformities reflected by the wide postoperative range and has to be taken into account intraoperatively[20]. Accordingly, we observed a wide range of the MT1-P1 angle in our own cohort with an average value of 16.89 (-4.05 to 34.5). This has already been published long ago deeming an average value of 12 degrees (range 0-32) as physiologic [22,23].

Strengths of the present study are more certainly that a SB performed all surgeries, and the same implant and fixation technique were used in all cases. Limitations of this study include the short period of follow up and the lack of clinical scores to correlate radiological and clinical outcome. Future studies should particularly correlate radiological data with clinical scores to confirm their clinical relevance and superiority.

CONCLUSION

We were able to show that with our surgical technique, high union rates (98%) can be achieved using a compression screw and a dorsal variable-angle locking plate to treat degenerative diseases of the MTP1 even in diabetic and smoking patients.

ARTICLE HIGHLIGHTS

Research background

Fusion of the first metatarsophalangeal joint (MTP1) is a common surgery performed to correct hallux rigidus, hallux rigidus et valgus and other painful degenerative diseases of the MTP1. High patient satisfaction and union rates have been reported in the literature with union rates ranging from 77% to 100%. In our own cohort we were also able to show high fusion rates.

Research motivation

Analyze our own cohort regarding union rate and radiologic outcome.

Research objectives

The main objective of this study as to asses our own patient collective regarding fusion rate and radiologic outcome including degree of correction.

Research methods

Out of the institution's database every MTP1 arthrodesis that was executed between September 2011 and November 2020 was identified. The consecutive cohort consisted of 9 male patients and 62 female patients with 34 left and 38 right feet. Patients were followed and pre and postoperatively weight bearing radiographs (anterior-posterior, oblique and lateral) were analyzed for fusion rate and various radiologic parameters.

Research results

Of 71 patients showed a fused arthrodesis (98.6%) at the latest follow-up with one patient suffering from malunion. One patient finally fused after 18 months showing a delayed union while being asymptomatic throughout the whole period. The preoperative Hallux-valgus angle was in average 25.2 (range 14-64) with a correction down to 12 in average (range 2-27) while the preoperative intermetatarsal angle was 13.48 (range 4.5-24) with a postoperative correction to 9.2 in average (range 3.5-15). The preoperative MT1-P1 angle was 8.7 (range -28.05 to 55) with postoperative values of in average 16.89 (-4.05 to 34.5) which was already shown.

Research conclusions

We were able to show that with our surgical technique, high union rates (98%) can be achieved using a compression screw and a dorsal variable-angle locking plate to treat degenerative diseases of the MTP1 even in diabetic and smoking patients.

Research perspectives

Future studies should particularly correlate radiological data with clinical scores to confirm their clinical relevance and superiority.

FOOTNOTES

Author contributions: von Deimling C wrote the manuscript, performed the data acquisition; Tondelli T contributed to the statisics, data acquisition; Andronic O main responsibility for the study plan and design; Brunner S and Graf AD are senior author.

Institutional review board statement: This retrospective study was approved by the ethics commission board of northwest- and central- Switzerland and was conducted entirely at the authors institution: BASEC Nr 2021-00837.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: SB is in the advisory board of DePuy Synthes and receives advisory fees.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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Observational Study

Chondroitin sulfate and glucosamine combination in patients with knee and hip osteoarthritis: A long-term observational study in Russia

Alexander M Lila, Lyudmila I Alekseeva, Andrey A Baranov, Elena A Taskina, Natalya G Kashevarova, Natalia A Lapkina, Evgeny A Trofimov

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Abstract

BACKGROUND

Oral treatment of glucosamine (GA) combined with chondroitin sulfate (CS) was reportedly effective for pain relief and function improvement in osteoarthritis patients with moderate to severe knee pain in clinical trials. While the effectiveness of GA and CS on both clinical and radiological findings has been demonstrated, only a few high-quality trials exist. Therefore, controversy regarding their effectiveness in real-world clinical practice remains.

AIM

To investigate the impact of GA + CS on clinical outcomes of patients with knee and hip osteoarthritis in routine clinical practice.

METHODS

A multicenter prospective observational cohort study included 1102 patients of both genders with knee or hip osteoarthritis (Kellgren & Lawrence grades I-III) in 51 clinical centers in the Russian Federation from November 20, 2017, to March 20,

2020, who had started to receive oral capsules of glucosamine hydrochloride 500 mg and CS 400 mg according to the approved patient information leaflet starting from 3 capsules daily for 3 wk, followed by a reduced dosage of 2 capsules daily before study inclusion (minimal recommended treatment duration is 3-6 mo). Changes in subscale scores [Pain, Symptoms, Function, and Quality of Life (QOL)] of the Knee Injury and Osteoarthritis Outcome Score (KOOS)/Hip Disability and Osteoarthritis Outcome Score (HOOS) questionnaires during the observational period (up to 54-64 wk with a total of 4 visits). Patients' treatment satisfaction, data on the combined oral use of glucosamine hydrochloride and CS, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), and adverse events (AEs) were also evaluated.

RESULTS

A total of 1102 patients with knee and hip osteoarthritis were included in the study. The mean patient age was 60.4 years, most patients were women (87.8%), and their average body mass index was 29.49 kg/m^2. All subscale scores (Pain, Symptoms, Function, and QOL) of the KOOS and HOOS demonstrated clinically and statistically significant improvements. In patients with knee osteoarthritis, the mean score increases from baseline to the end of Week 64 were 22.87, 20.78, 16.60, and 24.87 on Pain, Symptoms, Physical Function (KOOS-PS), and QOL subscales ($P < 0.001$ for all), respectively. In patients with hip osteoarthritis, the mean score increases were 22.81, 19.93, 18.77, and 22.71 on Pain, Symptoms, Physical Function (HOOS-PS), and QOL subscales ($P < 0.001$ for all), respectively. The number of patients using any NSAIDs decreased from 43.1% to 13.5% ($P < 0.001$) at the end of the observation period. Treatment-related AEs occurred in 2.8% of the patients and mainly included gastrointestinal disorders [25 AEs in 24 (2.2%) patients]. Most patients (78.1%) were satisfied with the treatment.

CONCLUSION

Long-term oral GA + CS was associated with decreased pain, reduced concomitant NSAID therapy, improved joint function and QOL in patients with knee and hip osteoarthritis in routine clinical practice.

Key Words: Glucosamine; Chondroitin sulfate; Knee osteoarthritis; Hip osteoarthritis; Knee injury and osteoarthritis outcome score; Hip disability and osteoarthritis outcome score

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Core Tip: Long-term 64-wk treatment by oral capsules of glucosamine hydrochloride 500 mg and chondroitin sulfate 400 mg three times a day for the first 3 wk, then twice daily, was associated with clinically significant improvements in all subscale scores (Pain, Symptoms, Function, and Quality of Life) of the Knee Injury and Osteoarthritis Outcome Score/Hip Disability and Osteoarthritis Outcome Score and a decreasing number of patients with knee and hip osteoarthritis receiving any non-steroidal anti-inflammatory drugs in real-world clinical practice. Incidence of drug-related adverse events was low, and their nature was consistent with known safety profile of glucosamine hydrochloride and chondroitin sulfate combination.

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INTRODUCTION

Osteoarthritis (OA), the most common musculoskeletal disease worldwide, is associated with significant morbidity and mortality[1]. According to the 2017 Global Burden of Disease study, OA is the 12th leading cause of years lived with disability (YLDs) of all ages. YLDs due to OA increased substantially by 31.5% from 2006 to 2016 in the world[2]. This burdensome syndrome has become more common due to the combined effects of the aging population, the increasing proportion of obese individuals worldwide, and the increasing number of joint injuries. By estimate, 250 million people are currently suffering from OA worldwide[3]. In an epidemiological study, approximately 13% of the Russian population over the age of 18 suffered from knee or hip OA[4].

Knee or hip OA is one of the most frequent and burdensome joint diseases, with knee OA being more common than hip OA. The clinical manifestations and symptoms of OA include pain, stiffness and impaired joint function, gradual pain onset, crunching, muscle atrophy, joint deformation, and joint enlargement[5]. By estimate, OA treatment costs in some high-income countries were 1%-2.5% of the gross domestic product, with hip and knee replacements accounting for the major share of such healthcare costs[3].

Management guidelines for OA patients by the Osteoarthritis Research Society International (OARSI) and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases recommend a combination of non-pharmacological and pharmacological interventions[6,7]. Non-pharmacological options include exercise therapy, walking aids, weight loss, physical therapy, patient education, and self-help programs. Non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, opioids, duloxetine, intra-articular injections of corticosteroids and hyaluronic acid are the most common medicinal treatment products. Long-term usage of symptomatic slow-acting drugs for OA (SYSADOAs) is also considered a treatment option for symptomatic OA by several medical associations[7-10]. SYSADOAs reportedly had a structure-modifying effect in OA, based on their ability to activate anabolic processes in the cartilage matrix, suppress the activity of lysosomal enzymes, and stimulate chondrocyte function[11]. Regarding structure-modifying effects, standalone therapies of glucosamine (GA) as well as chondroitin sulfate (CS) achieved a statistically significant reduction in joint space narrowing[12].

The SYSADOA class comprises many products (GA, CS, diacerein, and unsaponifiables of soy and avocado oils), with various degrees of clinical efficacy. The most commonly investigated and recommended SYSADOAs are GA, CS, and their combinations. The increase in effectiveness of the combination of GA and CS as compared to each drug alone could be explained by the differences in their mechanisms of action[11]. However, their efficacy in clinical studies remains inconsistent for various reasons[7,13-17].

While many randomized controlled trials (RCTs) showed a significant treatment effect and remarkable safety for GA and CS, controversy regarding their relative effectiveness as compared to placebo or other treatments, their cost-effectiveness, and the need for insurance coverage of the cost of the therapy remains[18-20]. A recent meta-analysis[21] demonstrated clinical and radiological effectiveness of GA and CS. However, only a few high-quality trials exist, and the validity of these results was limited by a high risk of bias introduced in the studies[21]. Efficacious GA and CS treatment dosages, regimen of administration and treatment duration to provide symptom- and structure-modifying effects are not well investigated and properly justified[21], which emphasizes the importance of obtaining additional data on the effectiveness and safety of SYSADOA treatment in long-term studies, particularly in real-world clinical practice. The lower satisfaction with effectiveness of medication was strongly associated with treatment adherence[22].

Currently, GA and CS combination have been registered as an over-the-counter medicinal product in some countries (Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Mongolia, Russian Federation, Tajikistan, Turkmenistan, Ukraine, and Uzbekistan). GA and CS combination showed anti-inflammatory, analgesic, and chondroprotective activities in several clinical studies, including randomized studies[23,24]. Data on efficacy and safety of GA and CS combination therapy in routine clinical practice, particularly among patients with knee and hip OA receiving a long-term treatment, are of important practical interest.

This observational study aimed to assess pain dynamics, daily functional activity of joints, quality of life, and treatment satisfaction in patients with knee and hip OA, who received long-term GA and CS combination in routine clinical practice, and to collect data on the characteristics of OA patients receiving GA and CS combination treatment.

MATERIALS AND METHODS

Study design

This multicenter prospective observational cohort study was conducted in 51 clinical centers in the Russian Federation from November 20, 2017, to March 20, 2020. Patients with OA who had been prescribed GA and CS combination by a doctor during routine care or bought the medicine in a pharmacy on their own care were invited to participate in the study. The study planned to enroll no less than 1100 participants with OA (Kellgren & Lawrence stages I-III) in 80 centers, who were treated with GA and CS combination (capsules, 500 mg + 400 mg) for no longer than 2 wk at the time of study enrollment.

Patients used GA and CS combination according to the approved patient information leaflet, starting from 3 capsules daily for 3 wk, followed by a reduced dosage of 2 capsules daily. Theraflex® [capsules, glucosamine hydrochloride 500 mg and CS 400 mg, (GA + CS)] was authorized in Russia in 2008 for treatment of OA (grades I-III).

Inclusion criteria were as follows: Patients aged 45-75 years with hip or knee OA of stages I-III according to the Kellgren & Lawrence classification; patient who started GA + CS treatment (capsules, 500 mg + 400 mg) no longer than 2 wk before study enrollment; and patients who personally signed and dated informed consent. For OA of several joints or bilateral knee or hip OA, only one "target" joint, in which the patient experienced the most pronounced pain at the time of study enrollment, was selected for evaluation.

Patients were considered ineligible for the study if: They had participated in any other studies involving interventions other than standard clinical practice; they had hip or knee OA stage 0 or stage IV; they had received GA + CS or other slow-acting drug for symptomatic treatment within the past 5 mo; they had received intra-articular corticosteroid injections within the past 3 mo, or hyaluronic acid injections, and/or intra-articular lower extremity autologous platelet-rich plasma injections within the past 6 mo; and women who were pregnant or breastfeeding.

Observational visits were scheduled based on routine clinical practice and GA + CS prescription by a consulting physician. The study protocol included an initial visit, two follow-up visits (Weeks 16-24 and Weeks 36-44 after GA + CS treatment initiation), and a final visit (Weeks 56-64 after treatment initiation). Once consent was obtained, patient demographics, lifestyle, medical history, and OA grades according to the Kellgren & Lawrence classification were recorded. During all visits, data on GA + CS usage were collected, patients' basic vital signs and body mass index (BMI) were recorded, a physical examination was performed, and concomitant therapy and adverse events (AEs) were noted. Patients completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) or the Hip Disability and Osteoarthritis Outcome Score (HOOS) questionnaires (depending on selected "target" joint). HOOS is used to evaluate patients' opinions about their hip joint and related problems. This scale is intended for adults with hip joint disability with or without osteoarthritis[25]. KOOS is used to evaluate the opinion of patients about their knee and related problems. It can be used for short-term and long-term monitoring[26]. HOOS and KOOS are widely used questionnaires for patient reported joint-specific assessment of symptoms and functions in subjects with knee/hip injury and osteoarthritis. Both questionnaires are available on-line.

KOOS/HOOS consist of 5 subscales: Pain, other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee/hip related Quality of life (QOL). Standardized answer options are given (5 Likert boxes) and each question gets a score from 0 to 4. Questionnaire scores range from 0 to 100 with a score of 0 indicating the worst possible knee/hip symptoms and 100 indicating no knee/hip symptoms. To simplify the process of completing the questionnaires and reduce the amount of information provided, the subscales "Function in daily living" and "Function in sport and recreation" of the KOOS/HOOS questionnaires were replaced by the KOOS Physical Function (KOOSPS) and the HOOS Physical Function (HOOSPS) short forms, respectively.

Additionally, during the post-baseline visit, patients were asked to rate their satisfaction with the treatment on a 5point scale (very satisfied - 5, satisfied - 4, neither satisfied nor dissatisfied - 3, dissatisfied - 2, very dissatisfied - 1).

An interim analysis after completion of follow-up visits on Week 16-24 by the first 550 enrolled patients was performed during the study. Its main purpose was to investigate changes in pain, functions of daily living, and quality of life in patients with knee and hip OA after the first treatment course with GA + CS. A report on the results of the interim analysis was presented at the European League Against Rheumatism online congress in 2020[23].

This study was approved by the Intercollegiate Ethics Committee of the Russian Federation (protocol number 08/17, dated on September 14, 2017) and by the Bayer Protocol Review Committee (held on June 14, 2017). Patients provided informed consent for data collection before starting any study-related procedures. Study was registered on ClinicalTrials.gov resource before patient enrollment with the study Identifier NCT03330288 on November 6, 2017[27].

Outcomes

Changes in parameters of the KOOS/HOOS subscales were assessed as the primary outcome of the study. Other outcomes, such as patient satisfaction with the study treatment, data on the use of GA + CS, frequency of concomitant use of analgesics and other pain medications, were also evaluated as additional study outcomes.

Data source

Data for the study were collected through clinical interviews with patients and from source documents available at the center. Source documents were original documents, data, and records, which could include laboratory data/information or assessment checklists, pharmacy records, *etc.* The KOOS/HOOS and treatment satisfaction questionnaires were completed by the patients themselves with touch-screen tablets provided to them.

Statistical analysis

Statistical analysis was performed using SAS 9.4 software package for Windows (SAS Institute Inc., Cary, NC, United States). Since the study was observational, descriptive analysis was used to process

the data. All variables were analyzed in a full analysis set (FAS) that included all screened patients who received at least one dose of GA + CS and who had data to evaluate at least one efficacy and/or safety parameter. Categorical data were expressed as absolute numbers and percentages, and continuous data were expressed as mean values with standard deviations or 95% Wald confidence intervals (CI). The Student's paired *t*-test and the Bonferroni-Holm correction for *P* value were used in the analysis of the dynamics of KOOS and HOOS scales. The null hypothesis was tested: No changes on the visits. According to the results of testing, the hypothesis is rejected on all visits. The analysis of treatment satisfaction was carried out using median values and 25 and 75 quantiles.

RESULTS

Patient characteristics

A total of 1111 participants were screened over the course of the study, of which 1102 participants were enrolled. The study group included male and female patients aged 45-75 years with knee (824 participants) or hip (278 participants) OA.

A total of 38 patients (3.4%) discontinued the study prematurely. The main reason was loss of contact with patient (33 patients), the remaining 5 patients discontinued participation by withdrawal of consent due to treatment switch to another SYSADOA, planned hip arthroplasty, or patient inability to visit the study center. A total of 1102 patients received at least one dose of GA + CS and were included in the FAS population for efficacy and safety analysis. Among these patients, 97.1% completed the visit for Weeks 16-24, and 96.6% completed visits for Weeks 36-44 and Weeks 56-64 (Figure 1).

Patient demographics and baseline characteristics were summarized in Table 1. Most patients (74.8%) had knee OA. Approximately, 87.8% of patients were women, 99.6% were Caucasians, and their mean age was 60.4 years. Notably, the average BMI of patients was 29.49 kg/m^2, and most patients were obese or overweight.

At study enrollment, data on concomitant diseases were collected. The most common diseases were cardiovascular diseases (52.6%), metabolic and nutritional disorders (34.3%), and gastrointestinal disorders (22.1%). Hypertension (44.6%), obesity (23.2%), chronic gastritis (15.6%), varicose veins (9.3%), and type 2 diabetes mellitus (8.4%) were most often reported. Treatment of concomitant diseases was the main reason for the prescription of concomitant therapy during the observation period. At least one concomitant treatment was reported by 813 (73.8%) patients, the most commonly used concomitant medications were selective betaadrenergic blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers (in 19%, 13.9% and 12.9% of patients, respectively).

Changes in the KOOS scale

According to the KOOS questionnaire, patients with knee OA noted a significant improvement during the observation period. The mean score increases from baseline to the end of Week 64 were 22.87 (95%CI: 21.56-24.18), 20.78 (95%CI: 19.43-22.13), 16.60 (95%CI: 15.59-17.61), and 24.87 (95%CI: 23.41-26.34) on Pain, Symptoms, Physical Function (KOOS-PS), and Quality of Life subscales, respectively, ($P < 0.001$ for all). Notably, for all KOOS subscales, the largest score increases were achieved by Week 16-24 (observation for 4-6 mo), and the achieved effects further remained at the mean values for all subscales with a tendency to increase ($P < 0.001$ for all) (Table 2, Figure 2).

The most important questions (pain frequency and knee stiffness) of the KOOS questionnaire were analyzed separately. By the end of the 64-week observation period, the percentage of patients who reported pain frequency as "daily" or "always" decreased from 62.7% to 12.9% (Figure 3A). The percentage of patients who reported knee stiffness in the morning as "moderate", "severe" or "extremely severe" decreased from 55.3% to 18.1%, and the percentage of patients with knee joint stiffness in the evening decreased from 60.9% to 18.6%. A significant improvement of quality of life was observed. According to answers to the question of how much the patient's life was complicated by knee joint problems, the percentages of patients reported "not at all" and "slightly" increased from 1.9% to 28.7%, and from 19.5% to 38.5%, respectively, while the percentages of patients with "moderate", "severe, and "extremely severe" decreased from 47.0% to 27.0%, 27.7% to 4.8%, and 3.9% to 1.0%, respectively.

Changes in the HOOS scale

Patients with hip OA showed positive dynamics in all HOOS subscales during the observation period. The mean increases from baseline to the end of Week 64 were 22.81 (95%CI: 20.47-25.16), 19.93 (95%CI: 17.49-22.36), 18.77 (95%CI: 16.61-20.93), and 22.71 (95%CI: 20.14-25.28) on Pain, Symptoms, Physical Function (HOOS-PS), and Quality of Life subscales, respectively. Similar to changes in the KOOS scale, the highest score increases in the HOOS subscales were achieved by Week 16-24 with a tendency to increase during further follow-up ($P < 0.001$ for all) (Table 3, Figure 4).

Similar to patients with knee OA, the percentage of subjects with less frequent and less severe symptoms, problems, or difficulties in the specified joint during the observation period increased among patients with hip OA. By the end of the 64-week follow-up, the percentage of patients with

Table 1 Main characteristics of the study population, *n* (%)

	Knee osteoarthritis (*n* = 824)	Hip osteoarthritis (*n* = 278)	All (*n* = 1102)
Age, (yr), mean (SD)	60.4 (6.9)	60.3 (7.2)	60.4 (7.0)
Gender			
Female	728 (88.3)	240 (86.3)	968 (87.8)
Male	96 (11.7)	38 (13.7)	134 (12.2)
Ethnicity			
Caucasian	820 (99.5)	278 (100.0)	1098 (99.6)
Black	1 (0.1)	0	1 (0.1)
Asian	3 (0.4)	0	3 (0.3)
BMI, mean (SD)	29.77 (5.5)	28.66 (5.3)	29.49 (5.5)
Scale of stages of osteoarthritis according to Kellgren & Lawrence			
Stage 1	81 (9.8)	35 (12.6)	116 (10.5)
Stage 2	617 (74.9)	211 (75.9)	828 (75.1)
Stage 3	125 (15.2)	32 (11.5)	157 (14.2)
No data available	1 (0.1)		1 (0.1)

BMI: Body mass index.

Table 2 Change in Knee Injury and Osteoarthritis Outcome Score subscale scores (Full analysis set)

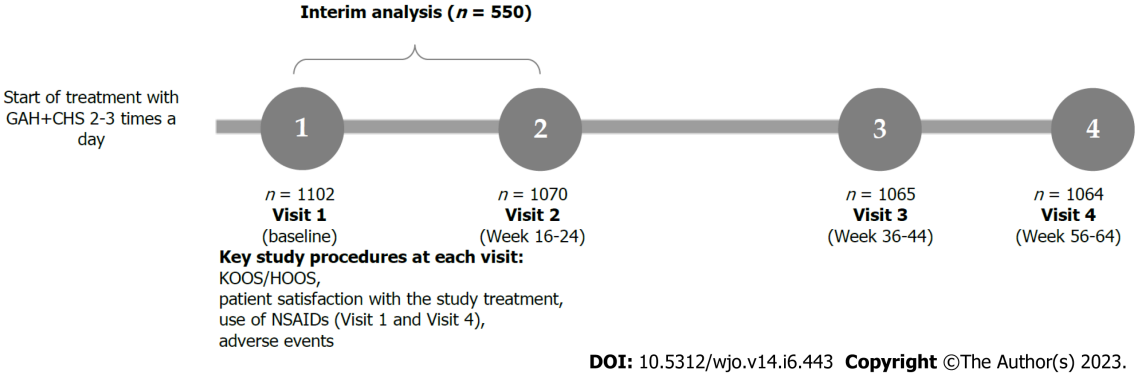
Subscale	Knee osteoarthritis (*n* = 824) – KOOS scale					*P* value[a]
	Visit 1, baseline, *n* = 824	Visit 2, week 16-24, *n* = 798	Visit 3 week 36-44, *n* = 794	Visit 4, week 56-64, *n* = 794	Changes from baseline on visit 4	
Pain	61.48 (60.36-62.61)	79.59 (78.48-80.70)	82.50 (81.45-83.56)	84.24 (83.15-85.34)	**22.87** (21.56-24.18)	**< 0.001**
Symptoms	62.25 (61.02-63.48)	77.65 (76.46-78.84)	81.09 (79.97-82.21)	82.80 (81.66-83.93)	**20.78** (19.43-22.13)	**< 0.001**
Functional activity of the joint	61.46 (60.73-62.18)	72.48 (71.63-73.34)	75.78 (74.86-76.69)	78.03 (77.06-78.99)	**16.60** (15.59-17.61)	**< 0.001**
Quality of life	44.99 (43.83-46.16)	61.40 (60.10-62.69)	65.91 (64.54-67.27)	69.92 (68.45-71.39)	**24.87** (23.41-26.34)	**< 0.001**

[a]with Holm-Bonferroni method. Mean data are presented (95%CI). CI: Confidence interval; KOOS: Knee Injury and Osteoarthritis Outcome Score.

Table 3 Change in Hip disability and Osteoarthritis Outcome Score subscale scores (Full analysis set)

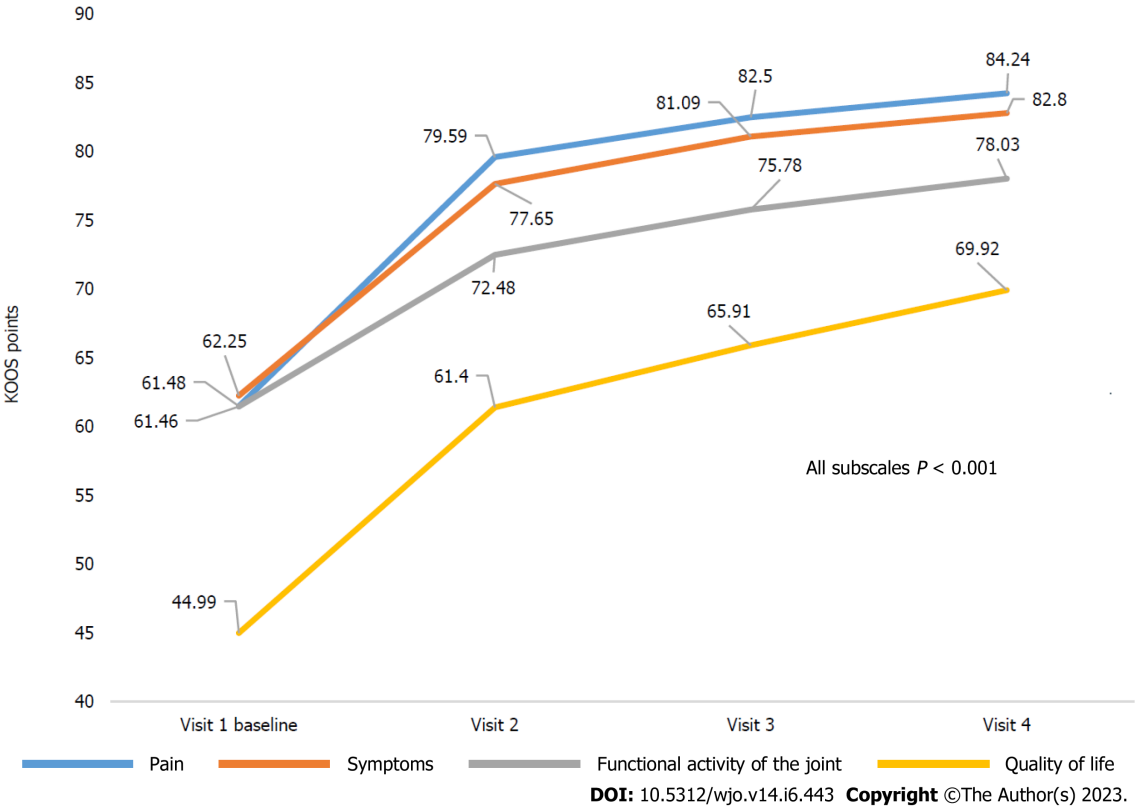
Subscale	Hip osteoarthritis (*n* = 278) – HOOS scale					*P* value[a]
	Visit 1, baseline, *n* = 278	Visit 2, week 16-24, *n* = 272	Visit 3, week 36-44, *n* = 271	Visit 4, week 56-64, *n* = 270	Changes from baseline on visit 4	
Pain	60.97 (58.93-63.02)	76.36 (74.34-78.38)	80.89 (78.95-82.84)	83.63 (81.64-85.62)	**22.81** (20.47-25.16)	**< 0.001**
Symptoms	61.17 (59.08-63.26)	73.73 (71.62-75.84)	78.17 (76.21-80.14)	81.19 (79.21-83.16)	**19.93** (17.49-22.36)	**< 0.001**
Functional activity of the joint	65.57 (63.62-67.52)	78.46 (76.72-80.21)	81.59 (79.93-83.26)	84.11 (82.45-85.76)	**18.77** (16.61-20.93)	**< 0.001**
Quality of life	46.79 (44.72-48.85)	60.75 (58.50-63.01)	65.41 (63.09-67.72)	69.33 (66.83-71.82)	**22.71** (20.14-25.28)	**< 0.001**

[a]with Holm-Bonferroni method. Mean data are presented (95%CI). CI: confidence interval; HOOS: Hip disability and Osteoarthritis Outcome Score (HOOS).



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Figure 1 Study design profile and recruitment of patients. Explanations for the participants excluded from the study were given in the Results section of this manuscript. GAH+CHS: 500 mg glucosamine hydrochloride and 400 mg chondroitin sulfate in one capsule; HOOS: Hip Disability and Osteoarthritis Outcome Score; KOOS: Knee Injury and Osteoarthritis Outcome Score; NSAID: Non-steroidal anti-inflammatory drugs.



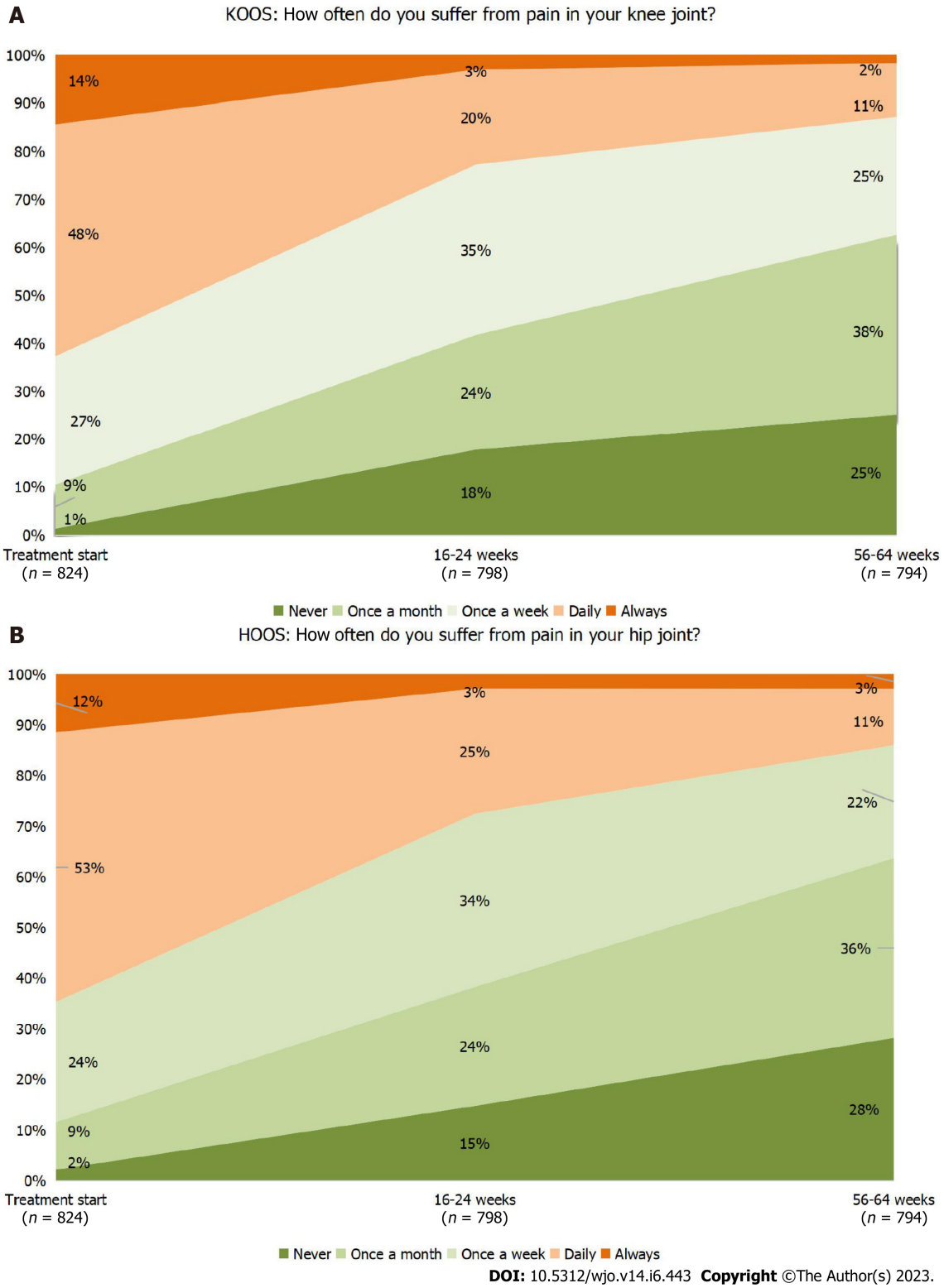
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Figure 2 Dynamics of Knee Injury and Osteoarthritis Outcome Score subscale scores. KOOS: Knee Injury and Osteoarthritis Outcome Score.

"daily" or "always" pain frequency decreased from 64.7% to 13.7% (Figure 3B), and those of patients with "moderate", "severe", or "extremely severe" morning hip stiffness and evening knee stiffness decreased from 55.4% to 15.9%, and from 61.9% to 17.0%, respectively. The percentages of patients who answered "not at all" and "slightly" in response to the HOOS question on complications due to hip joint problems increased from 1.8% to 23.7%, and from 22.7% to 41.5%, respectively, while the percentages of patients with "moderate", "severe", and "extremely severe" complications decreased from 46.4% to 28.1%, 25.5% to 4.8%, and 3.6% to 1.9%, respectively.

Duration of GA + CS usage

During the observation period, most patients (749/1102, 68%) were treated with GA + CS capsules for more than 6 mo. Treatment duration was 3-6 mo for 261 patients (23.7%), 1-3 mo for 78 patients (7.1%), and less than 1 mo for 14 patients (1.3%). A total of 1006 (91.3%) patients complied with the recommendations for the use of GA + CS.

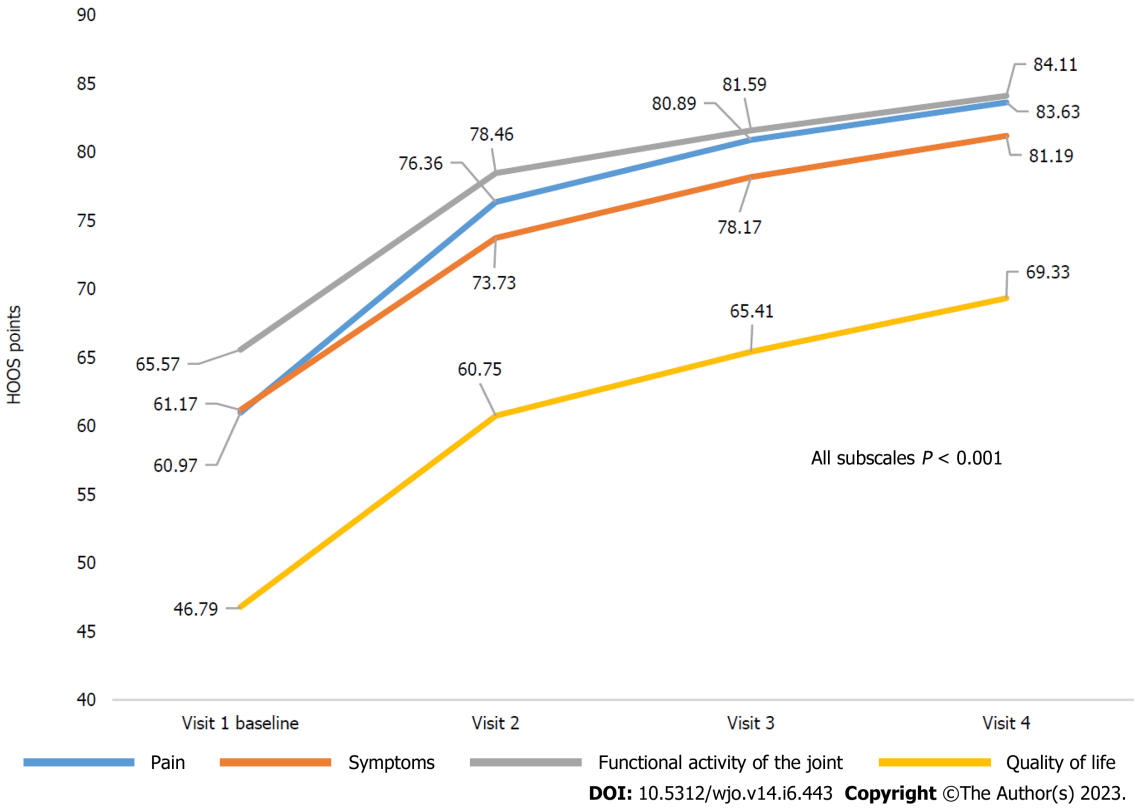


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Figure 3 Dynamics of pain during the study (analysis of "Pain Frequency" questions in Knee Injury and Osteoarthritis Outcome Score and Hip Disability and Osteoarthritis Outcome Score). A: Knee osteoarthritis; B: Hip osteoarthritis. HOOS: Hip Disability and Osteoarthritis Outcome Score; KOOS: Knee Injury and Osteoarthritis Outcome Score.

Patient satisfaction with treatment

The patient satisfaction response rates of "satisfied" or "very satisfied" on Visits 2, 3, and 4 were 78%, 79.9%, and 78.1%, respectively. Notably, over the visits, the proportion of patients who gave a rating of "very satisfied" tended to increase. In this regard, at Visit 2, 218/1070 (20.4%) patients rated treatment satisfaction as "very satisfied". This rating was given by 261/1065 (24.5%) patients and 312/1064 (29.3%) patients at Visits 3 and 4, respectively. The results of patients with knee OA and hip OA were generally comparable.



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Figure 4 Dynamics of Hip Disability and Osteoarthritis Outcome Score subscale scores. HOOS: Hip Disability and Osteoarthritis Outcome Score.

Concomitant analgesics therapy

At the end of each patient's observation period, the investigators were asked for their opinion on the need for concomitant analgesic therapy for patients during the study. According to the data at the initiation of GA + CS treatment, 200/1102 patients (18.1%) with knee or hip OA received regular NSAID/analgesic therapy, and 276 patients (25.0%) received analgesic therapy episodically. For the majority of these cases, oral treatment was used (375 patients). However, some patients required only topical anti-inflammatory products (45 patients) or a combination of topical and oral analgesics (56 patients).

At the end of the study, the number of patients using any types of analgesics or NSAIDs decreased from 43.6% to 12.68% ($P < 0.001$) in the knee OA group, and from 44.36% to 10.58% ($P < 0.001$) in the hip OA group (Figure 5). The majority of patients [953/1102 (86.5%) patients] did not require analgesic therapy by NSAIDs at the end of follow-up, showing significant reduction in the need of concomitant NSAIDs or analgesics therapy. Notably, a decrease in the need for the use of topical and oral analgesic therapy was observed in both knee OA and hip OA groups ($P < 0.001$ for both) (Figure 5).

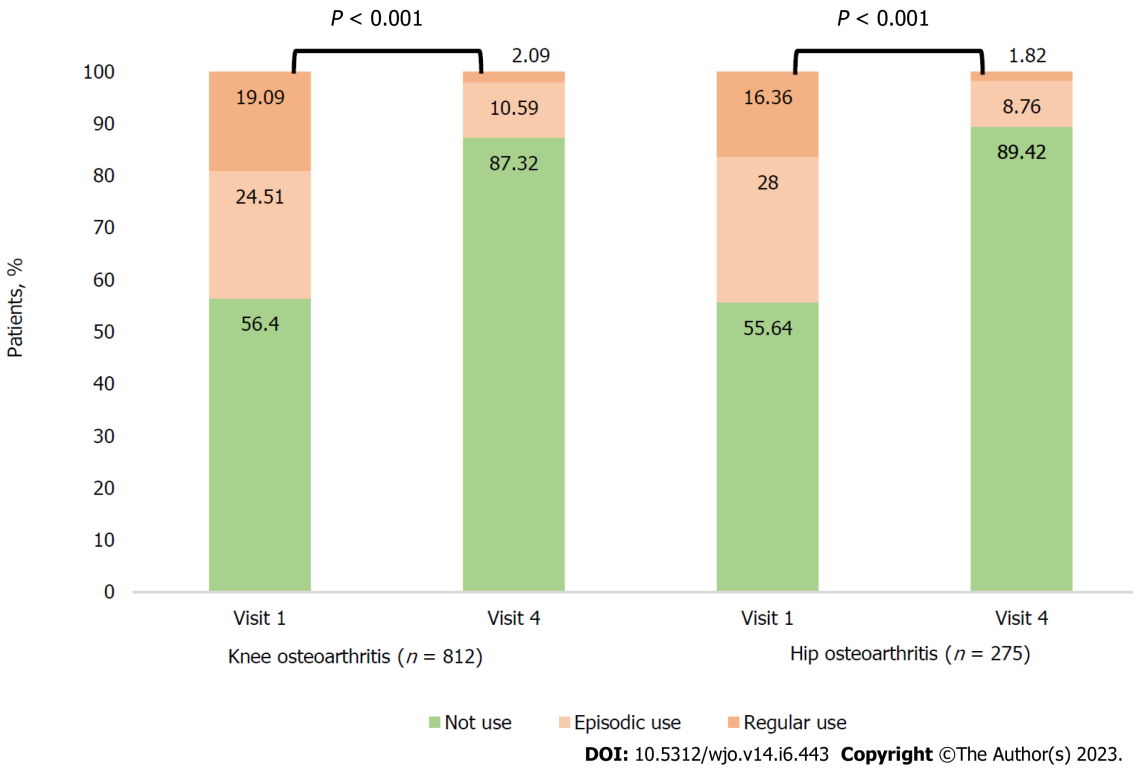
Adverse events

During the study, 307 AEs were reported in 190 (17.2%) participants. The most common AEs for systemorgan classes of MedDRA were: "Musculoskeletal and connective tissue disorders" (5.3%), "Gastrointestinal disorders" (4.7%), and "Infections and infestations"4.4%). The most common AEs by the Preferred Term included OA (worsening of the main diagnosis) (1.2%), upper abdominal pain (1.3%), upper respiratory tract infections (2.3%), and headache (1.3%). In most patients, AEs were mild [108 patients (9.8%)] or moderate [78 patients (7.1%)].

AEs considered by the investigators as "related to the study product" were reported for 31 (2.8%) patients (a total of 33 AEs) and mainly included gastrointestinal disorders [25 AEs in 24 (2.2%) patients]. The most common AE was upper abdominal pain [12 (1.1%) patients].

The dosage of GA + CS was reduced in 7 (0.6%) patients due to AEs (upper abdominal pain, diarrhea, dyspepsia, flatulence, stomach upset, hypothyroidism secondary to diffuse nodular goiter, and hyperuricemia). In 19 (1.7%) patients, AEs led to the cancellation of therapy with GA + CS. The most common cause was gastrointestinal disorders [12 (1.1%) patients]. Additionally, AEs, such as myalgia, cerebrovascular disorder, hypertension, essential hypertension, angina pectoris, peripheral edema, and hip arthroplasty were recorded.

Serious AEs (SAEs) were reported in 14 (1.3%) patients, including atrial fibrillation (2 patients), cholecystectomy, coronary bypass, hip arthroplasty, knee arthroplasty, hemorrhoids, ischemic thrombotic stroke, radicular pain syndrome, cholelithiasis, foot fracture, and myositis (one patient for



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Figure 5 The need for concomitant symptomatic therapy with non-steroidal anti-inflammatory drugs for target joints at baseline and at the end of the observation period.

each SAE). Additionally, one patient had several cardiac-related SAEs (atrial fibrillation, angina pectoris, chronic heart failure, ischemic cardiomyopathy, myocardial ischemia, and tachycardia) and another patient had gastrointestinal disorders (gastric ulcer and gastric ulcer bleeding, which was fatal). None of the SAEs were considered "related to the study product" by the investigator.

DISCUSSION

OA of knee and hip joints is one of the most common causes of disability and chronic pain worldwide. OA also implies significant medical and social costs, both directly due to treatment and indirectly because of reduced productivity and early retirement[3].

The main objectives of OA medication treatment are to alleviate pain, support quality of life, and maintain functional independence. Additionally, patients and doctors are concerned about possible adverse events caused by long-term use of NSAIDs[28,29]. The meta-analysis of the preferences of OA patients demonstrated, that patients evaluate side effects in the first place, when choosing medications, and the effectiveness of treatment significantly less affects the choice of therapy[29].

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SYSADOAs, including the combination of GA and CS, have been observed as effective and safe. SYSADOAs exert a delayed effect that persists after they are discontinued. These drugs have a symptomatic effect and could potentially slow down OA progression by influencing several pathways in the pathogenesis of the disease[30]. The effectiveness of GA or CS as monotherapies has been confirmed by several studies, which provided the prerequisites for the combination therapy[31,32]. In an experimental model, the combination of GA and CS increased the production of glycosaminoglycans in chondrocytes by 96.6% as compared to a 32% increase with the administration of each agent alone [33].

One of the most recent RCTs showed that combination of GA and CS was non-inferior to celecoxib in terms of reduction of pain, stiffness, and functional limitation after 6 mo in patients with painful knee OA, with a good safety profile[14]. In contrast, there are studies demonstrating inconsistent effects of GA and CS for OA treatment. For example, one of the largest studies [Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)] showed no difference among the response rates, following the criteria recommended by OARSI, of CS alone, GA alone, and their combination in all OA patients[34]. However, a potentially high clinical efficacy was demonstrated in patients with moderate to severe knee

pain. The proportion of patients whose pain syndrome had decreased by ≥ 20% by Week 24 was higher in the combination therapy group than in the placebo group (79.2% *vs* 54.3%, $P = 0.002$)[34]. Notably, a significant effect was demonstrated for the combination treatment, but not for the monotherapy of GA or CS[34]. The safety of GA and CS in OA has also been confirmed in a recent meta-analysis[35].

The aim of this prospective multicenter observational cohort study was to assess changes in pain, functions of daily living, and quality of life in patients with knee and hip OA who received long-term treatment with GA + CS (capsules, 500 mg + 400 mg) in a real-world clinical setting, using the KOOS and HOOS questionnaires. We consider that the initial characteristics of patients and the treatment results are consistent with the data accumulated to date on the effectiveness of the drug.

During this real-world clinical study, patients with knee OA and hip OA showed positive dynamics in all subscales of the KOOS and HOOS questionnaires (increases in the mean scores relative to the baseline values) at each visit during the observation period, with the most pronounced changes observed during the visit after the first treatment course of GA + CS (week 16-24). Hereafter, the effect achieved by the therapy was maintained with a tendency to increase during the entire observation period (Visit 3/week 36-44, Visit 4/week 56-64). Importantly, mean score increases in all KOOS subscales exceeded 8-10 points, which were consistent with the Minimal Clinically Significant Change (MCSC) according to Roos *et al*[36]. For the HOOS questionnaire, the mean score increases across all subscales were also higher than 8-10 points. While the MCSC score for the HOOS questionnaire currently remains under assessment, the results obtained in this study on the HOOS questionnaire could be considered clinically significant according to literature data[37,38]. It's also worth noting that positive dynamics was observed for each question of the KOOS and HOOS questionnaires. In this regard, the proportion of patients with less frequent and less intense symptoms and difficulties associated with OA increased.

Data on patients' satisfaction with the long-term treatment also demonstrated beneficial efficacy and safety profile. At the end of the treatment, almost 80% patients with knee or hip OA were "very satisfied" or "satisfied". Satisfaction with the result of treatment is an important guideline in the choice of therapy tactics. The Guidance for Osteoarthritis by The National Institute for Health and Care Excellence (NICE) says that OA patients may be able to self-manage their condition effectively after getting information and guidance on management strategies. So, healthcare professionals should focus on the person's needs, so there are some situations in which planned follow-up may be necessary[39].

In general, during the observation period, patients showed a decrease in the need for concomitant pain therapy. Initially, 18.1% of the patients received regular analgesic therapy, and 25.0% of the patients received this therapy on demand (episodically). In most cases, systemic oral drug products were taken. By the end of the observation period, most patients (86.5%) did not require analgesic therapy with NSAIDs. This decrease in the need of analgesics over the observation period might be attributed to the overall improvements in functionality and well-being of the joints.

Notably, patients complied with the recommendations for the treatment duration of GA + CS. According to the evaluation results of treatment duration, therapy lasted for more than 6 mo in most patients (68.0%), 3-6 mo in 23.7%, 1-3 mo in 7.1%, and up to 1 mo in 1.3%. Therefore, the majority of patients (91.7%) generally complied with the treatment recommendations given in approved local patient information leaflet (minimal recommended treatment duration is 3-6 mo).

The baseline characteristics of our patients were consistent with the population of patients with knee and hip OA. Most patients (75.1%) had secondstage OA according to the Kellgren & Lawrence classification. The most frequent comorbidities were primary arterial hypertension (44.6%) and obesity (23.2%).

AEs associated with GA + CS usage were registered only in 31 patients (2.8%), and mainly included gastrointestinal events, which was consistent with available information on the side effects of GA + CS. SAE was reported in 14 (1.3%) patients, which could be explained by the prevalence of older people with many comorbidities in the study population (average patient age: 60.4 years). However, no SAEs were related to GA + CS therapy.

Notably, usage of patient-reported outcomes (KOOS and HOOS questionnaires) is one of the strengths of this study. Patient used touch-screen tablets to report their daily functionality and quality of life during OA treatment. Currently, data regarding patient-reported outcomes in long-term observation of OA patients are lacking.

Limitations

This study had several limitations. First, it was not possible to directly assess the effectiveness of GA + CS, since the study was observational in its nature and did not include a control group. However, long-term follow-up of patients up to 64 wk greatly offsets this limitation and increases value of received real-world data. Additionally, the standard clinical setting implied certain limitations. For example, the inability to control the use of concomitant treatment and the inability to obtain data at all time points, which could adversely affect data interpretation. To simplify the process of completing the questionnaires and reduce the amount of information provided, the subscales "Everyday Life" and "Sports and Health Activities" of KOOS/HOOS questionnaires were replaced by the KOOS-PS and HOOS-PS short forms, respectively. Nonetheless, these scales demonstrated changes in OA symptoms, improvements in functionality of the joints and quality of life, and safety.

CONCLUSION

In the framework of routine clinical practice, after long-term treatment with a fixed combination of GA and CS, a decrease in pain syndrome and significant improvements in the functional state and quality of life of patients were observed. There was a significant reduction in the need for concomitant usage of analgesics. Most patients (approximately 80%) were satisfied with the treatment. The results of this real-world clinical study confirmed the potential benefit of the combination of GA and CS for the treatment of knee and hip OA.

Long-term supplementation with GA and CS combination could be considered a standard pharmacological option on top of non-pharmacological treatment measures during any disease stage. The results of this study were considered during the preparation of national clinical guidelines on the treatment of knee and hip OA in Russia[8,9].

ARTICLE HIGHLIGHTS

Research background

High prevalence of osteoarthritis (OA) forces healthcare professionals to look for efficient and safe long-term treatment options. Combined oral treatment with glucosamine (GA) and chondroitin sulfate (CS) was shown to be efficient for pain relief and function improvement in OA patients with moderate to severe knee pain in clinical trials. There is still need in additional data regarding their effectiveness in routine clinical practice.

Research motivation

Considering high prevalence of OA and its frequent co-existence with concurrent diseases, as well as the absence of proven long-term disease-modifying treatment options, the authors aimed to evaluate the effectiveness and safety of long-term therapy of GA and CS in the framework of real clinical practice. One of the key questions was to assess the effectiveness of this therapy in the treatment of the two most common OA affected joints – knee and hip. It was important to assess the dynamics of OA symptoms, including patients who were using non-steroidal anti-inflammatory drugs (NSAIDs), and assessment of the following need of concomitant analgesic therapy.

Research objectives

The main objective of the study was to evaluate dynamics of pain syndrome, functions of living, quality of life and satisfaction of patient as well as of actual study product utilization by patients with OA for an observation period up to 64 wk. The study was also aimed to evaluate the HCP approach to the treatment and management of patients with OA to understand the place of the combination of GA and CS in their recommendations and formed the basis for the development of clinical practice guidelines.

Research methods

An open-label multicenter non-interventional prospective cohort study enrolled patients with Hip or Knee OA stage I to III who started a treatment with combination of GA and CS to evaluate health status by physical examination and validated patient questionnaires for an observation period up to 64 wk. Patients visited clinical sites up to 4 study visits. During all visits data was collected by Investigators within the routine clinical practice. In addition, during each visit patient reported outcomes were generated, assessing Knee or Hip OA outcome, as well as a simple patient satisfaction questionnaire. Depending on the target joint, one of the questionnaires, either the Knee injury and Osteoarthritis Outcome Score (KOOS) or the Hip Osteoarthritis Outcome Score (HOOS) was used.

Research results

Mean improvement on Pain subscale in patients with knee and hip OA was 22.87 and 22.81 respectively, on the Symptoms subscales – 20.78 and 19.93, on the Physical Function subscale – 16.60 and 18.77, and on the Quality-of-Life subscale – 24.87 and 22.71 from baseline to the end of observation (up to 64 wk). Number of patients using any NSAIDs decreased from 43.1% to 13.5% by the end of the observation period. Treatment-related AEs were reported for 2.8% of patients and mainly included gastrointestinal disorders [25 AEs in 24 (2.2%) patients]. Most patients (78.1%) were satisfied with the treatment. Most patients (91.3%) generally complied with the recommended duration of treatment (not less than 3 mo per year).

Research conclusions

This observational study showed that long-term oral treatment with GA + CS is associated with decrease of pain, improvements of joint function, quality of life and decrease of concomitant usage of NSAIDs in patients with knee and hip OA in routine clinical practice. Treatment with GA + CS combination showed low incidence of drug-related AEs, and high level of patients' satisfaction with the

treatment along with high compliance with long duration of the treatment.

Research perspectives

In the long term perspective, this study will contribute to the enhancement of guidelines for the treatment of OA and improve the long-term outcomes for patients with OA. Authors believe, that application of the results of this study will help to reduce the medicinal load on the patient with analgesics and NSAIDs, which ultimately can reduce the number of concomitant adverse events and increase the safety profile of the therapy.

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FOOTNOTES

Author contributions: Lila AM and Alekseeva LI were the guarantors and designed the study, and reviewed study protocol. Baranov AA, Taskina EA, Kashevarova NG, Lapkina NA, and Trofimov EA participated in the acquisition, analysis, and interpretation of the data. Alekseeva LI and Taskina EA drafted the initial manuscript; Lila AM, Baranov AA, Taskina EA, LapkinaNA, and Trofimov EA critically revised the article for important intellectual content.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent for data collection prior to study enrollment.

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SYSTEMATIC REVIEWS

Cost-effectiveness of patient specific *vs* conventional instrumentation for total knee arthroplasty: A systematic review and meta-analysis

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Abstract

BACKGROUND

Over the past years, patient specific instrumentation (PSI) for total knee arthroplasty (TKA) has been implemented and routinely used. No clear answer has been given on its associated cost and cost-effectiveness when compared to conventional instrumentation (CI) for TKA.

AIM

To compare the cost and cost-effectiveness of PSI TKA compared to CI TKA.

METHODS

A literature search was performed in healthcare, economical healthcare, and medical databases (MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Library, EconLit). It was conducted in April 2021 and again in January 2022. Relevant literature included randomised controlled trials, retrospective studies, prospective studies, observational studies, and case control studies. All studies were assessed on methodological quality. Relevant outcomes included incremental cost-effectiveness ratio, quality-adjusted life years, total costs, imaging costs, production costs, sterilization associated costs, surgery duration costs and

readmission rate costs. All eligible studies were assessed for risk of bias. Meta-analysis was performed for outcomes with sufficient data.

RESULTS

Thirty-two studies were included into the systematic review. Two were included in the meta-analysis. 3994 PSI TKAs and 13267 CI TKAs were included in the sample size. The methodological quality of the included studies, based on Consensus on Health Economic Criteria-scores and risk of bias, ranged from average to good. PSI TKA costs less than CI TKA when considering mean operating room time and its associated costs and tray sterilization per patient case. PSI TKA costs more compared to CI TKA when considering imaging and production costs. Considering total costs per patient case, PSI TKA is more expensive in comparison to CI TKA. Meta-analysis comparing total costs for PSI TKA, and CI TKA showed a significant higher cost for PSI TKA.

CONCLUSION

Cost for PSI and CI TKA can differ when considering distinct aspects of their implementation. Total costs per patient case are increased for PSI TKA when compared to CI TKA.

Key Words: Total knee arthroplasty; Patient specific instrumentation; Instrumentation for total knee arthroplasty; Cost-effectiveness; Systematic review

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Core Tip: Patient specific instrumentation (PSI) for total knee arthroplasty (TKA) has become a frequently used technique for performing TKA. In the past decade the use of PSI TKA has not proven superior nor inferior when compared to conventional instrumentation (CI) for TKA in terms of prosthetic alignment, prosthetic survival, and patient satisfaction. However, PSI TKA has been associated with a higher healthcare cost. In this review, we critically analysed the cost of PSI TKA compared to CI TKA, focusing on all facets of their cost.

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INTRODUCTION

Total knee arthroplasty (TKA) has become a commonplace surgery worldwide. Indication for TKA is disabling osteoarthritis which is often accompanied by pain, reduced range of motion and intra-articular wear and tear[1]. New technology has emerged during the past decades to improve surgical techniques and equipment. Among these developments, patient specific instrumentation (PSI) for TKA was brought to the market, which could possibly prove superior to conventional instrumentation (CI) for TKA in terms of outliers in alignment. PSI may be used as a drill guide for pin placement and/or as cutting blocks to perform the femoral and tibial bony resections.

Numerous studies have been conducted on this subject with differing results[2-10]. For example, femoral and tibial implant alignment precision has shown improved[6], declined[7] or not differing when compared to CI TKA[2-5]. Decreased blood loss[4,8], shortened hospital stay[6], and reduced operating time[3,6,8] have been reported more consistently when using PSI TKA compared to CI TKA. These factors could be associated with decreased healthcare costs and an improved efficiency of patient care. Additionally, no difference in patient reported outcome measures between PSI TKA and CI TKA have been found in a 1-, 2-, 3- and 5-year follow-up study done by Schoenmakers *et al*[10]. Clinically, PSI TKA has thus far not proved to be superior to CI TKA. However, some logistic improvements have been suggested, which may lead to a decreased cost of surgery.

Studies on cost-effectiveness of PSI show mixed results[11,12]. The included outcomes of these studies differ and thus do not allow for a concluding statement on the cost-effectiveness of PSI TKA.

The aim of this study was to systematically review literature about the cost-effectiveness of PSI for TKA and perform a meta-analysis on the available data. Thereby, the aim was to provide an evidence-based answer on the cost-effectiveness of PSI TKA compared to CI TKA.

MATERIALS AND METHODS

Review and protocol

This systematic review was performed in accordance with PRISMA statement and in line with the five-step approach for constructing a review on cost-effectiveness by PeerJ[13], Moher *et al*[14], Shamseer *et al*[15], Van Mastrigt *et al*[16], Thielen *et al*[17], and Wijnen *et al*[18]. The following research question was postulated:

Is PSI TKA cost-effective when compared to CI TKA when used for adults with disabling osteoarthritis of the knee? All included articles were examined on methodological quality. The protocol for this systematic review and meta-analysis was registered in the PROSPERO database, in December 2021 (protocol number CRD42021269209)[19].

Search strategy and eligibility criteria

The following databases were systematically searched: OVID MEDLINE, EMBASE.com, CINAHL (*via* EBSCO), The Cochrane Library and The Cochrane Central of register for Controlled Trials (CENTRAL)/ Wiley, Web of Science/Clarivate Analytics and Econlit. Additionally, ongoing unpublished trials were identified on clinical trials.gov, the World Health Organization trial registry portal and PROSPERO. Reference lists of all papers about cost effectiveness of PSI TKA and/or CI TKA have been searched manually to ensure no papers were missed in the search. No search limitations were applied. The search strategy was in accordance with the Cochrane Highly Sensitive Search Strategy[20].

Studies meeting the following criteria were included into the review: (1) TKA for disabling osteoarthritis in adults; (2) PSI TKA and/or CI TKA; and (3) Cost-analysis and/or cost-effectiveness for TKA. Articles that included patients undergoing TKA for any other reason than osteoarthritis were excluded.

Study selection and data collection

All searched and eligible articles were independently reviewed by two reviewers (ID, LG) using RefWorks[21]. The studies searched in the databases were de-duplicated and selected titles were examined on titles and abstracts based on the eligibility criteria named above. Thereafter the reviewers examined the full text independently and decided whether articles should be included or excluded. Disagreement regarding the inclusion or exclusion was resolved by discussion between the reviewers and if required a third reviewer (MS) was consulted. Once articles were included the two reviewers (ID, LG) objectively and independently extracted data from the included articles. The reviewers were blinded to each other's extractions. The following data items were obtained during the extraction process, if available: Study ID (author, year), number of patients (*n*), age of patients in years (mean), number of female and male patients, country of study conduction, study design, length of hospital stay, operation time, tray sterilization cost, PSI production cost, imaging cost, staff cost, hospital stay cost, data on Quality-Adjusted Life Years (QALYs) and Incremental Cost-Effectiveness Ratio (ICER). Other study results include length of hospital stay, operation duration, readmission rates and patient characteristics and the costs tied to these.

All costs were converted to 2018 United States Dollars using a web-based tool. This tool was developed by the Campbell and Cochrane Economics Methods Group and the Evidence for Policy and Practice Information and Coordinating Centre (v.1.6, updated last April 2019)[22]. If studies reported an index year, this year was used for conversion. This tool was able to adjust costs up to 2018. Studies performed after 2018 were therefor indexed to 2018 despite them reporting later index years. If studies did not specify an index year, it was set using the year in which the last patients were included. If this was not applicable due to study design, year of study receival (in revised form) was used.

Quality assessment

Included studies were assessed by the two reviewers separately (ID, LG) for quality and risk of bias (RoB). The assessment for RoB was performed using the Cochrane Risk of Bias Tool. For randomised studies the RoB Tool 2.0 was used, for non-randomised studies the RoB-I Tool was used. Both tools were retrieved from the Cochrane Handbook for Systematic Reviews of Interventions[23]. Evidence level of the included articles has been determined using the level of Evidence Guidelines from the Oxford centre for Evidence-Based Medicine[24].

To evaluate the methodological quality of economic evaluations the Consensus on Health Economic Criteria (CHEC) list was used[25]. The CHEC-list scores range from 0 to 19 (0 being the lowest score and 19 being the highest).

Agreement on RoB, methodological quality and evidence level was reached through discussion between the two reviewers (ID, LG) after separate and individual assessment was performed.

Statistical analysis and meta-analysis

Studies have been stratified by geographical location, year of conduction, study design, level of evidence, RoB and CHEC scores. All costs, including QALYs and ICER values, have been adjusted for inflation using a web-based tool by Campbell and Cochrane Economics Methods Group and the

Evidence for Policy and Practice Information and Coordinating Centre (v.1.6, updated last April 2019) [22]. Due to differing sourcing of costs and a variety of countries of study conduction, results were expected to show heterogeneity. Results are therefore not presented as means. The reported costs are presented in ranges.

Review Manager version 5.3 (2014) was used to perform a meta-analysis of the study data. For the meta-analysis, a fixed effects model was used and relative risk was reported with a 95% confidence interval (CI), which was used when there was similarity in included study execution. Mean difference was selected as the effect measure. Results were statistically significant if $P \leq 0.05$. To quantify the statistical heterogeneity in the studies, the I^2 value was used. I^2 values of > 75% were interpreted as high heterogeneity[26]. Only if studies were sufficiently clinically, methodologically, and statistically homogenous, the data was pooled in a meta-analysis.

Data which could be included into the meta-analysis but was presented as ranges with a 95%CI were converted to standard deviations.

RESULTS

Search results

An extensive overview of the search can be found in Supplementary Table 1. The first search was conducted on April 26, 2021. The second and last search was conducted on January 24, 2022. The systematic search of the databases resulted in 16454 studies. The manual search of the relevant reference lists resulted in 6 additional examined studies. De-duplication was performed which resulted in a remainder of 10366 studies. These were screened on titles and abstracts by the two independent reviewers. Of these studies, 15 possible relevant titles had unavailable abstracts. They were sought for retrieval by a clinical epidemiologist (MH). Six of these titles were not retrieved. Out of all screened studies, 81 articles were eligible for full text analysis. After full-text analysis, 28 articles were included into the study. Three more studies were included after reference-list analysis. A second search was conducted with the exact search terms on January 24, 2022, to include any new literature. One additional study was eligible for inclusion. This resulted in the inclusion of a total of 32 studies. A full overview of the study selection procedure is shown in the PRISMA-flowchart in Figure 1. An overview of the included studies is presented in Table 1.

Study traits

The characteristics and patient demographic of the 32 included studies are summarized in Supplementary Table 2[11,12,27-56].

Of the included studies three were randomised controlled trials[27,38,44], twenty-one were retrospective studies[11,12,28-31,33,34,36,37,40-43,46,49-52,56], seven were prospective studies[32,35,39,45,47,48,55] and one was a theoretical cohort study[54]. Publication years ranged from 1998 to 2020. Of the included studies sixteen were cost-effect analyses, fifteen were financial studies, and two studies used financial decision models.

Eleven studies directly compared PSI TKA to CI TKA. Eight papers compared CI TKA to another type of TKA (robot-assisted, unicondylar, single-use). Six papers only analysed CI TKA. Six papers compared CI TKA to total hip arthroplasty. One single paper compared PSI TKA to CI TKA and single-use instruments for TKA.

Twelve studies assessed costs from a societal perspective[12,32-35,37,39,43,46,53-55], all other studies assessed costs from a hospital perspective. Studies obtained cost estimates by either using their own hospital data set, diagnosis-related group codes, Medicare data (for studies conducted in the United States) or other national cost databases.

The main outcome measure was QALYs for sixteen studies, TKA procedure related costs for eleven studies, and surgical instrumentation and sterilization costs for five studies.

In all studies determining cost-effectiveness based on QALYs, quality of life before and after TKA was determined using health-related quality of life (HRQoL) scores. Thirteen studies used the EQ-5D, SF-6D, SF-12, SF-36, 15D HRQoL or WOMAC to determine QALY gain for TKA. Three other studies determining QALY gain for TKA used a Markov model design.

The total sample size consisted of 19331 patients and 19360 performed TKAs. Of these, 3994 PSI TKAs and 13267 were CI TKAs. All other 2099 TKAs were either unicondylar, computer-assisted, single-use or robot-assisted TKAs.

Methodological quality of included studies

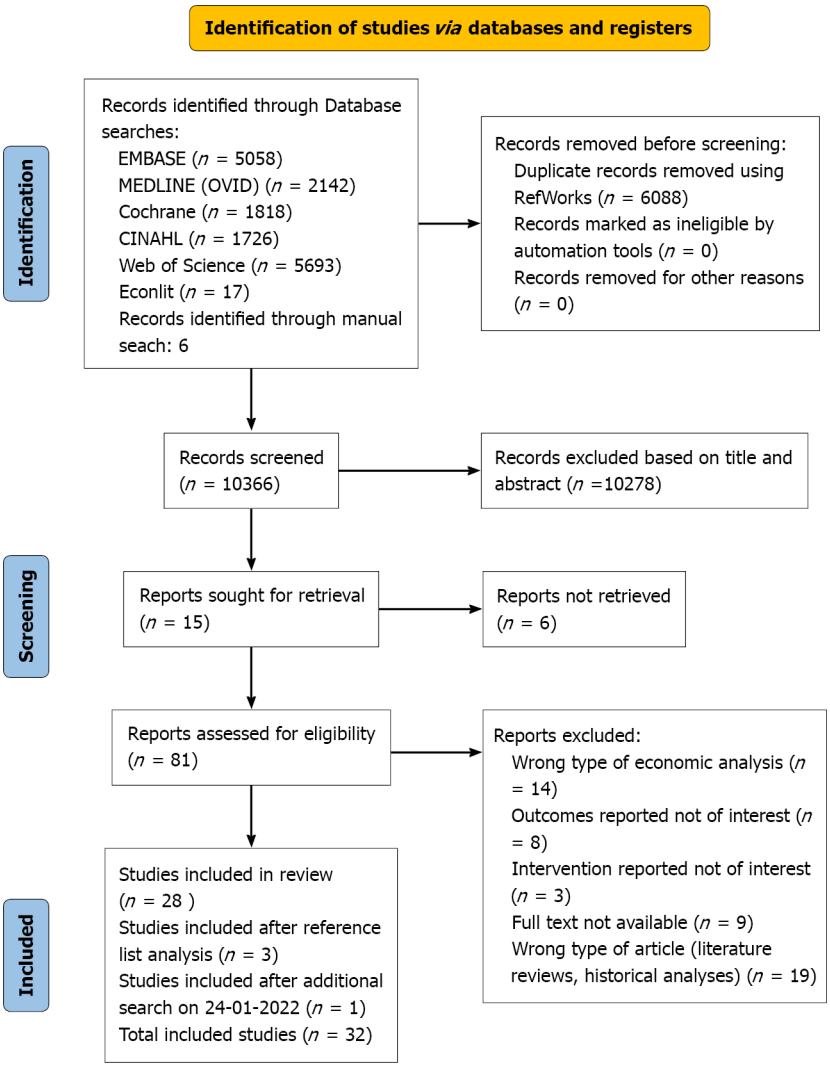
All three randomised studies had some concerns for RoB[27,38,44]. This was mainly caused by the presence of randomization bias. Thirteen non-randomised studies were assessed, of which eleven had a moderate risk of bias[11,31,36,41,42,48,49,51,52,55,56]. One single study showed a low risk of bias[40] and one study showed serious risk of bias[34]. The main domains in which studies showed moderate risk of bias were the possible presence of bias in measurement of outcome and bias in the selection of participants. The 17 remaining studies could not be assessed for risk of bias as they did not compare two

Table 1 Included articles and article attributes

Ref.	Country of conduction	Study design	Studied TKA types	Type of economic analysis
Attard *et al*[44], 2019	United Kingdom	RCT	PSI TKA *vs* CI TKA *vs* Single use inserts for TKA	Financial study
Barrack *et al*[31], 2012	United States	Retrospective	PSI TKA *vs* CI TKA	Financial study
Cotter *et al*[42], 2022	United States	Retrospective	CI TKA *vs* other[1] TKA	Financial study
Dakin *et al*[43], 2012	United Kingdom	Retrospective RCT-analysis	CI TKA	Cost-effectiveness analysis
Dakin *et al*[33], 2020	United Kingdom	Retrospective	CI TKA *vs* Total hip arthroplasty	Cost-effectiveness analysis
DeHaan *et al*[49], 2014	United States	Retrospective	PSI TKA *vs* CI	Financial study
Elmallah *et al*[29], 2017	United States	Retrospective comparative cohort	CI TKA *vs* Total hip arthroplasty	Cost-effectiveness analysis
Goldberg *et al*[30], 2019	United States	Retrospective	CI TKA *vs* other TKA	Financial decision model
Jenkins *et al*[32], 2013	United Kingdom	Prospective	CI TKA *vs* Total hip arthroplasty	Cost-effectiveness analysis
Konopka *et al*[37], 2018	United States	Retrospective	CI TKA *vs* Total hip arthroplasty	Cost-effectiveness analysis
Krummenauer *et al*[35], 2009	Germany	Prospective	CI TKA	Cost-effectiveness analysis
Lionberger *et al*[27], 2014	United States	RCT	PSI TKA *vs* CI TKA	Financial study
Losina *et al*[46], 2009	United States	Retrospective population analysis	CI TKA	Cost-effectiveness analysis
Moerenhout *et al*[36], 2021	Switzerland	Case control, retrospective chart	PSI TKA *vs* CI TKA	Financial study
Mont *et al*[48], 2012	United States	Prospective controlled trial	CI TKA *vs* other TKA	Financial study
Navarro Espigares and Hernández Torres[47], 2008	Spain	Prospective cohort	CI TKA *vs* Total hip arthroplasty	Cost-effectiveness analysis
Nunley *et al*[11], 2012	United States	Retrospective	PSI TKA *vs* CI TKA	Financial study
Peersman *et al*[53], 2014	Belgium	Retrospective	CI TKA *vs* other TKA	Cost-effectiveness analysis
Räsänen *et al*[45], 2007	Finland	Prospective	CI TKA *vs* Total hip arthroplasty	Cost-effectiveness analysis
Rorabeck and Murray[50], 1996	Canada	Retrospective	CI TKA	Financial study
Schilling *et al*[28], 2017	Australia	Retrospective	CI TKA	Cost-effectiveness analysis
Siegel *et al*[40], 2015	United States	Retrospective	CI TKA *vs* other TKA	Financial study
Slover *et al*[54], 2006	United States	Theoretical cohort	CI TKA *vs* other TKA	Cost-effectiveness analysis
Slover *et al*[12], 2012	United States	Retrospective	PSI TKA *vs* CI TKA	Financial decision model
Stan *et al*[34], 2015	Romania	Retrospective	CI TKA *vs* other TKA	Cost-effectiveness analysis
Teeter *et al*[38], 2019	Canada	RCT	PSI TKA *vs* CI TKA	Financial study
Thienpont *et al*[41], 2015	Belgium	Retrospective	PSI TKA *vs* CI TKA	Financial study
Thomas *et al*[56], 2022	United States	Retrospective	PSI TKA *vs* CI TKA	Financial study
Tibesku *et al*[51], 2013	Germany	Retrospective	PSI TKA *vs* CI TKA	Financial study
Waimann *et al*[39], 2014	United States	Prospective	CI TKA	Cost-effectiveness analysis
Watters *et al*[52], 2011	United States	Retrospective	PSI TKA *vs* CI TKA	Financial study

Xie *et al*[55], 2010	Singapore	Non-randomized prospective observational cohort	CI TKA *vs* other TKA	Cost-effectiveness analysis

[1]Other type of total Knee arthroplasty (TKA) includes robot-assisted, unicondylar or single-use TKA.
PSI: Patient specific instrumentation; CI: Conventional instrumentation; TKA: Total knee arthroplasty; RCT: Randomised controlled trial.



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Figure 1 PRISMA-flowchart of searches in databases and registers. This figure was generated using the PRISMA-diagram provided in the PRISMA statement.

or more interventions or used an economical model without patient population (*e.g.* Markov-model) to calculate cost-effectiveness[12,25,26,28-30,32,33,35,37,39,43,45-47,50,53,54].

The three included randomised studies have an evidence level of II[27,38,44]. One single study, a case control study, has a level of evidence of IV[36]. All other included studies have an evidence level of III [11,25,26-30,31,32,34,37,39-43,45-55]. The level of evidence and RoB of the included studies have been summarized in Supplementary Table 3.

Economic quality of the included studies according to the CHEC-score were moderate. CHEC-scores ranged from 11 to 17, with an average of 14. CHEC-scores are not available for two of the included studies (Rorabeck and Murray[50], Nunley *et al*[11])[11,50]. The scoring-system was not applicable for studies in which no costing-models or mean costs were used and/or presented. Basis for lower CHEC-scores was due to inappropriate study design for an economic analysis, a lack of incremental analysis of costs and outcomes, a lack of sensitivity analysis of costs and outcomes, a lack of discounting of costs for appropriate index years and a lack of analysis on ethical aspects of intervention costs. A summary of CHEC scores per study can be found in Supplementary Table 4.

Study results

Reported costs and inflation-adjusted costs, are summarized in Supplementary Table 5.

Imaging costs

Imaging costs were defined as all imaging needed for patients preoperatively. For CI TKA, this included standard X-ray imaging of the affected knee. Imaging costs for CI TKA ranged from $52.51 to $901.48 [39,42,50,54]. Imaging for PSI TKA was defined as MRI-imaging needed to model the PSI. The reported costs ranged from $226.79 to $13942.40[12,27,31,41,44,49,51]. A single study directly compared imaging costs for PSI TKA and CI TKA[51]. The study reported an increased imaging cost of $12091 for PSI TKA.

PSI TKA production costs

PSI production costs were defined as the cost of producing the PSI model. Costs were reported to range from $377.98 to $119.35 per model[12,31,44,49,51,52]. The types of PSI models used in the included studies were the patient-specific cutting blocks from MyKnee (Medacta), KneePlan (Symbios), Visionaire (Smith & Nephew's) and Zimmer-Biomet's Signature knee system. For CI TKA, no additional production costs were reported.

Sterilization costs

Sterilization costs were defined as the cost of sterilizing surgical instrument trays per surgical case. Studies have reported a decrease in tray usage when TKA is performed using PSI. The amount of trays needed for CI TKA in all studies ranged from 6 to 34 trays per patient case[41,48,51,52]. For PSI TKA the amount of trays needed per patient case ranged from 1 to 5 trays[41,49,51,52].

A decrease of 4 trays per case have been reported in two studies when using PSI TKA[49,51]. A decrease of 5 trays per case have been reported in two other studies when using PSI TKA[41,52]. Tray sterilization costs ranged from $353.89 to $1533.32 per case for CI TKA[30,41,42,44,51,52]. For PSI TKA, tray sterilization costs ranged from $67.60 to $495.50 per case[36,44,49,52]. In three studies costs of tray sterilization between PSI TKA and CI TKA were directly compared. All three studies reported cost decrease when using PSI TKA[44,51,52]. However, they do not report the amount of decrease in a monetary value.

Operating room time and costs

Operating room (OR) time was defined as time from patients entering the OR to leaving the OR, patient preparation time combined with surgery time, and time from the start of the patient case to the start of the next patient case.

When using CI TKA, studies reported mean OR times that ranged from 63.10 ± 38.02 min to 141.3 ± 22.1 min[11,41,42,44,49,51,52]. When using PSI TKA, studies reported mean OR times that ranged from 58.10 ± 23.04 min to 148.2 ± 16.2 min.

Six studies directly compared mean OR time differences between CI and PSI TKA. One study reported a prolonged mean OR time of 2 min, resulting in associated $1985 in costs when using PSI TKA [41]. The remaining five studies reported a reduced mean OR time when using PSI TKA[40,44,49,51,52]. Time savings reported in these studies ranged from 5 min to 30 min when using PSI TKA.

Additionally, five studies reported the comparison of OR time and their associated costs between CI TKA and PSI TKA. One study does not give exact OR times for CI or PSI TKA. They reported that PSI TKA usage is associated with a mean OR time decrease of 11 min which translated to saving $226.54 per patient case[31]. The three remaining studies observe a decrease in mean OR time when using PSI TKA [49,51,52]. The decrease in mean OR time per patient case for PSI TKA was reported to be between 13 and 30 min[49,51,52]. The associated decrease in cost is respectively between $117.36 and $1416.38[49,51, 52].

Readmission rates

One study reports lower readmission rates when using PSI TKA compared to CI TKA[56]. Patients who received a TKA using PSI had statistically significant ($P \leq 0.05$) lower readmission rates at 30 d (2.03% *vs* 2.92%), 60 d (2.65% *vs* 4.02%), 90 d (3.19% *vs* 4.62%), and at one year (6.46% *vs* 8.76%).

Total TKA costs

Total costs for TKA were defined as the sum of costs per patient case for OR time, inpatient stay, sterile processing, surgeon cost, imaging costs, PSI production, TKA implant, and/or postoperative care.

Nine studies solely reported total costs for CI TKA[28-30,32,39,42,43,47,55]. The reported mean cost for CI TKA ranged from $1391 to $29163.16 per patient case.

One study solely reported total cost for PSI TKA[27]. The reported mean cost for PSI TKA was $12642.27 per patient case.

Four studies compared mean PSI TKA costs directly to mean CI TKA costs[38,51,52,56]. In three of the comparing studies, PSI TKA was more costly than CI TKA[38,51,52]. In one study PSI TKA was less costly than CI TKA[56].

The first study found a mean costs per patient case of $9337.17 ± 5446.83 for CI TKA compared to $13352.33 ± 10783.22 for PSI TKA[38]. The following studies found these mean costs per patient case to be respectively; $8177.77 compared to $8264.76[51], $2989.46 compared to $3608.84[52], and $16379.17 (16182.84-16577.55) compared to $15246.19 (15067.24-15427.18)[56]. An overview of total TKA costs for PSI and CI is presented in Figure 2.

QALY gain

QALY gain was determined as the amount of QALYs gained in a certain number of years after TKA. Seven studies reported data on this for CI TKA[28,29,34,35,37,45,46], no studies reported data on QALY gain for PSI TKA. QALY gain was determined using the EQ-5D in three studies and the SF-12, SF-6D, 15D HRQol and SF-36 were used in the remaining four studies. QALY gain per year for CI TKA was reported as; 0.77/1 year[28], 0.768/1 year[29], 2.6/1 year[34], 0.17/1 year[37], 0.359/1 year[45], 2.93/0.25 years[35] and 1/7.957 years[46].

Cost per QALY

Costs per QALY were determined in eight of the included studies. QALY outcomes were based on EQ-5D in four studies[34,35,43,47], EQ-5D-3L in two studies[32,33], 15D HRQoL in one study[45] and a Markov model in one other study[12].

One study compared PSI and CI TKA directly[12]. PSI TKA costs $4700/QALY compared to $2900/QALY for CI TKA. Costs per QALY gained determined for CI TKA ranged from $1275.84 per QALY to > $20000 per QALY[32-35,43,45,47].

ICER per QALY

ICER per QALY was defined as the price per QALY gained for TKA. Four studies presented data on this for CI TKA[29,46,53,55]. No studies presented this data for PSI TKA. ICER per QALY ranged from $20090.25/QALY to $76384.09/QALY.

Meta-analysis

A meta-analysis was performed using the data on total cost for PSI TKA and CI TKA. Two studies were included into the meta-analysis[38,56]. Two other studies (Tibesku *et al*[51], Watters *et al*[52]) comparing total cost for both techniques could not be included into the analysis due to lack of ranges or standard deviation[51,52].

The forest plot is presented in Figure 3. Study heterogeneity was high, with an I^2 of 78% (P = 0.03). The overall effect was in favour of CI TKA, with a significant mean difference of $1132.98 [850.00-1383.32] 95%CI (P > 0.00001) less when compared to PSI TKA.

DISCUSSION

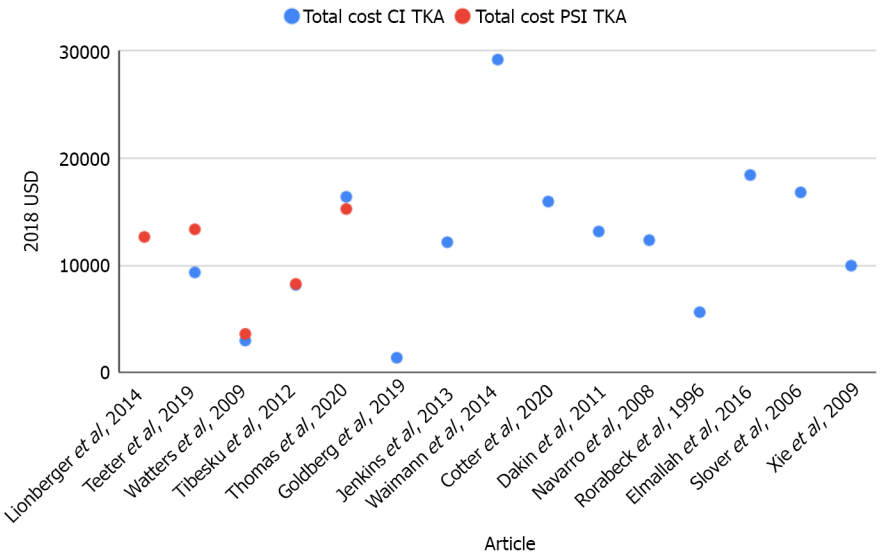
The goal of this systematic review was to assess the cost-effectiveness of PSI TKA compared to CI TKA. Additionally, results were pooled into a meta-analysis. The study aimed to combine the most accurate results available on this topic to produce a clear answer as to whether PSI TKA is a cost-effective alternative to CI TKA.

The main conclusion is that there is a lack of literature on PSI TKA when it comes to data on QALYs and ICER. Furthermore, data on costs of PSI TKA and CI TKA show heterogeneity. Due to this, no definite conclusion can be drawn on the cost-effectiveness of PSI TKA when directly compared to CI TKA. This systematic review has shown that PSI TKA costs less when considering OR time and tray sterilization. PSI TKA costs are increased when considering imaging, production, and costs per total patient case.

There was a large heterogeneity in costs due to differences in calculation methods of costs and patient charges per study. Additionally, country of study conduction has an impact on prices. Furthermore, differences in patient population (such as age, comorbidities, anatomic variance of knee joints) per study could influence the cost outcome. In this systematic review costs were directly compared, but the abovementioned factors should be considered when interpreting the outcome of these comparisons. For example, studies performed in the United States often reported much higher costs than studies performed in Europe.

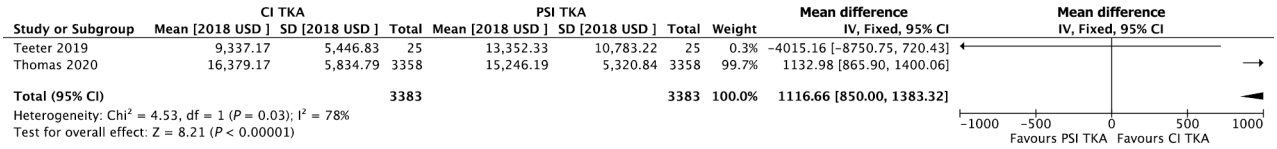
A meta-analysis was performed, the results were heterogeneous and therefore did not provide conclusive evidence. Furthermore, no meta-analysis could be performed on the QALY or ICER data as no studies were found that directly compared these for PSI TKA and CI TKA. In the future, studies should directly assess and directly compare cost-effectiveness using QALYs and ICER.

Multiple studies have investigated whether PSI TKA is superior to CI TKA when it comes to prosthetic placement, peri- and post-operative outcomes. Schotanus *et al*[57] described that PSI TKA was ready for primetime after performing a comparative study with CI TKA. The study compared four different PSI TKA systems to CI TKA in a total of 117 knees. PSI TKA was showed to have a lower number of significant outliers[57]. Predescu *et al*[58] performed a comparative study, where PSI and CI



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Figure 2 Scatter plot of total cost for patient specific instrumentation total knee arthroplasty and conventional instrumentation total knee arthroplasty per study. Total costs for patient specific instrumentation (PSI) total knee arthroplasty (TKA) and conventional instrumentation (CI) TKA per paper. This figure present costs without variance. The figure shows the heterogeneity of total cost per patient case for PSI TKA and CI TKA when compared in multiple different studies. When directly compared PSI TKA costs more per patient case in three[38,51,52] out of four[56] studies. PSI: Patient specific instrumentation; TKA: Total knee arthroplasty; CI: Conventional instrumentation; USD: United States Dollars.



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Figure 3 Forrest plot of meta-analysis of total cost of patient specific instrumentation total knee arthroplasty compared to conventional instrumentation total knee arthroplasty. PSI: Patient specific instrumentation; TKA: Total knee arthroplasty; CI: Conventional instrumentation; USD: United States Dollars. This figure has been generated using Review Manager version 5.3 (2014).

TKA were compared in a population of 80 patients. They found that PSI TKA did not prove superior however posed as an alternative for CI TKA or computer assisted TKA[58]. Furthermore, Sassoon *et al* [59] described in their systematic review that PSI TKA has not reliably demonstrated improvement of postoperative limb or component alignment[59]. Despite this, PSI TKA has remained popular due to its relatively easy production and especially its usefulness as an additional planning tool in anatomically challenging cases. This systematic review shows that in most cases, more costs are associated with the use of PSI TKA. The results of this review could be taken into consideration when making decisions on whether and when to use PSI TKA.

One single study included into this systematic review determined additional costs for readmission rates related to either PSI or CI use for TKA[55]. The results from this study showed that CI TKA was associated with higher readmission rates, which is associated with increased costs of $6753 ± 175[60]. Thus, more investigation into cost-effectiveness related to readmission rates could be useful for future decision-making regarding instrumentation choices in general. This should also be reconsidered now that robotics are being introduced for TKA at a rapid pace, which entails the additional necessary costs [61].

Results from this systematic review were extracted from a variety of countries. As a result of this, pricing may vary for developing countries or countries with different types of health care pricing systems.

In regards to study quality, multiple studies received sponsoring or funding through prosthetic and/or orthopaedic manufacturers[28,30,33,41,42,46,50]. Minimal influence on the results is expected due to these sponsorships since not all authors were associated with the sponsorships, nor did they receive any payment for the conducted study. Additionally, variety in definition of utilities per study should be considered as pricing may not be based on the exact same parameters per case. Therefore, not all costs in this systematic review should be considered as directly comparable to any or every country. However, these costs are an indication of true cost of PSI and CI TKA worldwide.

This systematic review provided a detailed overview of relevant literature on costs and cost-effectiveness of PSI compared to CI TKA. Systematic reviews on PSI TKA which investigate facets of its costs, such as tray sterilization, are available[59]. However, this systematic review aimed to present relevant literature on all facets of costs associated with PSI TKA and CI TKA.

The strength of this systematic review is its methodological quality. It was executed in accordance with the five-step approach for constructing a review on cost-effect by Van Mastrigt *et al*[16] and the PRISMA statement[13-18]. Furthermore, a large patient population and all the attributed costs for CI and PSI TKA were analysed.

Its limitation is, however, the possibility of biased results due to exclusion of non-full texts.

CONCLUSION

This study showed that costs for PSI TKA and CI TKA can differ when considering different aspects of their implementation in a hospital setting. A comprehensive overview of the contributing components to the pricing of CI and PSI TKA is provided. When considering total costs, PSI TKA is more costly when directly compared to CI TKA.

ARTICLE HIGHLIGHTS

Research background

Over the years, extensive research into the clinical outcomes of patient specific instrumentation (PSI) for total knee arthroplasty (TKA) compared to conventional instrumentation (CI) for TKA have been performed. Clinically, the instrumentation techniques are considered equal. However, decreased operating time and sterilization tray usage have been reported when using PSI TKA. These factors could influence the healthcare cost.

Research motivation

Multiple studies into the cost and cost-effectiveness of PSI and CI TKA have been performed since its introduction. Most studies consider specific aspects of their costs, such as: Additional imaging costs, PSI production costs, operating time costs, and tray sterilization costs. Furthermore, studies on Quality Adjusted Life Years (QALY) and Incremental Cost Effectiveness Ratio (ICER) for PSI and CI TKA have been performed. Despite the abundance of research, no clear overview or comparison has been presented. The motivation for this systematic review was to give a clear overview of the cost and cost-effectiveness of PSI TKA compared to CI TKA.

Research objectives

The objective of this research was to present the different aspects of cost of PSI TKA and CI TKA. Furthermore, cost-effectiveness was investigated. By doing this, the secondary objective was to advise orthopaedic surgeons in their decision making when choosing either PSI TKA or CI TKA.

Research methods

A systematic literature search was performed in healthcare, economical healthcare, and medical databases (MEDLINE, EMBASE, CINAHL, Web of Science, Cochrane Library, EconLit). Relevant literature included randomised controlled trials, retrospective studies, prospective studies, observational studies, and case control studies. Data extraction was performed to obtain the following results: ICER, QALYs, total costs, imaging costs, production costs, sterilization associated costs, surgery duration associated costs and readmission rates and associated costs. Meta-analysis was performed for outcomes with sufficient data.

Research results

Thirty-two studies were included into the systematic review. Two were included in the meta-analysis. 3994 PSI TKAs and 13267 CI TKAs were included in the sample size. We found that when considering mean OR time and its associated costs and tray sterilization per patient case, PSI TKA costs less than CI TKA. PSI TKA is more costly compared to CI TKA when considering imaging and production costs. Considering total costs per patient case, PSI TKA is more expensive in comparison to CI TKA. Meta-analysis comparing total costs for PSI TKA, and CI TKA showed a significant higher cost for PSI TKA.

Research conclusions

This study showed that costs for PSI TKA and CI TKA can differ when considering different aspects of their implementation. When directly comparing PSI and CI TKA, results showed that total costs per patient case are more for PSI TKA.

Research perspectives

Based on the results presented, we recommend orthopaedic surgeons worldwide make careful decisions when deciding on which instrumentation technique to use for TKA. In anatomically challenging cases PSI is a helpful planning modality for TKA. However, this systematic review showed that the total cost of its implementation is higher per patient case. Surgeons are advised to take the cost-effectiveness and total cost into consideration.

FOOTNOTES

Author contributions: Dorling IM designed the research; Dorling IM and Geenen L performed the research; Heymans MJLF performed the systematic search; Dorling IM and Geenen L performed the data analysis; Most J, Boonen B, and Schotanus MGM supervised the research and revised the manuscript; Dorling IM wrote the paper.

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SYSTEMATIC REVIEWS

Return to sport following toe phalanx fractures: A systematic review

Greg A J Robertson, Amit Sinha, Thomas Hodkinson, Togay Koç

Specialty type: Orthopedics

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

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Abstract

BACKGROUND

Evidence-based guidance on return to sport following toe phalanx fractures is limited.

AIM

To systemically review all studies recording return to sport following toe phalanx fractures (both acute fractures and stress fractures), and to collate information on return rates to sport (RRS) and mean return times (RTS) to the sport.

METHODS

A systematic search of PubMed, MEDLINE, EMBASE, CINAHL, Cochrane Library, Physiotherapy Evidence Database, and Google Scholar was performed in December 2022 using the keywords 'Toe', 'Phalanx', 'Fracture', 'injury', 'athletes', 'sports', 'non-operative', 'conservative', 'operative', 'return to sport'. All studies which recorded RRS and RTS following toe phalanx fractures were included.

RESULTS

Thirteen studies were included: one retrospective cohort study and twelve case series. Seven studies reported on acute fractures. Six studies reported on stress fractures. For the acute fractures (n = 156), 63 were treated with primary conservative management (PCM), 6 with primary surgical management (PSM) (all displaced intra-articular (physeal) fractures of the great toe base of the proximal phalanx), 1 with secondary surgical management (SSM) and 87 did not specify treatment modality. For the stress fractures (n = 26), 23 were treated with PCM, 3 with PSM, and 6 with SSM. For acute fractures, RRS with PCM ranged from 0 to

100%, and RTS with PCM ranged from 1.2 to 24 wk. For acute fractures, RRS with PSM were all 100%, and RTS with PSM ranged from 12 to 24 wk. One case of an undisplaced intra-articular (physeal) fracture treated conservatively required conversion to SSM on refracture with a return to sport. For stress fractures, RRS with PCM ranged from 0% to 100%, and RTS with PCM ranged from 5 to 10 wk. For stress fractures, RRS with PSM were all 100%, and RTS with surgical management ranged from 10 to 16 wk. Six cases of conservatively-managed stress fractures required conversion to SSM. Two of these cases were associated with a prolonged delay to diagnosis (1 year, 2 years) and four cases with an underlying deformity [hallux valgus (n = 3), claw toe (n = 1)]. All six cases returned to the sport after SSM.

CONCLUSION

The majority of sport-related toe phalanx fractures (acute and stress) are managed conservatively with overall satisfactory RRS and RTS. For acute fractures, surgical management is indicated for displaced, intra-articular (physeal) fractures, which offers satisfactory RRS and RTS. For stress fractures, surgical management is indicated for cases with delayed diagnosis and established non-union at presentation, or with significant underlying deformity: both can expect satisfactory RRS and RTS.

Key Words: Acute; Stress; Fracture; Toe; Phalanx; Return; Sport; Rate; Time

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Core Tip: We performed a systematic review, assessing studies that recorded return rates (RRS) and return times (RTS) to sports following acute and stress fractures of the toe phalanges. Thirteen studies were included. Seven studies reported on acute fractures (n = 156); six studies on stress fractures (n = 26). For acute fractures, 63 underwent primary conservative management (PCM), 6 primary surgical management (PSM), and 1 sary surgical management (SSM). For stress fractures, 23 underwent PCM, 3 PSM, and 6 SSM. For acute fractures, PCM conferred acceptable RRS and RTS. PSM was indicated for displaced intra-articular proximal phalanx fractures. For stress fractures, PCM, when successful, conferred acceptable RTS. Significant delays to diagnosis or associated deformity often necessitated the conversion to SSM: this was invariably successful at returning athletes to sport.

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INTRODUCTION

Acute toe phalanx fractures are a relatively common injury, comprising 3%-4% of all traumatic fractures [1-4]. Most of these fractures occur within the first and fifth toes, with the majority being undisplaced or minimally displaced, and suitable for conservative management[5]. The functional results following these injuries have shown promising results[5].

While 16% of all acute toe fractures occur during sport, the incidence and outcome of these fractures in the athlete remain poorly defined[6]. Traumatic toe phalanx fractures have been found to comprise 4.5% of all sport-related fractures, and occur at an incidence of 0.06 per 1000 of the general population [6].

By comparison to acute fractures, the epidemiology of toe phalanx stress fractures is less well described[7]. While a significant proportion of these fractures are sport-related, the current literature on this injury type comprises a limited number of case series and case reports[7]. While there are emerging theories that link biomechanical deformities to their occurrence (*e.g.* hallux valgus and great toe proximal phalanx stress fractures), a comprehensive description of this fracture type has yet to be presented[8].

The most common causative sports for acute toe phalanx fractures are soccer, gymnastics, and judo [9]. The most common causative sports for stress-toe phalanx fractures are sprinting, soccer and long-distance running[7]. For acute toe phalanx fractures, the common sporting mechanisms of injury include tackle and dismount[9].

Regarding treatment, with the vast majority of acute toe phalanx fractures being undisplaced or minimally displaced and extra-articular, they are managed conservatively, with toe strapping and

protected weight-bearing[5,9]. Those that are significantly displaced or intra-articular, are often managed with closed +/- open reduction with k-wire or screw fixation[9]. Open fractures require fracture site washout +/- fixation[9]. Stress fractures of the toe phalanx are routinely managed conservatively in the first instance, with protected weight-bearing and avoidance of relevant sporting activities [7]. However, those with significantly delayed presentation (> 1 year) and established non-union, or those that are associated with a significant causative deformity, often require surgical intervention[7].

Despite this treatment framework, there is very limited information in the current literature to guide the optimal management of these fractures in the athlete[7,9-11]. Similarly, there is very limited published data, which illustrates the expected morbidity that such fractures will have on the athlete[7,9-11].

This systematic review aims to provide a comprehensive overview of the current literature which records return to sport following acute fractures and stress fractures of the toe phalanges in the athlete.

MATERIALS AND METHODS

Literature search

The authors performed a systematic analysis of the listed databases in December 2022: PubMed, MEDLINE, EMBASE, CINAHL, Cochrane Library, Physiotherapy Evidence Database (PEDro), and Google Scholar.

The search aimed to identify all peer-reviewed studies, which recorded return rates to sport (RRS) and return times to sport (RTS) in patients who sustained toe phalanx fractures. The search terms used were 'toe', 'phalanx', 'fracture', 'injury', 'athletes', 'sports', 'non-operative', 'conservative', 'operative', 'surgical', and 'return to sport'. All articles were considered, regardless of the date of publication or level of the sport.

The review was structured along the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[12]. Two authors (X.X.X., X.X.X.) searched for and reviewed the articles. Table 1 records the inclusion and exclusion criteria. The QUOROM Process for the review is illustrated in Figure 1.

The authors excluded technical notes, case reports, instructional course reports, biomechanical reports, articles of expert opinion, and literature reviews, unless these manuscripts contained relevant patient data. Similarly, articles reporting on return to sport following toe sesamoid fractures were excluded. A stepwise process of article assessment was performed, first reviewing all the relevant titles, then abstracts, then full-length articles as required. Relevant reference lists and review studies were also assessed to locate further studies, which were appropriate for inclusion. Any disagreement in article inclusion was confirmed through consensus agreement or liaison with the senior author.

Data extraction

The recorded data from each study included: Demographic details, mechanism of injury (for acute fractures), duration of preceding symptoms (for stress fractures), pre-operative imaging investigations, fracture location, fracture nature (acute *vs* stress) and fracture severity, conservative and surgical treatment methods, RRS, RTS, return rates to pre-injury level of sport, complications, outcome scores recorded, and relevant predictive factors.

Acute fractures and stress fractures were grouped separately. For the acute fracture studies, some papers recorded the fractures with no differentiation regarding fracture type or location: These studies were grouped as 'general cohort' studies. Other studies specifically described the management of intra-articular (physeal) fractures of the base of the great toe proximal phalanx: These were grouped as 'Intra-Articular (Physeal) Base of Proximal Phalanx Fractures'.

Outcome measures

The primary outcome data was RRS and RTS. The secondary outcome data included 'return to pre-injury level of sport' rates and relevant complications.

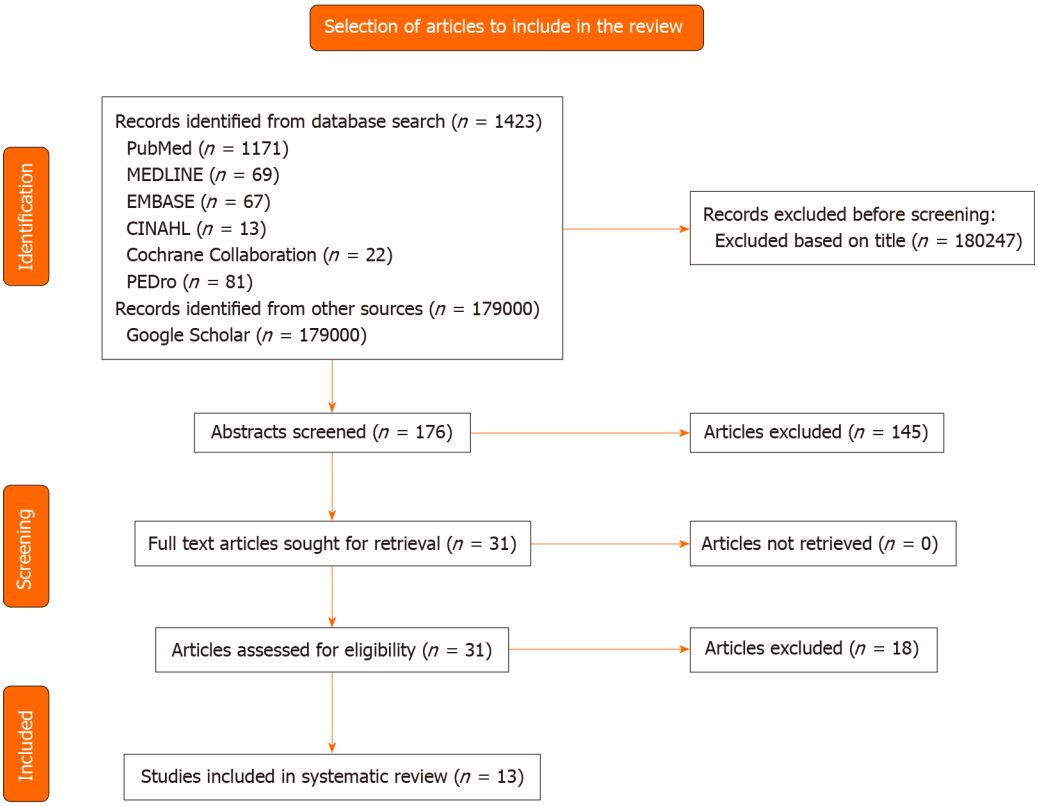
Study definitions

RRS was defined as the percentage of athletes who successfully returned to sport with the designated treatment modality. Where conversion to a further treatment was required, with RRS not possible from the initial treatment method, this was recorded as a non-return to sport for the method in question. For conservative treatment, RTS was defined as the time from the commencement of conservative treatment to return to sport. For surgical treatment, RTS was defined as the time from the commencement of the relevant surgical treatment to return to sport[13].

If surgical management was chosen as the first-line treatment, this was referred to as 'primary surgical management' (PSM). If surgical management was chosen following failed conservative management, this was referred to as 'secondary surgical management' (SSM). Return times to sport for 'secondary surgical management' were recorded from the relevant surgical procedure.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Acute toe phalanx fractures	Toe sesamoid fractures
Stress toe phalanx fractures	Toe joint dislocation without fracture
Elite or recreational athletes	Toe joint fracture dislocation
Return rate to sporting activity reported	Toe ligament injuries
Time to return to sporting activity reported	No sporting outcome data reported
Two or more injuries reported	Concomitant upper or lower limb fractures
Peer-reviewed journals	Reviews, case reports, abstracts, or anecdotal articles
English language	Animal, cadaver, or *in vitro* studies



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Figure 1 Selection of articles to include in for inclusion in the review by in accordance with the PRISMA protocol[12].

Quality assessment

Study quality was quantified by the modified Coleman Methodology Score (CMS), as described by Coleman *et al*[14]. Study quality was also assessed by the Methodological Index for Non-Randomized Studies (MINORS) Score. Two of the authors calculated the modified CMS and the MINORS Score for each study (X.X.X, X.X.X). Inter-observer reliability of the modified CMS and MINORS scoring processes were quantified using the intra-class correlation co-efficient statistic. For the modified CMS, this was 0.98 (95%CI: 0.96-1.00). For the MINORS scores, this was 0.92 (95%CI: 0.89-0.94).

Statistics

There was insufficient data to perform data synthesis or meta-analysis comparisons within the data. Thus, the available data was presented as a systematic review, without the use of analytic statistics. The intra-class correlation co-efficient statistic was used to assess the inter-observer reliability of the Modified Coleman Scores and the Methodological Index for Non-Randomized Studies Scores using IBM SPSS Statistics, Version 27.0 (Armonk, NY, United States).

RESULTS

Search

The details of the review process for the included articles are provided in Figure 1. In total, 176 abstracts and 31 articles were reviewed.

Quality of the included studies

The mean CMS for all the studies was 49.6 (range 34-67)[8,15-26] (Tables 2 and 3). For the studies reporting on acute fractures, the mean CMS was 53.1 (range 39-67)[15-21] (Table 2). For the studies reporting on stress fractures, the mean CMS was 45.5 (range 34-55)[8,22-26] (Table 3).

The mean MINORS score for all the studies was 10.3 (range 8-18)[8,15-26] (Tables 2 and 3). For the studies reporting on acute fractures, the mean MINORS score was 12.1 (range 9-18)[15-21] (Table 2). For the studies reporting on stress fractures, the mean MINORS score was 8.2 (range 8-9)[8,22-26] (Table 3).

Patient demographics

13 relevant studies[8,15-26] were identified, (year of publication from 1986[22] to 2022[18]), which recorded return to sports data for patients who sustained toe phalanx fractures (Table 2). One of these studies was a retrospective cohort study[18], and 12 were case series[8,15-17,19-26].

There were 156 acute toe phalanx fractures and 26 stress fractures. Eight of the acute fractures were specifically described as intra-articular (physeal) (all great toe bases of the proximal phalanx). Of the acute fractures, 14 occurred in the great toe, 1 in the second toe, and 1 in the third toe, and the location was not specified for 140. Of the stress fractures, 22 occurred in the proximal phalanx of the great toe and 4 in the proximal phalanx of the second toe. Of the 26 stress fracture patients, 16 (of the 22 great toe proximal phalanx stress fracture patients) had associated 'hallux valgus' deformity, and 1 (of the 4-second toe proximal phalanx stress fracture patients) had associated 'claw toe' deformity (Table 3). Regarding the etiology of the deformities, only one case noted the deformity to have developed secondary to the stress fracture[26].

Of the 156 acute fractures, 129 (83%) occurred in male patients, 23 (15%) in female patients, and 4 (3%) failed to specify gender. None of the studies reported bilateral fractures. Follow-up data were available for 154 (99%) of the 156 acute fractures. The mean age at the time of injury ranged from 12.5 years[19,21] to 21.1 years[15], and the causative sports included soccer, gymnastics and judo (Table 2).

Of the 26 stress fractures, 10 (38%) occurred in male patients, and 16 (62%) in female patients. None of the studies reported bilateral fractures. Follow-up data were available for all 26 (100%) of the stress fractures. The mean age at the time of injury ranged from 13.7 years[23] to 29.0 years[24], and the causative sports included sprinting, soccer, long-distance running, rugby, Japanese Fencing/Kendo, triathlon, gymnastics, baseball and volleyball (Table 3). The recorded duration of symptoms before diagnosis ranged from 1 wk to 2 years[24,26].

Fracture nature and classification

Seven of the studies reported on acute toe phalanx fractures exclusively[15-21]. Three of these studies reported on acute intra-articular (physeal) fractures of the base of the great toe proximal phalanx specifically[19-21]. Six of the studies reported on stress-toe phalanx fractures exclusively[8,22-26].

Of the acute fracture studies, one 'general cohort' study used the AO classification to describe the fracture types[15]. All of the acute 'intra-articular (physeal) fracture' studies used the Salter-Harris Fracture Classification to describe the fracture types[19-21]. None of the stress fracture studies used classification systems to describe the fracture patterns[8,22-26].

Of the 156 acute fractures, 69 (44%) specified treatment modality. Of these, 63 (91%) were treated with 'primary conservative management', and 6 (9%) with 'primary surgical management'. One fracture was converted to 'secondary surgical management' after failed conservative treatment (Table 4). Of the 8 intra-articular (physeal) acute fractures, all (100%) specified treatment modalities: 6 (75%) underwent 'primary surgical management' and 2 (25%) underwent 'primary conservative management'. One intra-articular fracture was converted to 'secondary surgical management' after failed conservative treatment. This was following a re-fracture on return to sport (Table 4).

Of the 26 stress fractures, all (100%) specified treatment modality: 23 (88%) were treated with 'primary conservative management', and 3 (12%) were treated with 'primary surgical management' (Table 5). Six stress fractures were converted to 'secondary surgical management' after failed conservative treatment (Table 5). Of these six, two were associated with a delayed diagnosis (1 year and 2 years respectively), and 4 were associated with an underlying deformity [hallux valgus (n = 3), claw toe (n = 1)] (Table 5).

Choice of radiological imaging

Plain radiography was the diagnostic imaging modality used in acute fracture studies[15-21]. All the stress fracture studies used plain radiography as first-line diagnostic imaging[8,22-26]. In addition to this, one stress fracture study used magnetic resonance imaging/computed tomography Scan to aid diagnosis[26], and another study used Tc-99 Bone scanning as second-line imaging[22].

Table 2 Demographic data - acute fractures

Ref.	*n*	Study type	Mean age (yr)	Male:Female	Follow-up, %	Sport	Level of sport	Most common MOI	Location	Modified coleman score	MINORS score
General cohort											
Robertson *et al*[15], 2012	8	Case series	21.1	8:0	6 (75)	Soccer	General population	Tackle (50%)	Great toe (n = 6) 2nd Toe (n = 1); 3rd Toe (n = 1)	44	12
Larsson *et al*[16], 2016	18	Case series	N/A	18:0	18 (100)	Soccer	Elite/Professional	N/A	N/A	39	12
Chan *et al* [17], 2021	53	Case series	N/A	32:21	53 (100)	US Collegiate Sports	Collegiate	N/A	N/A	54	12
Diaz *et al* [18], 2022	69	RCS	N/A	69:0	69 (100)	Soccer	Elite	N/A	N/A	41	18
Intra-Articular (Physeal) base of proximal phalanx fractures											
Maffulli [19], 2001	2	Case series	12.5	2:0	2 (100)	Soccer (n = 1), Judo (n = 1)	Recreational	Tackle	Great toe proximal phalanx	65	9
Perugia *et al*[20], 2014	4	Case series	13-15	N/A	4 (100)	Gymnastics (n = 4)	Adolescent high level	Dismount	Great toe proximal phalanx	67	11
Bariteau *et al*[21], 2015	2	Case series	12.5	0:2	2 (100)	Gymnastics (n = 2)	Elite	Dismount	Great toe proximal phalanx	62	11

MOI: Mechanism of injury; RCS: A retrospective cohort study.

Table 3 Demographic data - stress fractures

Ref.	*n*	Study type	Mean age (yr)	Male:Female	Follow-up, %	Sport	Level of sport	Location	Associated deformity	Modified coleman score	MINORS score
Yokoe *et al* [22], 1986	3	Case series	16.3 (12-21)	1:2	3 (100)	Sprinting (n = 1), Rugby (n = 1), Kendo (n = 1)	Amateur	Great Toe Proximal Phalanx	Hallux valgus (n = 3)	34	8
Shiraishi *et al*[23], 1993	3	Case series	13.7 (12-17)	1:2	3 (100)	Volleyball (n = 1), Long Distance Running (n = 1), Soccer (n = 1)	Amateur	Great toe proximal phalanx		51	9
Yokoe *et al* [8], 2004	10	Case series	16.3 (12-21)	2:8	10 (100)	Sprinting (n = 6), Distance Running (n = 1), Basketball (n = 1), Rugby (n = 1), Kendo (n = 1)	N/A	Great toe proximal phalanx	Hallux valgus (n = 9)	35	8
Pitsis *et al* [24], 2004	2	Case series	29 (17-41)	0:2	2 (100)	Triathlon (n = 1), Gymnastics (n = 1)	Non-professional/Elite	Great toe proximal phalanx	Hallux valgus (n = 1)	46	8
Munemoto *et al*[25], 2009	4	Case series	14.5 (13-17)	2:2	4 (100)	Short track running (n = 3), Soccer (n = 1)	Amateur	Great toe proximal phalanx	Hallux valgus (n = 3)	55	8
Yamaguchi *et al*[26], 2017	4	Case series	14.8 (13-16)	4:0	4 (100)	Soccer (n = 3), Baseball (n = 1)	N/A	2nd toe proximal phalanx	Claw toe (n = 1)	52	8

Management

Acute fractures: Conservative management: There were 63 acute fractures treated with 'primary conservative management' (Table 4).

Table 4 Outcome data - acute fractures

Ref.	*n*	Treatment (%)	Return to sport (%)	Return to the same level of sport (%)	Return time to sport	Secondary surgery - return rate (RR)/Return time (RT)	Persisting symptoms (%)	Complications
General cohort								
Robertson *et al* [15], 2012	6	PCM (100)	3 (50)	3 (50)	7.0 wk (mean)		3 (50)	Nil
Larsson *et al* [16], 2016	18	N/A	N/A	N/A	26 d (mean)		N/A	1 re-fracture
Chan *et al*[17], 2021	53	PCM (100)	53 (100)	N/A	8.5 d (median)		N/A	1 re-fracture
Diaz *et al*[18], 2022	69	N/A	N/A		30 d (median)		N/A	Nil
Intra-articular (Physeal) base of proximal phalanx fractures								
Maffulli[19], 2001	2	PCM (50) PSM (50)	2 (100)	2 (100)	By 6 mo		0 (0)	0 (0)
Perugia *et al* [20], 2014	4	PSM (100)	4 (100)	4 (100)	By 3 mo		0 (0)	0 (0)
Bariteau *et al* [21], 2015	2	PCM (50) PSM (50)	1 (50) (PSM)	1 (50) (PSM)	5 mo	1 – RR 100%/RT 14 wk	0 (0)	1 re-fracture (PCM)

PCM: Primary conservative management; PSM: Primary surgical management.

Table 5 Outcome data - stress fractures

Ref.	*n*	Treatment (%)	Return to sport (%)	Return to the same level of sport (%)	Time to return to sport (mean)	Secondary surgery - return rate (RR)/Return time (RT)	Factors associated with secondary surgery	Persisting symptom (%)	Complications (%)
Yokoe *et al* [22], 1986	3	PCM (67) PSM (33)	3 (100)	N/A	PCM - 3 mo; PSM - N/A			0 (0)	0 (0)
Shiraishi *et al* [23], 1993	3	PCM (100)	3 (100)	3 (100)	6 wk			1 (33)	1 non-union for a patient who did not stop training (33)
Yokoe *et al* [8], 2004	10	PCM (100)	6 (60)	6 (60)	N/A	4 (40) – RR 100%	Hallux valgus deformity (n = 3)	0 (0)	3 delayed unions with PCM (50)
Pitsis *et al* [24], 2004	2	PCM (100)	0 (0)[a]	0 (0)[a]	N/A	1 (50) – RR 100%	2-yr delay to diagnosis	0 (0)	1 non-union with PCM (50)
Munemoto *et al*[25], 2009	4	PCM (50) PSM (50)	4 (100)	4 (100)	PCM - 8.5 wk, PSM - 10 wk			0 (0)	1 mild deformity with PCM (50)
Yamaguchi *et al*[26], 2017	4	PCM (100)	3 (75)	3 (75)	5 wk	1 (25) – RR 100%/RT 4 mo	1-yr delay to diagnosis/Claw toe deformity	0 (0)	1 non-union and claw toe deformity with PCM (25)

[a]1 no return due to fear of re-injury. PCM: Primary conservative management; PSM: Primary surgical management.

Only two of the 'general cohort' studies specified the type of management[15,17]. Both studies used conservative management for the fractures[15,17]. The type of conservative management was not described[15,17].

All the 'intra-articular (physeal) fracture' studies described the type of management selected[19-21]. Of the two which employed conservative management, the techniques included: heel weight-bearing in a forefoot offloading shoe for 6 wk, referral to physiotherapy at 6 wk, the commencement of training at 12 wk[19]; and 6 wk of non-weight bearing with immobilization, with a return to sport at 3 mo[21].

Surgical management: There were six acute 'intra-articular (physeal) fractures' treated with primary surgical management[19-21]. The described techniques included: open reduction with K-wire fixation (n

= 4), open reduction with screw fixation and cancellous bone graft (n = 1), and open reduction with no fixation (n = 1)[19-21]. One fracture was managed with secondary surgical management, using open reduction and screw fixation[21].

The post-operative regimes included heel weight-bearing in a forefoot offloading shoe for 6 wk, with the removal of K-wire and referral to physiotherapy at 6 wk, and commencement of training at 12 wk [19]; non-weight bearing with cast immobilization for 4 wk, with subsequent removal of K-wire at 4 wk and commencement of weight-bearing[20]; non-weight bearing in a moon boot orthotic for 6 wk, with progressive weight-bearing for the next 4 wk in the orthotic, then gradual weaning from the orthotic, with the commencement of impact activities at 10 wk post-op[21].

Stress fractures

Conservative management: There were 23 stress fractures treated with 'primary conservative management' (Table 5). All studies described the management techniques used[8,22-26].

The management techniques fell into three categories: cessation of sporting activities, with no formal immobilization or other restrictions, for 4 to 8 wk[22,23,25,26]; immobilization of the foot in a cast for 5 wk[25]; non-weight bearing on the affected side with crutches for 3 to 6 wk[24].

All regimes were then followed with a graduated return to sporting activities[8,22-26], which could be supplemented by shoes with shock-absorbing insoles[23], foot orthoses with medial arch support, and a metatarsal pad[26] or a 2nd to 5th metatarsal bar orthosis[24].

Surgical management: There were 3 stress fractures treated with 'primary surgical management' (Table 5). The reported techniques were: Open reduction with drilling, screw and K-wire fixation (n = 1), open reduction with drilling and screw fixation (n = 1), and osteotomy for hallux valgus correction (n = 1)[22,25]. There were 6 stress fractures treated with 'secondary surgical management' (Table 5). The reported techniques were: Open reduction internal fixation (n = 3), osteotomy for hallux valgus correction (n = 1), open reduction with scar tissue debridement, screw and K-wire fixation (n = 1), surgical excision of the non-union, open reduction with cancellous bone graft and screw fixation (n = 1) [8,24,26].

The post-operative regimes included: immediate weight-bearing, with the commencement of activities 8 wk post-operatively[25] (– 'primary surgical management'); non-weight bearing for 4 wk, with the removal of K-wire and commencement of heel weight-bearing at 4 wk, and commencement of mobilization exercises at 6 wk[26] (– 'secondary surgical management'); non-weight bearing for 6 wk, then partial weight bearing in a walker boot for 6 wk, then a graduated return to training[24] (– 'secondary surgical management').

Functional assessment

Two of the acute fracture studies used formal scores to record post-treatment outcomes[20,21]. These included: a 'Visual Analog Pain' scale, the 'American Orthopaedic Foot and Ankle Society (AOFAS) Hallux Metatarsal Phalangeal' scale, the 'Short Form-36 (SF-36) Physical Component Summary (PCS)' and the 'Short Form-36 (SF-36) Mental Component Summary (MCS)'[20,21].

None of the stress fracture studies used formal scores to record post-treatment outcomes[8,22-26].

Return rates to sports

Acute fractures: Conservative management: Four studies recorded RRS following conservative management of acute fractures[15,17,19,21]. The RRS ranged from 0 to 100%[15,17,19,21] (Table 4 and Figure 2A).

The return rates to pre-injury level sports for the conservatively-managed acute fractures ranged from 0% to 100%[15,19,21] (Table 4).

Surgical management: Three studies recorded RRS following PSM of acute fractures[19-21], and one study recorded RRS following SSM of acute fractures[21]. The recorded RRS were 100% for PSM[19-21], and 100%% for SSM[21] (Table 4 and Figure 2A).

The return rates to pre-injury level sports for the surgically-managed acute fractures were all 100% [19-21] (Table 4).

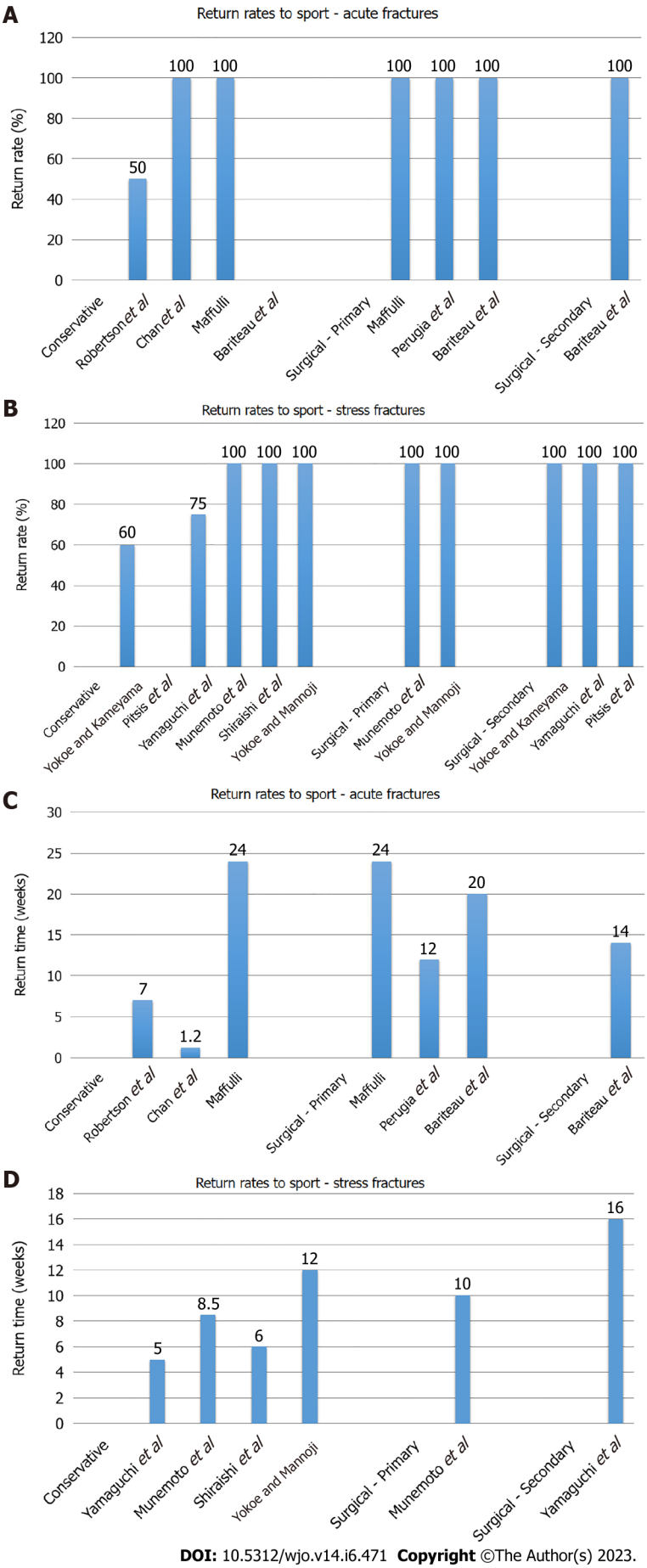
Stress fractures

Conservative management: Six studies recorded RRS following conservative management of stress fractures[8,22-26]. The RRS ranged from 0 to 100%[8,22-26] (Table 5 and Figure 2B).

The return rates to pre-injury level sports for the conservatively-managed stress fractures ranged from 0% to 100%[8,23-26] (Table 5).

Surgical management: Two studies recorded RRS following PSM of stress fractures[22,25], and three studies recorded RRS following SSM of stress fractures[8,24,26]. The recorded RRS was 100% for PSM [22,25], and 100% for SSM[8,24,26] (Table 5 and Figure 2B).

The return rates to pre-injury level sports for the surgically-managed stress fractures were 100%[25] (Table 5).



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Figure 2 Return rates to sport. A: Acute Fractures; B: Stress Fractures; C: Acute Fractures; D: Stress Fractures.

Return times to sports

Acute fractures: Conservative management: Three studies recorded RTS following conservative management of acute fractures[15,17,19]. The RTS ranged from 8.5 d to 6 mo[15,17,19] (Table 4 and Figure 2C).

Surgical management: Three studies recorded RTS following PSM of acute fractures[19-21], and one study recorded RTS following SSM of acute fractures[21]. The RTS ranged 3 to 6 mo for PSM[19-21], and was 14 wk for SSM[21] (Table 4 and Figure 2C).

Stress fractures

Conservative management: Four studies recorded RTS following conservative management of stress fractures[22,23,25,26]. The RTS ranged from 5 wk to 3 mo[22,23,25,26] (Table 5 and Figure 2D).

Surgical management: One study recorded RTS for PSM of stress fractures[25], and one study recorded RTS for SSM of stress fractures[26]. The recorded RTS for PSM was 10 wk[25], and for SSM was 4 mo[26] (Table 5 and Figure 2D).

Radiographic union

One of the acute fracture studies recorded radiographic union, with a 100% final union rate[21]. Five of the stress fracture studies recorded radiographic union[22-26]. Four of the studies reported a 100% final union rate[22,24-26], and one study reported a 67% final union rate[23].

Complications

Acute fractures: Three of the acute fracture studies recorded complications, which were re-fracture (Table 4).

Stress fractures: Five of the stress fracture studies recorded complications, which were delayed union with primary conservative management, non-union with primary conservative management, and residual deformity (Table 5).

Predictive factors

While the majority of sport-related toe phalanx fractures were treated with 'primary conservative management', acute intra-articular (physeal) fractures had high rates of 'primary surgical management', especially when displaced[19-21].

Sixteen of the twenty-two 'great toe' phalanx stress fractures had an associated hallux valgus deformity[8,22-25]. One of the four 'second toe' proximal phalanx stress fractures had an associated claw toe deformity[26].

Three of the four 'second toe' proximal phalanx stress fractures had a history of stress fractures at other locations, with two of the patients having a history of stress fractures at multiple locations[26].

Of the six stress fractures that required 'secondary surgical management', one-third of cases (n = 2) had a significant delay to diagnosis (1 year and 2 years respectively)[24,26], and two-thirds of cases (n = 4) had an associated deformity [hallux valgus (n = 3)/claw toe (n = 1)][8,26].

DISCUSSION

This systematic review found that the majority of sport-related toe phalanx fractures are treated with 'primary conservative management', with satisfactory results for RRS and RTS. For acute fractures, intra-articular (physeal) fractures, especially when displaced, had high rates of 'primary surgical management'. Such fractures had uniform good RRS, though had prolonged RTS, due to the required post-operative restrictions. For stress fractures, those with significantly delayed diagnosis or with significant underlying causative deformity were at risk of requiring surgical intervention. Again, such fractures, when treated surgically, demonstrated good overall RRS, though with prolonged RTS due to the required post-operative restrictions. However, given the limited, heterogenous data available, it was difficult to draw firm conclusions from this review.

The quality of the included studies in this review was lower than that of similar studies[13,27-31], with a mean CMS of 49.6. This was particularly true for the stress fracture studies, with a mean CMS of 45.5.

From the review data, it is difficult to conclude the optimal management of acute sport-related toe phalanx fractures[15-21]. The results appear to support 'primary conservative management' of extra-articular, non or minimally displaced fractures, with overall acceptable RRS and RTS[15-21]. 'Primary surgical management' should be reserved for extra-articular fractures which are significantly displaced, rotated, or open[9]. However, there is no evidence to guide such recommendations[15-21]. Surgery is also indicated for displaced, intra-articular (physeal) fractures[9]. There is moderate evidence to support this recommendation, with the need to restore joint surface congruency, especially in the adolescent athlete[19-21]. However, if these fractures are non or minimally displaced, they can be treated with

'primary conservative management'[19-21]. The review shows reasonable RRS and RTS for both primary conservative and surgical management of these fractures, however, surgical management has longer RTS, due to post-operative restrictions[15-21]. Refractures following 'primary conservative management' necessitating 'secondary surgical management' is associated with a notably prolonged RTS[21].

Regarding the optimal surgical technique for intra-articular fractures, several methods have been described, though the evidence is inadequate to conclude which is best[19-21]. Compared to K-wire fixation, screw fixation avoids the risk of pin-track infection and may allow for a quicker return to non-contact training activities (no risk of catching and dislodging the K-wire), but such theories are yet to be proved[19-21,32].

With a variety of rehabilitation techniques described, it is difficult to confirm which is the optimal method[15-21]. It would appear that heel weight-bearing in a forefoot offloading shoe can be recommended, both with 'primary surgical management' and 'primary conservative management'[15-21]. This avoids the need for complete non-weight bearing, allowing more muscle mass preservation[15-21]. Following such restrictions, for between 4 to 6 wk, a graduated return to activities can be commenced[15-21].

Reviewing the common sporting mechanisms of injury (tackle and dismount), it would appear there may be a future role for improved protective footwear, to reduce the incidence of traumatic toe phalanx fractures[15,19-21]. Modification of technique, especially in gymnastics, may also allow for future reduction in the incidence of such fractures. However, further research on this topic is required to confirm such theories[32].

Similar to acute fractures, with the limited, heterogeneous data available, it remains difficult to conclude the optimal management for sport-related, toe phalanx stress fractures[8,22-26]. Anatomically, these should be 'low-risk' stress fractures, so conservative management should form the first line of treatment[7,33,34]. This has been shown to provide acceptable RRS and RTS[8,22-26]. However, due to variations in the anatomy of the foot, some of these fractures can be associated with an underlying deformity (*e.g.* hallux valgus), which can create a biomechanically 'tension-sided', 'high risk' type[8,22,24-26,33,34]. For instance, with hallux valgus, it has been advocated that the medial-sided structures (medial collateral ligament and abductor hallucis) provide an adverse traction force, that potentiates a shear force during exercise, which propagates the stress fracture[8]. In such cases, 'primary surgical management' may be necessary to correct the fracture or the deformity[8,22].

Assessing the data available, it would appear that conservative management is acceptable first-line management for all toe phalanx stress fractures[8,22-26]. 'Primary surgical management', however, can be considered for cases with significant underlying deformity, especially when they show delayed healing with initial conservative management. It can also be considered for cases with significant delays to diagnosis (> 1 year), with evidence of established non-union at presentation[8,22-26]. Such 'primary surgical management' could prevent delayed recovery, due to unnecessary prolonged initial conservative management[8,22-26].

Regarding the optimal surgical technique, there is insufficient data to conclude this[8,22,24-26]. One may consider that the surgeon must correct any underlying significant deformity, at the time of surgical treatment[8,22,24-26]. However, the available data shows that this is not always necessary, to facilitate a successful, timely return to sport[8]. Deformity correction at the time of surgery may reduce the chance of recurrence of the stress fracture on return to sport[8]. However, the more complex surgical technique required may incur a higher risk of complications, prolonged post-operative immobilization and a prolonged return to sport[8]. As such, the optimal strategy for this problem remains to be defined[8]. With established non-unions, the adjunct of biological stimulus (*e.g.* bone grafting) should be considered [24].

Regarding the optimal rehabilitation with 'primary conservative management', it would appear that initial cessation of sporting activities for around 4 to 8 wk is an appropriate first-line plan[8,22-26]. If successful, this should be followed by a graduated return to sport[8,22-26]. For surgical management, heel weight-bearing in a forefoot offloading shoe for 6 wk, followed by a graduated return to sports is similarly an appropriate regime[8,22,24-26].

While modifiable predisposing factors have been extensively reviewed for stress fractures as a whole, with important findings such as sub-optimal physiological condition (*e.g.* female athlete triad), excessive repetitive training, and abnormal physiological load, there is limited information regarding this for toe phalanx stress fractures[7,8,22,24-26,34]. As discussed previously, the associated deformity is a significant predisposing factor for these fractures, and this should be actively sought and monitored appropriately[8,22,24-26]. Similarly, tight footwear, which exacerbates such deformities, should be avoided[8]. Further research is required to determine optimal methods by which to prevent such injuries in the future[8,22-26].

There are several limitations to this study. These are predominantly based on the limited, heterogeneous data on the topic[8,15-26].

The lack of available literature on toe phalanx fractures has been previously highlighted[5]. This is likely a consequence of most toe phalanx fractures being managed directly from emergency departments, with limited input from orthopedic services[35]. Future collection of data on this subject should be encouraged, through the relevant services, to increase the information on this topic.

Despite this, of the studies retrieved, several of those with high cohort numbers failed to stratify the fractures by toe or phalanx injured, or by treatment type received[16-18]. Such limitations prevent accurate analysis of these datasets and subsequently preclude data synthesis and meta-analysis of the available studies.

As such, it was not possible to draw firm conclusions on the optimal treatment and rehabilitation of these injuries, nor the expected RRS and RTS[8,15-26]. Further more detailed, research on this topic is required, stratifying outcome data by fracture location and a treatment selected.

CONCLUSION

There is limited information on return to sport following toe phalanx fractures. The majority of acute fractures are treated with 'primary conservative management', with overall satisfactory RRS and RTS. 'Primary surgical management' is reserved for significantly displaced fractures or displaced intra-articular fractures and has been found to achieve good RRS and RTS. Conservative management forms the first line of treatment for sport-related, toe phalanx stress fractures. When successful, this can result in appropriate RTS. Surgical management is indicated with associated deformity and delayed union, or with significantly delayed presentation and established non-union. In both instances, good RRS and RTS can be achieved. Further research is required to better define the optimal treatment and rehabilitation of sport-related, toe phalanx fractures.

ARTICLE HIGHLIGHTS

Research background

There is very little evidence available to guide the management of toe phalanx fractures in the athletic population.

Research motivation

This is the first systematic review to assess return to sport following toe phalanx fractures. It provides a comprehensive overview of the available literature, assessing both acute fractures and stress fractures.

Research objectives

To systemically review all studies recording return to sport following toe phalanx fractures (including acute fractures and stress fractures), and to collate information on return rates to sport (RRS) and return times (RTS) to the sport.

Research methods

A systematic search of all relevant scientific databases was performed followed by manual screening of articles according to the eligibility criteria.

Research results

Most toe phalanx fractures were treated conservatively. Surgical management was reserved for displaced or intra-articular acute fractures, as well as symptomatic stress fracture non-unions, and stress fractures with significant underlying deformity. RRS for both acute fractures and stress fractures managed conservatively ranged from 0% to 100%. RRS for both acute fractures and stress fractures managed surgically was 100%. RTS after conservative management ranged from 8.5 d to 6 mo for acute fractures, and 5 wk to 3 mo for stress fractures. RTS after surgical management ranged from 3 to 6 mo for acute fractures, and 10 wk to 4 mo for stress fractures.

Research conclusions

The majority of sport-related toe phalanx fractures (acute and stress) are managed conservatively with overall satisfactory RRS and RTS.

Research perspectives

Currently, the available literature regarding return to sport after toe phalanx fractures is limited, with most studies being low-volume case series. Further research is required to better define the optimal treatment and rehabilitation of sport related toe phalanx fractures.

FOOTNOTES

Author contributions: Robertson GAJ conceived the methodology for the manuscript, performed the literature search and analysis for the study and wrote the manuscript; Sinha A performed the literature search and analysis for the study, and reviewed and edited the manuscript; Hodkinson T advised on the study, and reviewed and edited the manuscript; Koç T advised on the study, and reviewed and edited the manuscript.

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META-ANALYSIS

Effectiveness of platelet-rich plasma in the treatment of Achilles tendon disease

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Abstract

BACKGROUND

The effectiveness of Platelet-Rich Plasma (PRP) in the treatment of patients with Achilles tendon rupture (ATR) and Achilles tendinopathy (AT) has been controversial.

AIM

To assess PRP injections' effectiveness in treating ATR and AT.

METHODS

A comprehensive review of relevant literature was conducted utilizing multiple databases such as Cochrane Library, PubMed, Web of Science, Chinese Science and Technology Journal, EMBASE, and China Biomedical CD-ROM. The present investigation integrated randomized controlled trials that assessed the effectiveness of platelet-rich plasma injections in managing individuals with Achilles tendon rupture and tendinopathy. The eligibility criteria for the trials encompassed publications that were published within the timeframe of January 1, 1966 to December 2022. The statistical analysis was performed utilizing the Review Manager 5.4.1, the visual analogue scale (VAS), Victorian Institute Ankle Function Scale (VISA-A), and Achilles Tendon Thickness were used to assess outcomes.

RESULTS

This meta-analysis included 13 randomized controlled trials, 8 of which were randomized controlled trials of PRP for AT and 5 of which were randomized controlled trials of PRP for ATR. PRP for AT at 6 wk [weighted mean difference (WMD) = 1.92, 95%CI: -0.54 to 4.38, I^2 = 34%], at 3 mo [WMD = 0.20, 95%CI: -2.65 to 3.05, I^2 = 60%], and 6 mo [WMD = 2.75, 95%CI: -2.76 to 8.26, I^2 = 87%) after which there was no significant difference in VISA-A scores between the PRP and control groups. There was no significant difference in VAS scores between the PRP group and the control group after 6 wk [WMD = 6.75, 95%CI: -6.12 to 19.62, I^2 = 69%] and 6 mo [WMD = 10.46, 95%CI: -2.44 to 23.37, I^2 = 69%] of treatment, and at mid-treatment at 3 mo [WMD = 11.30, 95%CI: 7.33 to 15.27, I^2 = 0%] after mid-treatment, the PRP group demonstrated better outcomes than the control group. Post-treatment patient satisfaction [WMD = 1.07, 95%CI: 0.84 to 1.35, I^2 = 0%], Achilles tendon thickness [WMD = 0.34, 95%CI: -0.04 to 0.71, I^2 = 61%] and return to sport [WMD = 1.11, 95%CI: 0.87 to 1.42, I^2 = 0%] were not significantly different between the PRP and control groups. The study did not find any statistically significant distinction between the groups that received PRP treatment and those that did not, regarding the Victorian Institute of Sport Assessment - Achilles scores at 3 mo [WMD = -1.49, 95%CI: -5.24 to 2.25, I^2 = 0%], 6 mo [WMD = -0.24, 95%CI: -3.80 to 3.32, I^2 = 0%], and 12 mo [WMD = -2.02, 95%CI: -5.34 to 1.29, I^2 = 87%] for ATR patients. Additionally, no significant difference was observed between the PRP and the control groups in improving Heel lift height respectively at 6 mo [WMD = -3.96, 95%CI: -8.61 to 0.69, I^2 = 0%] and 12 mo [WMD = -1.66, 95%CI: -11.15 to 7.83, I^2 = 0%] for ATR patients. There was no significant difference in calf circumference between the PRP group and the control group after 6 mo [WMD = 1.01, 95%CI: -0.78 to 2.80, I^2 = 54%] and 12 mo [WMD = -0.55, 95%CI: -2.2 to 1.09, I^2 = 0%] of treatment. There was no significant difference in ankle mobility between the PRP and control groups at 6 mo of treatment [WMD = -0.38, 95%CI: -2.34 to 1.58, I^2 = 82%] and after 12 mo of treatment [WMD = -0.98, 95%CI: -1.41 to -0.56, I^2 = 10%] there was a significant improvement in ankle mobility between the PRP and control groups. There was no significant difference in the rate of return to exercise after treatment [WMD = 1.20, 95%CI: 0.77 to 1.87, I^2 = 0%] and the rate of adverse events [WMD = 0.85, 95%CI: 0.50 to 1.45, I^2 = 0%] between the PRP group and the control group.

CONCLUSION

The use of PRP for AT improved the patient's immediate VAS scores but not VISA-A scores, changes in Achilles tendon thickness, patient satisfaction, or return to sport. Treatment of ATR with PRP injections alone improved long-term ankle mobility but had no significant effect on VISA-A scores, single heel lift height, calf circumference or return to sport. Additional research employing more extensive sampling sizes, more strict experimental methods, and standard methodologies may be necessary to yield more dependable and precise findings.

Key Words: Platelet-Rich plasma; Achilles tendon rupture; Achilles tendinopathy; Systematic evaluation; Randomized controlled trial

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Core Tip: Achilles tendon rupture (ATR) and Achilles tendinopathy (AT) are commonly seen in orthopaedic outpatient clinics. The effectiveness of Platelet-Rich Plasma in the treatment of patients with ATR and AT has been controversial. This study aims to inform the decisions of physicians faced with challenges when making treatment choices.

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INTRODUCTION

Achilles tendon rupture (ATR) and Achilles tendinopathy (AT) are commonly seen in orthopaedic outpatient clinics. These conditions have serious complications and are treated clinically, mainly by conservative treatment. However, this treatment is ineffective and prone to recurrence[1]. The cause is

regular unreasonable or excessive exercise, which leads to repeated friction or overstretching of the Achilles tendon and its surrounding tissues beyond the repair capacity of the tendon itself, caused inflammatory reactions in the tendon tissue. Chronic inflammation leads to the tendon's collagen fibres and fatty tissue degeneration. This effect is diminished and can lead to spontaneous ATR[2].

The component of Achilles tendon tissue included tendon cells and fibrin collagen. Due to the lack of blood supply to the Achilles tendon, its healing rate is significantly lower than other damaged connective tissues[3].

AT and ATR are usually treated by surgical or non-surgical methods, which included non-steroidal anti-inflammatory drugs (NSAIDs), steroid hormone blocking treatment, low-frequency ultrasound stimulation, and hypothermia therapy. Steroid and lidocaine-blocking therapies brought excellent anti-inflammatory and analgesic results, which made it become the most popular treatments in physic therapist. However, collagen necrosis and decline in the Achilles tendon's mechanical properties may caused by repeated injections[4-6]. Gastric ulcers is one of likely complications of prolonged use of NSAIDs. Therefore, the clinical use of these drugs in the treatment of Achilles tendon rupture and AT has been controversial[7]. Growth factors have been identified to play a vital role in ATR, Therefore Certain researchers suggested the utilization of platelet-rich plasma (PRP) as a potential treatment for conditions affecting the Achilles tendon[8,9].

PRP injections, which are increasingly used in clinical practice, are platelet concentrates that often contain various growth factors within them. In some cases, an increase on following growth factors were noticed, including epidermal growth factor, platelet-derived growth factor (PDGF), transforming growth factor-b1, basic fibroblast growth factor, vascular endothelial growth factor, insulin-like growth factor and hepatocyte growth factor[10]. Therefore, platelet-rich plasma has attracted the curiosity of numerous researchers as a tissue regeneration-inducing factor[11-14]. Several current investigations have demonstrated that PRP is useful in the treatment of orthopedic injuries, including syndrome of the carpal tunnel[15-17], Rotator cuff rupture[18-20], AT[21,22], Achilles tendon injury[23], *etc*. Animal experimentation has demonstrated that PRP injections speed up the histopathological recuperation of the Achilles tendon, boost the overall strength of the tendon, relieve the inflammatory response, and facilitate tendon regeneration[24,25].

PRP has been shown to increase the histopathological recovery of the Achilles tendon in humans. However, the role of PRP in human Achilles tendon healing remains controversial[21,22,24-28]. Overall, additional research is required to investigate and uncover the efficacy of PRP treatment for individuals with AT to inform and guide clinical decision-making. This study aimed to determine whether PRP injection is viable for patients with AT. Treatment success depends on measuring Achilles tendon function scores, pain levels, return to sport rates, complication rates and the time taken to return to the pre-injury functional range. There are few studies on the effects of PRP injections on Achilles tendon disease. This study aims to inform the decisions of physicians faced with challenges when making treatment choices.

MATERIALS AND METHODS

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards, before initiating the investigation, we drafted a protocol delineating our objectives, criteria for eligibility literature search methodologies, statistical assessments, and outcome measures. The registration number for PROSPERO is CRD 42023388903.

Study design

This study employed meta-analysis to compile quantitative research on the efficacy of PRP for treating AT. The research was conducted in a structured manner, and the methodology employed in this study involved several steps. (1) A study strategy and criteria aligned with the study's objectives were developed; (2) The primary databases of interest were searched using specific search terms and formulas; (3) The studies were screened for eligibility based on the predetermined criteria; (4) The quality of the literature was evaluated using the Jadad scale to eliminate those of inferior quality; (5) Involves using a data extraction form to extract the required data meticulously; (6) Entails the utilization of Review Manager 5.4.1 for data examination; and (7) Involves analyzing and interpreting the results and marking decisions.

Data collection

The inclusion criteria were restricted to the following conditions: (1) The investigation focused on patients with AT or ATR; (2) The study intervention involved administering a local PRP injection to the experimental group; (3) Various outcome indicators, including the Victorian Institute Ankle Function Scale (VISA-A) score, visual analogue scale (VAS) for pain, variations in Achilles tendon thickness, rate of returning to sports activities, patient satisfaction, return to sport, ankle flexion, return to pre-injury heel-rise height, and incidence of adverse events, were utilized in this study; and (4) The focus of this research is on randomized controlled trials (RCTs) published prior to December 2022.

Exclusion criteria

The study excluded trials with the following criteria: (1) Non-randomized trials; (2) A follow-up duration of less than 6 wk; (3) No control group; (4) Used PRP with other drugs; and (5) Did not report results.

Search method

Searches were conducted in Cochrane Library, PubMed, Web of Science, Chinese Science and Technology Journal, EMBASE, and China Biomedical CD-ROM without restriction on language. The search terms were "PRP", "Platelet Concentrate", "platelet gel", "ATR", "Achilles tendon injury", "AT", and "AT", all the full text from 1966 to 2022 was download, carefully read.

Literature screening

At least two individuals conduct separate literature searches using predetermined keywords and formulas to access databases. The literature screening process outcomes were then consolidated through literature management tools, with duplicate papers being eliminated and insignificant literature being excluded based on title lists. Potentially appropriate research was downloaded and thoroughly read, with the final choice of literature determined by inclusion and exclusion criteria. In the event of divergent results, a third person was invited for Arbitration and selection.

Quality evaluation of the included studies

The present study conducted a methodological analysis of previous research about the research design protocol, randomization approach concealment, blinding implementation, and the incidence of missed visits. The Jadad scale was employed for this purpose. The total score achievable on this scale was seven. Research studies that obtained a cumulative score ranging from one to three were categorized as low-quality, while those that obtained a cumulative score ranging from four to seven were classified as high-quality. Studies with a score ≥ three or higher were deemed eligible for participation in this investigation[29-31].

Statistical analysis

Review Manager 5.4.1 (Revman 5.4) served as the statistical tool for this investigation. Following the evaluation criteria, all admissible data from the literature were extracted and inserted into Revman 5.4 for analysis. The risk difference or the odds ratio was used to describe count data (such as adverse events and return to sport rate).

All metrics (such as VISA-A score, ankle mobility, VAS score, *etc.*) were reported as weighted mean difference (WMD)[32]. The study assessed heterogeneity utilizing the I^2 index, which served as an indicator of the degree of heterogeneity. Studies with I^2 values below 31% were deemed homogeneous, while those with I^2 values above 56% were considered more heterogeneous. Studies with I^2 values between 56% and 70% could not be excluded from heterogeneity. When I^2 values were below 50%, the fixed-effects model Peto method was employed to combine effect sizes. Conversely, when I^2 values exceeded 50%, the random-effects model DerSimonian-Laird method was utilized for calculation. In cases where there was significant heterogeneity among groups, meta-analysis was abandoned in favor of descriptive analysis.

RESULTS

A total of 16 publications were screened, and 3 were excluded through further evaluation: 1 trial design protocol with no outcome indicators. One was a retrospective case-control study and not a true RCT trial. 1 had no primary outcome indicators. A total of 13 publications were included in the final results (Figure 1).

All 13 RCTs, comprising 857 cases, were included in this study. All trials were published in full text, with 13 being in English and none in Chinese. Eight trials included 526 subjects in a randomized controlled trial of PRP for AT, and five included 349 subjects in a randomized controlled trial of PRP for ART. All had modified Jadad scores greater than 3. Saline were used in eight studies as a control group, and blank controls were used in five studies; 12 were double-blind RCTs, and one was a single-blind RCT; the basic characteristics of the related literature are listed in Table 1. Every included studies were compared at baseline, and there found no significant differences in age, weight, gender and treatment between the two comparable groups. Regarding the risk of bias, Figures 2 and 3 shows the assessment results of the included studies.

Results of the analysis of AT

VISA-A rating: The VISA-A score changes were accurately and fairly stated in 8 articles, including 526 patients. The combined statistic was calculated using a random effects model due to statistical heterogeneity between studies (I^2 = 76%, P = 0.00001), The study revealed that the VISA-A score was greater in

Table 1 Characteristics of randomized controlled studies included in this meta-analysis

Ref.	Sample size (I/C)	Achilles tendon lesion	Location	Control	Follow-up	PRP injection frequency/interval/dose (mL)
de Vos *et al*[42], 2010	27/27	C-AT (> 2 mo)	Netherlands	Saline	6, 12, 24 wk	Once/-/4
de Jonge *et al*[41], 2011	27/27	C-AT (> 2 mo)	Netherlands	Saline	6, 12, 24, 48 wk	Once/-/4
Kearney *et al*[50], 2013	9/10	C-AT (> 8 mo)	United Kingdom	Blank	6 wk, 3 mo, 6 mo	Once/-/3 to 5
Krogh *et al*[22], 2016	12/12	C-AT (mean 33 mo)	Denmark	Saline	3, 6, 12 mo	Once/-/6
Boesen *et al*[21], 2017	19/19	C-AT (> 3 mo)	Denmark	Saline	6, 12, 24 wk	4 times/2-wk/4
van der Vlist *et al*[53], 2020	39/41	C-AT (> 6 mo)	Netherlands	Saline	2, 6, 12, 24 wk	Once/-/NR
Thermann *et al*[51], 2020	17/19	C-AT (> 6 mo)	Italy	Blank	6 wk, 3, 6, 12 mo	Once/-/NR
Kearney *et al*[52], 2021	121/119	C-AT (> 3 mo)	United Kingdom	Blank	2 wk, 3, 6 mo	Once/-/3
Schepull *et al*[28], 2011	15/14	A-ATR (< 3 d)	Sweden	Blank	6, 12 mo	Once/-/10/4
De Carli *et al*[49], 2015	15/15	A-ATR	Italy	Blank	1, 3, 6, 24 mo	2 times/2-wk/4
Zou *et al*[27], 2016	16 /20	A-ATR (< 3 wk)	China	Placebo	3 wk, 3, 6, 12, 24 mo	Once/-/NR
Keene *et al*[33], 2019	107/109	A-ATR (< 12 d)	United Kingdom	Placebo	4, 7, 13, 24 wk	Once/-/4
Boesen *et al*[34], 2020	19/19	A-ATR (< 3 d)	Denmark	Saline	8 wk, 3, 6, 12 mo	Once/-/4

PRP: Platelet-Rich Plasma; AT: Achilles tendinopathy; ATR: Achilles tendon rupture.

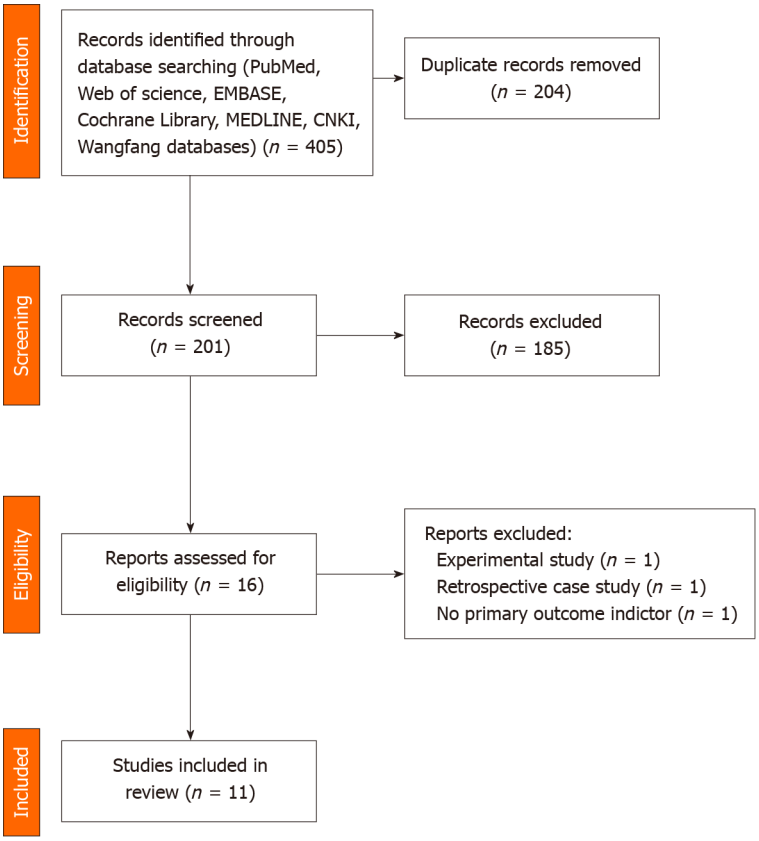
the PRP group as compared to the placebo group [WMD = 1.20, 95%CI: -0.94 to 3.34, P = 0.27]. No important statistical improvement was observed in the VISA-A score among those who had PRP therapy (Figure 4).

Change in Achilles tendon thickness: Changes in Achilles tendon thickness were accurately and appropriately reported by 98 individuals across 3 articles. Due to statistical heterogeneity among studies (I^2 = 61%, P = 0.08), we applied a model with random effects to calculate the pooled statistic, which indicated that the PRP group had thicker Achilles tendons than the placebo group [WMD = 0.34, 95%CI: -0.04 to 0.71, P = 0.08], a difference not supported by statistical evidence. This indicates no significant improvement in AT thickness in the PRP group (Figure 5).

VAS score: Changes in VAS score were accurately and appropriately reported by 93 individuals across 3 articles. The result shows there was a statistical heterogeneity among those studies (I^2 = 56%, P = 0.02), we used a random effects model to determine the pooled statistic, the result indicated that the VAS scores in PRP group was greater than the placebo group [WMD = 11.74, 95%CI: -7.45 to 16.02, P < 0.00001], with a significant statistical difference. According to this result, PRP treatment group brings significantly promotions on VAS scores compare to the placebo group (Figure 6).

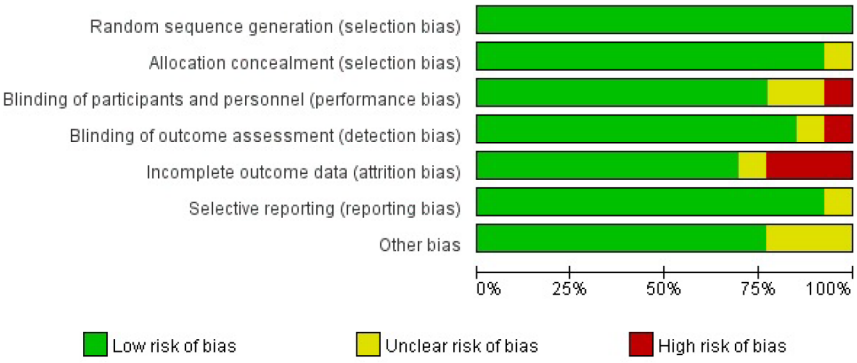
Patient satisfaction: Enhancements in patient satisfaction were accurately and appropriately reported by 222 patients across four studies. Because there was heterogeneity among due to the heterogeneity among the research papers (I^2 = 0%, P = 0.68), the study employed a fixed-effects approach to determine the paired statistic. The findings indicate that the level of patient satisfaction was higher in the group that received platelet-rich plasma compared to the group that received a placebo [Relative risk (RR) = 1.07, 95%CI: 0.84 to 1.35, P = 0.58], but there was no statistically significant difference between the two groups. According to this information, the level of patient satisfaction did not substantially increase in the PRP group compared to the placebo group (Figure 7).

Return to sport rate: 199 patients accurately and reasonably described their exercise resumption rates across 4 publications. The results indicated no statistical heterogeneity among studies (I^2 = 0%, P = 0.54), in present study we used a fixed-effects approach to determine the combined statistic, the result indicated that the ratio of return to exercise in the PRP-treated group (experimental group) was greater than in the placebo group (control group) [RR = 1.11, 95%CI: 0.87 to 1.42, P = 0.40]. This suggests that



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Figure 1 Flow diagram of study selection.



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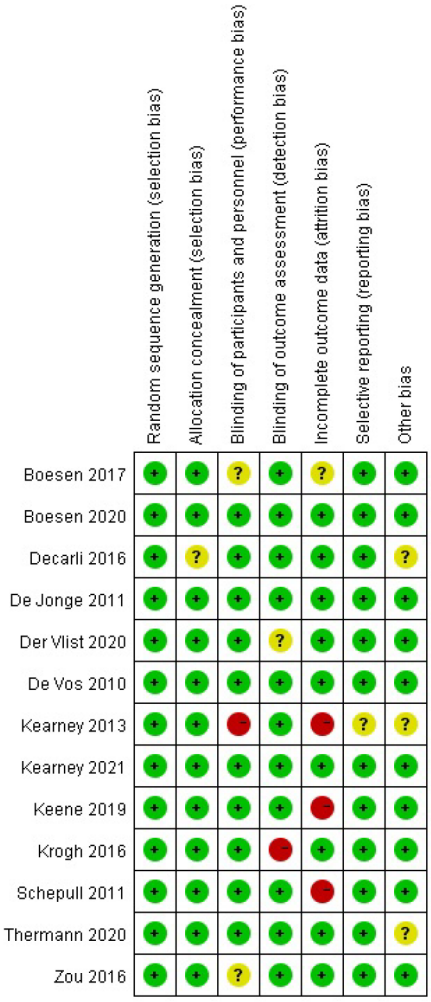
Figure 2 Proportional risk of bias graph: Judgement of the percentage of bias items arising from all included studies.

the PRP therapy group did not substantially increase the patient's return to activity rate compared to the placebo group (Figure 8).

Results of the analysis of the effectiveness of PRP in the treatment of ATR

VISA-A Rating: In total, 274 patients from three different articles gave an accurate and credible description of the value of the change in their VISA-A score. Because the statistical result shows no heterogeneity among the studies (I^2 = 39%, P = 0.13), we used a fixed-effects approach to generate the paired statistic. This result indicated that the PRP group had smaller VISA-A Scale scores compared to the placebo group [WMD = -1.28, 95%CI: -3.32 to 0.75, P = 0.22]; there was also no significant difference among both groups statistically (Figure 9).

Single-foot heel height: In three articles, 259 patients accurately and adequately defined the height of a single heel lift. Because the statistical result shows no heterogeneity among those studies (I^2 = 0%, P = 0.90), we used a fixed effects approach to determine the overall statistic, the results revealed that the



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Figure 3 Risk of bias summary diagram: Assessment of specific items of bias arising from all included studies.

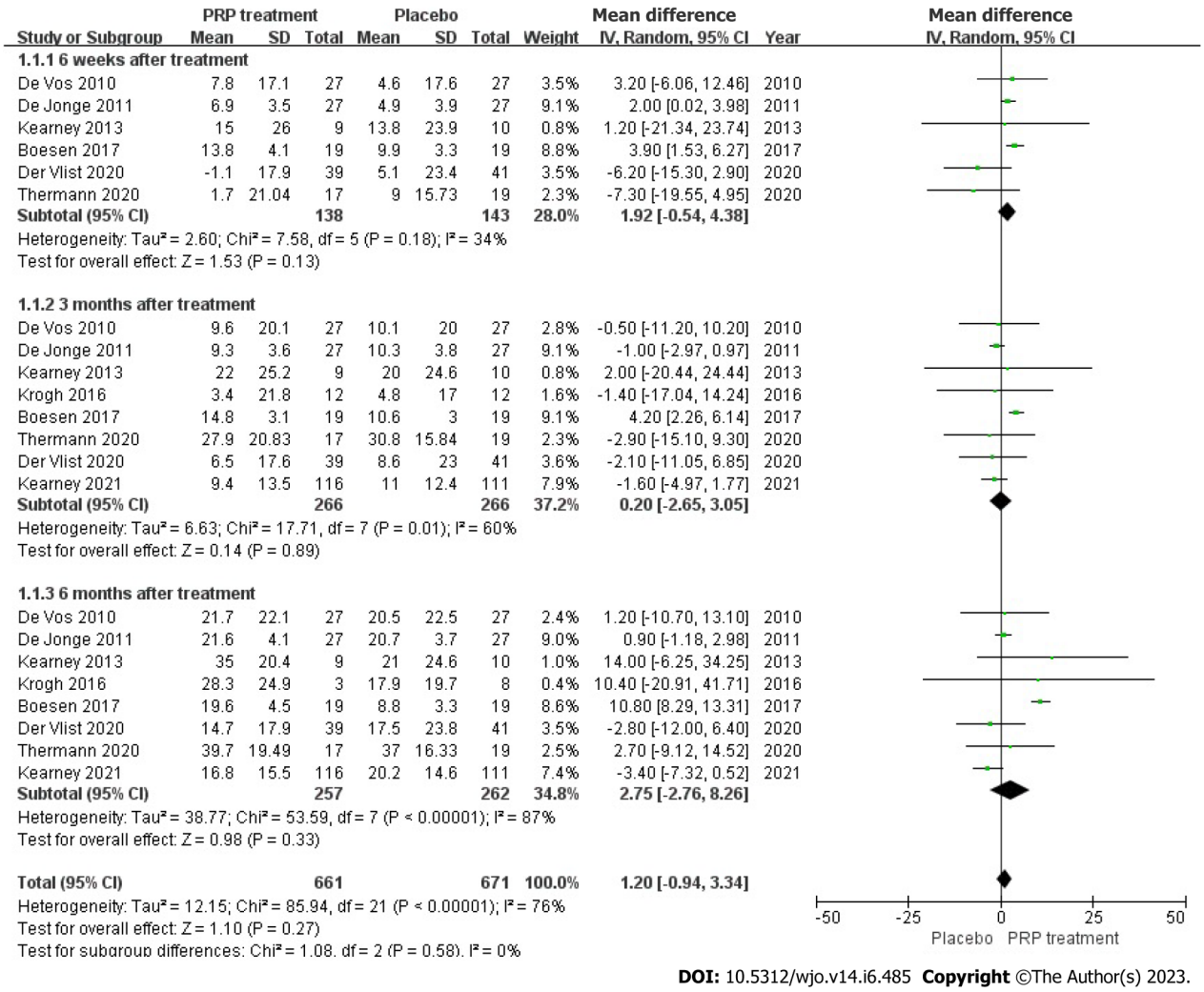
PRP group had a smaller single heel lift height compared to the placebo group. [WMD = -3.51, 95%CI: -7.69 to 0.66, P = 0.10], there was no statistical difference. This result suggested that the PRP group did not substantially enhance the single heel lift height among individuals with ATR (Figure 10).

Calf circumference: Two papers accurately and reasonably reported the calf circumference measurements of 75 patients. The statistical result shows no heterogeneity among those studies (I^2 = 24%, P = 0.27), we used fixed-effects approach to determine the paired statistic, the result indicated that calf circumference in the PRP group was greater compared to the placebo group [WMD = 0.17, 95%CI: -1.05 to 1.38, P = 0.79], there was no statistical difference. This suggests that the PRP therapy did not substantially improve calf circumference length in patients with ATR (Figure 11).

Ankle mobility: Ankle mobility was accurately and fairly assessed in 103 patients across 3 articles. The statistical result shows no heterogeneity among each study (I^2 = 81%, P < 0.0001), we used a random effects approach to determine the paired statistic, the result demonstrated that ankle mobility in the PRP group was lower compared to the placebo group [WMD = 0.93, 95%CI: -1.60 to -0.26, P = 0.007], the statistically difference was significant. This indicates that the PRP therapy did not substantially increase ankle mobility in individuals with ATR (Figure 12).

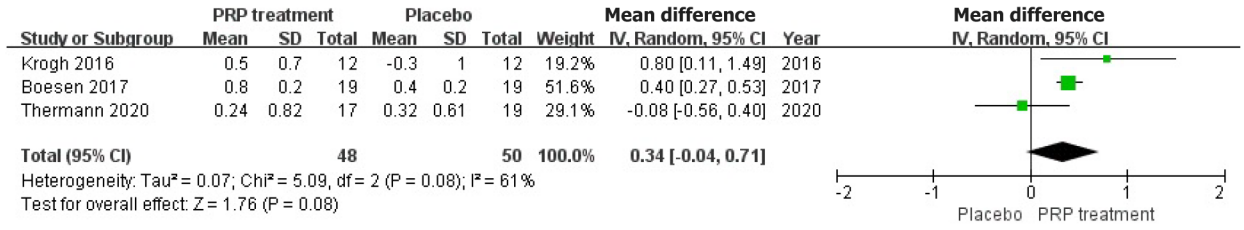
Return to sport rate: Two studies included 68 patients who accurately and sufficiently reported the ratio of their return to exercise. The statistical result shows no heterogeneity among those studies (I^2 = 0%, P = 1.00), we used a fixed-effects approach to determine the paired statistic, the outcome showed that there was no statistically significant difference in the ratio of return to sport in the PRP group and the placebo group [RR = 1.20, 95%CI: 0.77 to 1.87, P = 0.42]. This suggests that the PRP the therapy did not substantially increase the return-to-sport rate among individuals with ATR (Figure 13).

Incidence of adverse events: A total of 2 publications with 305 patients correctly and reasonably described the incidence of adverse events. The statistical result shows no heterogeneity among the



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Figure 4 Forest plot of change values for Victorian Institute Ankle Function Scale scores. PRP: Platelet-Rich Plasma.



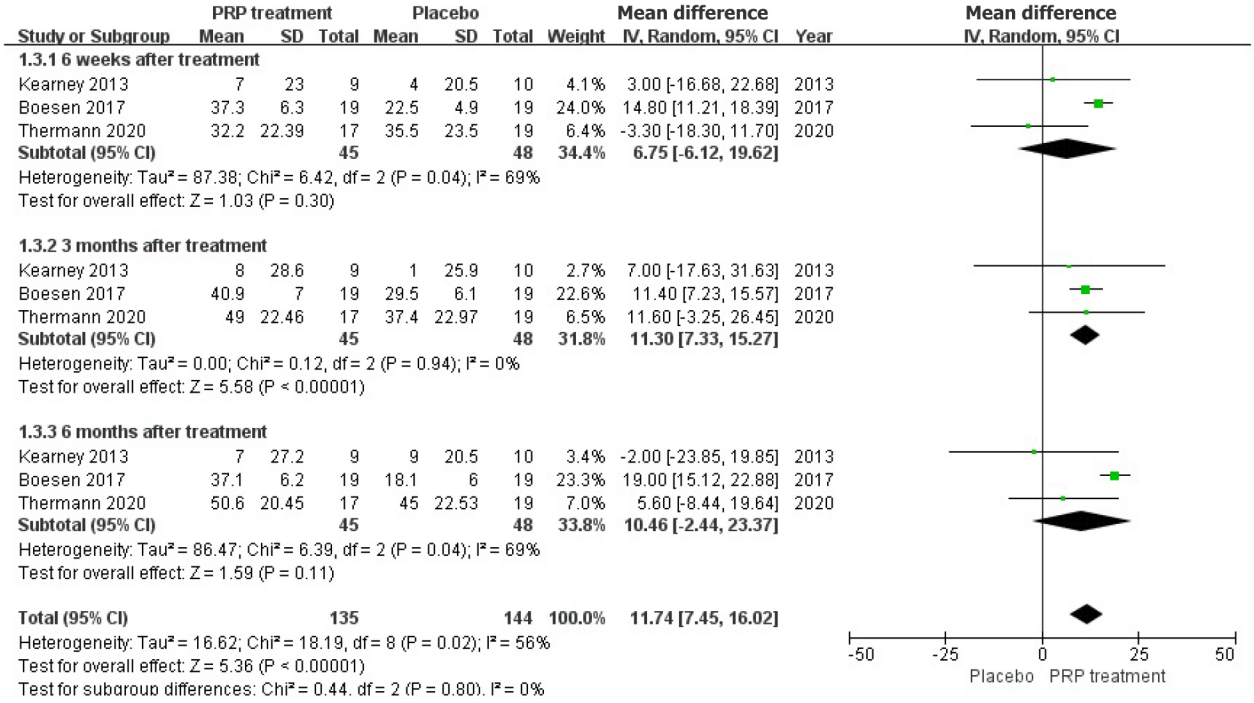
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Figure 5 Forest plot of Achilles tendon thickness variation. PRP: Platelet-Rich Plasma.

studies (I^2 = 0%, P = 0.66), we used a fixed-effects approach to determine the paired statistic, the PRP group's Achilles tendon re-rupture was greater than the placebo group [RR = 1.21, 95%CI: 0.43 to 3.47, P = 0.71]; no statistical difference existed. The prevalence of pain and distress in the PRP-treated group was greater compared to the placebo group [RR = 1.02, 95%CI: 0.51 to 2.01, P = 0.96]; however, the difference between the groups was not statistically significant. The results showed no statistically significant difference between the PRP-treated group and the control group in terms of re-rupture rate of the Achilles tendon, infection, and incidence of pain and discomfort (Figure 14).

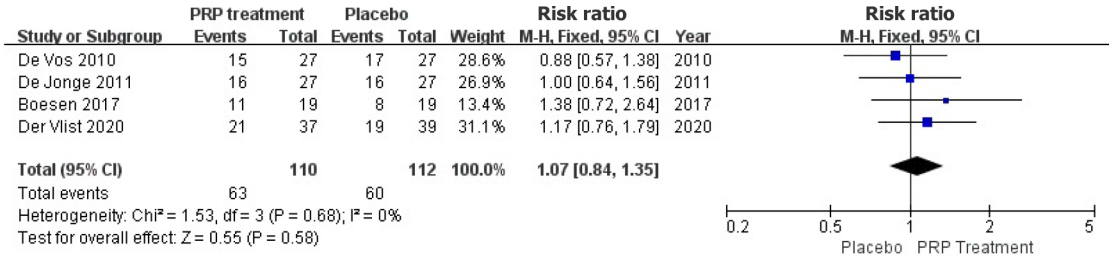
DISCUSSION

PRP is a platelet-rich plasma obtained by centrifugation of whole blood from animals or humans, to



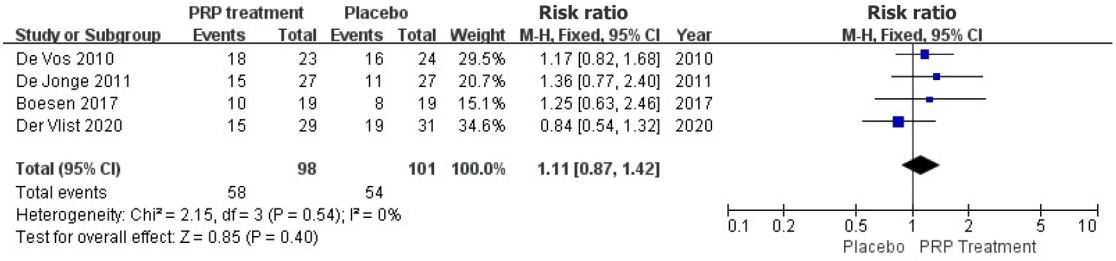
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Figure 6 Forest plot of change in visual analogue scale scores. PRP: Platelet-Rich Plasma.



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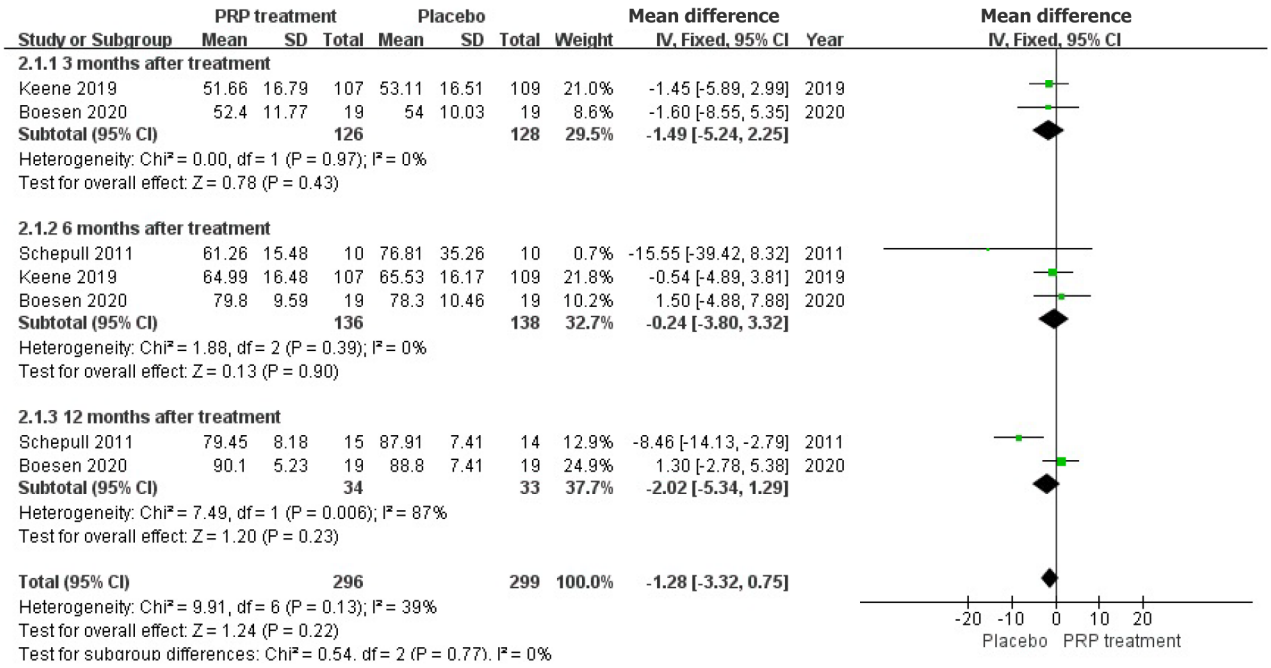
Figure 7 Forest plot of change in patient satisfaction. PRP: Platelet-Rich Plasma.



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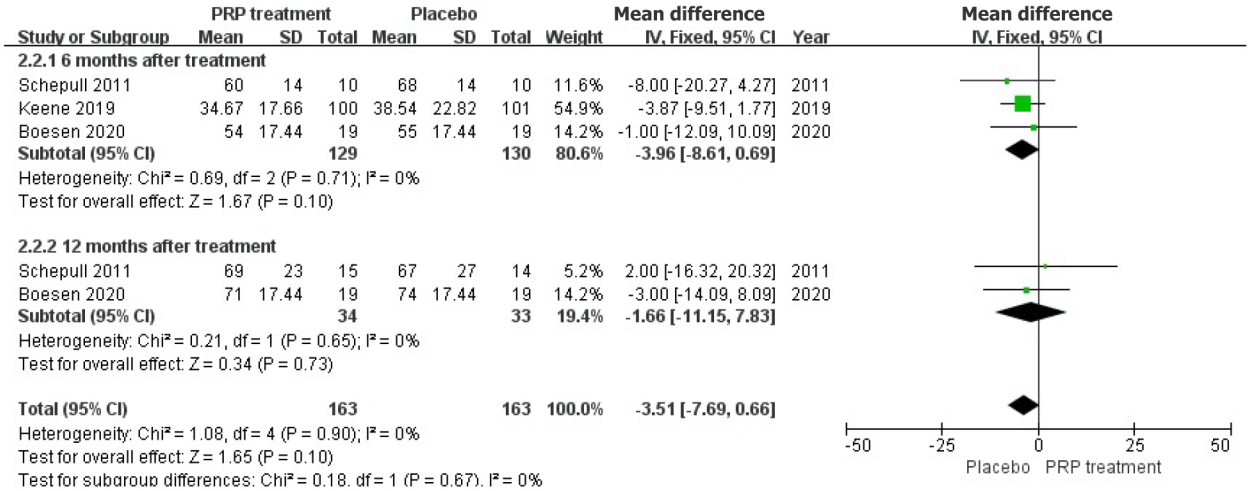
Figure 8 Forest plot of patient return to exercise rate. PRP: Platelet-Rich Plasma.

which thrombin is added to turn it into a gel, and the platelet concentration of PRP increases on average by a factor of two to six. Platelets contain high levels of growth factors such as growth-like insulin growth factor, PDGF, epidermal growth factor (EGF). Transforming growth factor-β, vascular EGF, *etc.* Theoretically, when platelet concentrates are activated, PRP injections can release supraphy siological concentrations of various autologous growth factors with healing and regenerative abilities for treating musculoskeletal disorders[33,34]. Theoretical In vitro and *in vivo* experiments have also demonstrated the mechanobiological properties of PRP to promote the healing of tendon injuries[24,35-37]. Li *et al*[38] demonstrated that PRP heals tendon tissue by reducing the number of cells, decreasing the number of blood vessels, promoting type I collagen deposition and increasing the glycosaminoglycan content. PRP



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Figure 9 Forest plot of Victorian Institute Ankle Function Scale scores in patients with Achilles tendon rupture. PRP: Platelet-Rich Plasma.

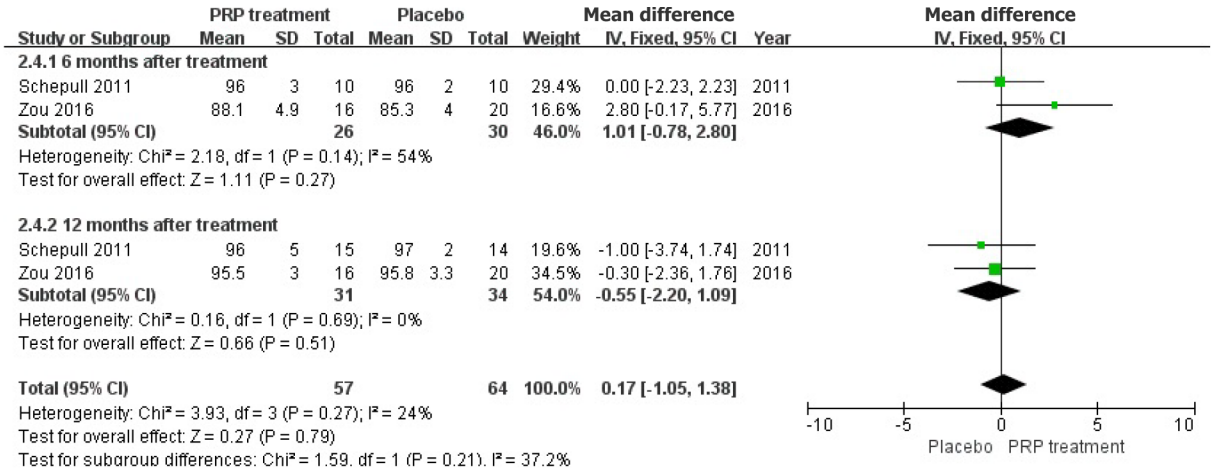


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Figure 10 Forest plot of single heel lift height in patients with Achilles tendon rupture. PRP: Platelet-Rich Plasma.

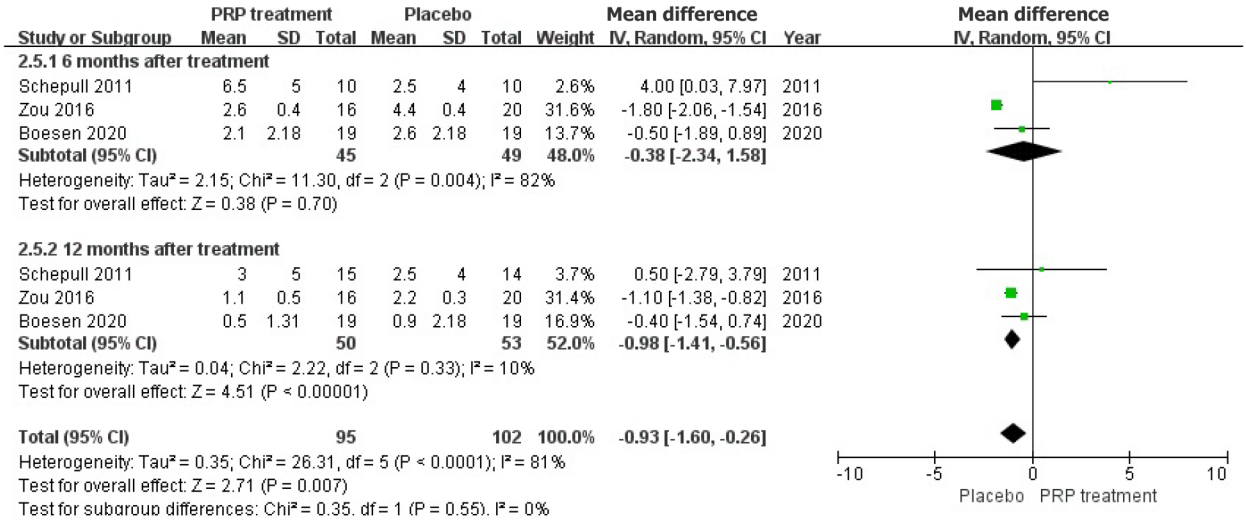
is also derived from the patient's own body. Furthermore, PRP is derived from the patient himself and is administered after a short period of *in vitro* centrifugation. PRP therapies have achieved satisfactory clinical results; however, there are no consistent results on their overall efficacy and inconsistencies in patient outcomes, and new insights challenge the usefulness of PRP for clinical use[39,40].

AT develops from many factors, and this disorder's exact mechanism is unknown. Most studies suggest that AT is primarily caused by anatomical abnormalities resulting from overexertion, incorrect exercise training, stiffness and weakness of the limbs. Various factors first lead to local inflammation of the Achilles tendon. These effects lead to degenerative changes and eventually to partial or complete Achilles tendon rupture. This meta-analysis found that the use of PRP for AT did not significantly change patients' VISA-A scores, patient satisfaction, return to sport rates, or Achilles tendon thickness compared to controls, and interestingly, patients' VAS scores at 3 mo were significantly improved compared to controls but did not significantly change long-term clinical outcomes. (This is similar to De Jonge's findings.) The randomized controlled trial by de Jonge *et al*[41] showed that PRP injections did not significantly improve pain and function in patients with tendonitis compared to placebo injections in patients with chronic Achilles tendonitis after 1 year of PRP treatment, and there was no advantage in ultrasound findings. deVos *et al*[42] conducted a randomized controlled trial utilizing a double-blind



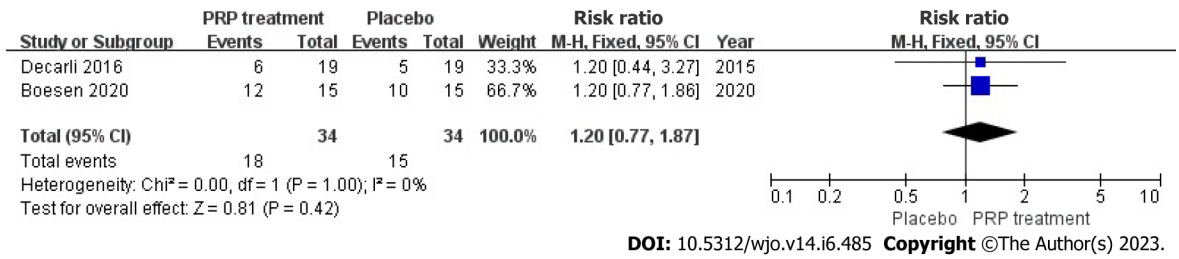
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Figure 11 Forest plot of calf circumference in patients with Achilles tendon rupture. PRP: Platelet-Rich Plasma.



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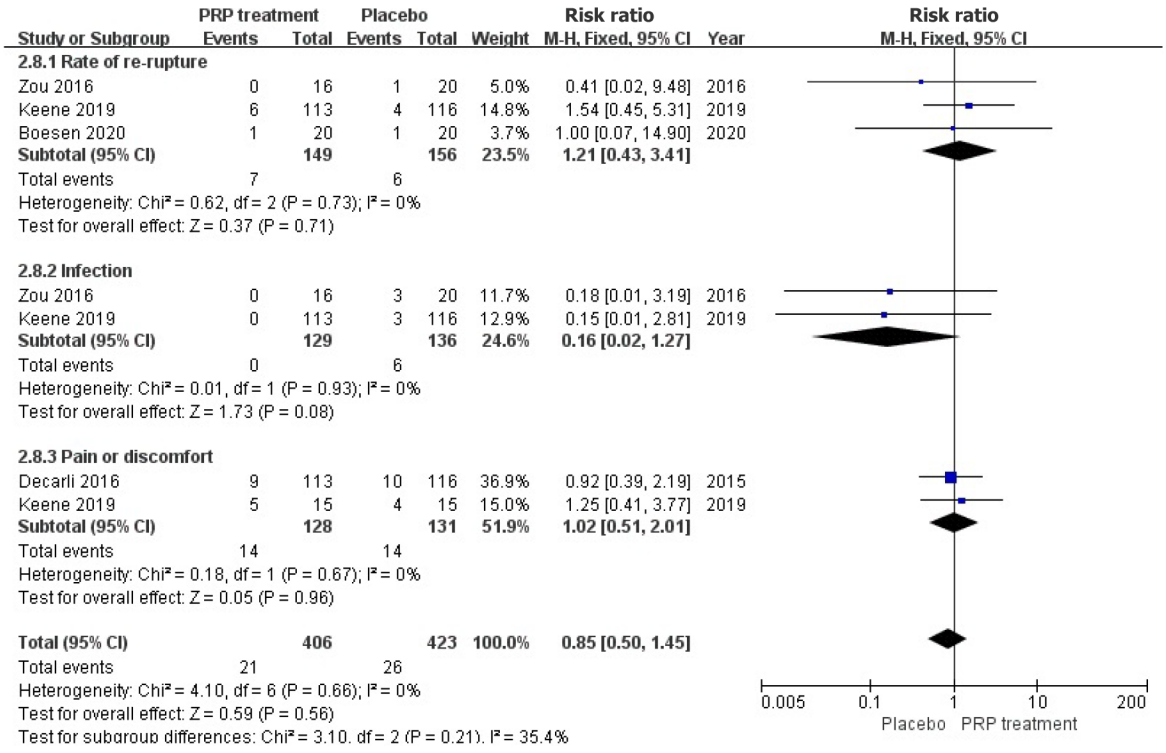
Figure 12 Forest plot of ankle mobility in patients with Achilles tendon rupture. PRP: Platelet-Rich Plasma.



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Figure 13 Forest plot of return to sport rates in patients with Achilles tendon rupture. PRP: Platelet-Rich Plasma.

method. The study involved 54 patients with chronic inflammatory Achilles tendon disease, all receiving PRP treatment. The study demonstrated that the administration of PRP therapy did not result in significant alterations in the ultrasound echo structure or neovascularisation scores associated with Achilles tendon injuries[42]. Neither study described a clinical benefit of PRP injection over placebo. The study by Krogh *et al*[22] also concluded that PRP injection had no additional value in treating AT. However, this study raises concerns about the quality of the method. Patients were blinded, but the outcome assessors were aware of the interventions implemented. Furthermore, they reported a 54% decline rate three months after PRP, making it almost impossible to observe a potential late effect of PRP. Interestingly Boesen *et al*[21] reported a significant improvement in VISA-A scores in the PRP



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Figure 14 Forest plot of the incidence of adverse events in patients with Achilles tendon rupture. PRP: Platelet-Rich Plasma.

group. This difference may be because Boesen *et al*[21] considered tendon healing a slow process, so they repeated PRP injections to achieve a prolonged effect of the growth factor on the tendon. Another possibility is that there were differences in the rehabilitation protocols of these studies; for example, Boesen *et al*[21] prescribed running to start 10 d after PRP injection, while other studies ranged from 4 d (Krogh) to 28 d (deVos)[22,42]. Thirdly, there were differences in the effects of PRP on vascular tendon distribution and tendon thickness, with Boesen *et al*[21] concluding that PRP administration reduced vascular distribution and tendon thickness within the tendon. de Jonge *et al*[41] reported an improvement in tendon structure in the PRP and placebo groups, but no significant difference was found between the two groups. These results did not confirm an association between PRP and changes in tendon structure. The results did not confirm an association between PRP and changes in the tendon structure. Finally, it is possible that the location of PRP injections was not uniform, with Krogh *et al*[22] injecting at the very back of the tendon and de Vos *et al*[42] injecting at the most severely affected site.

The Achilles tendon is a relatively blood-deprived tissue, with the blood supply to the Achilles tendon coming mainly from the posterior tibial artery return branch[43]. The surface skin blood supply system is fragile. As a result, healing after an injury is slower than in other tissues. Some studies have shown that growth factors can promote tendon repair[44]. Some studies have shown that growth factors can promote tendon repair. Some *in vitro* experiments have demonstrated that instantaneous injection of plasma-rich protein for tendon injury enhances tendon recovery in rats[45]. Zhang *et al*[46] found that the premature injection of plasma-rich protein into a tendon injury may have provided sufficient growth factors to promote angiogenesis, which ultimately shortened tendon healing time. However, Zou *et al*[27] found that leukocyte-rich platelets may be detrimental to treating tendon injuries in rabbits. Leukocyte-rich platelets caused catabolic gene expression, increased protein production, and promoted an increase in inflammatory mediators. This inflammatory mediator induces non-tendon cell differentiation[47,48].

PRP injections in the treatment of ATR as a new treatment method with no consistent results on its overall efficacy. Therefore, we performed a meta-analysis to provide evidence-based information on using PRP injections for ATR. The results showed that the PRP-treated group (experimental group) was not statistically significantly different from the control group in terms of VISA-A score, single heel lift height, return to motion rate, Achilles tendon re-rupture rate, infection, and incidence of pain and discomfort. There was no significant improvement in ankle mobility in the PRP-treated group at 6 mo, and after 12 mo, the results showed that PRP injection improved ankle mobility. Overall, our findings do not support using PRP for ATR; however, this meta-analysis has some limitations, and the findings need to be considered cautiously. This is because differences in PRP preparation methods can lead to differences in the biological characteristics of the final product. The frequency and dosage of PRP injections in the experimental groups varied in many studies, which may lead to uncertainty in clinical

outcomes. A study by Keene *et al*[33] described each component of PRP injections, as well as several representative growth factors; two studies by Schepull *et al*[28] and Zou *et al*[27] reported only the platelet concentrations of their PRP injections. Zou's study showed that PRP positively affected ankle function in short to medium term[27]. However, in a study by De Carli *et al*[49], there was no difference between the PRP and control groups after acute Achilles tendon rupture surgery as measured by the VISA-A score and the Foot and Ankle Outcome Score. Similar inconsistent results may be due to the inconsistencies in PRP concentrations, preparation protocols and injection sites described above.

Hence, additional research is required to determine the optimal concentration, injection duration, and injection location for PRP for ART and AT. The study results indicate a lack of statistical significance in the impact of PRP on ankle plantarflexion angle, ankle plantar flexion strength, and pain.

Limitations

Although clear inclusion and exclusion criteria have been established for this study, the small total sample size and a limited number of trials limit the strength of the evidence. Moreover, there remains a high degree of heterogeneity in the quantitative analysis of these randomized controlled trial studies. Heterogeneity may stem from the degree of tendinopathy, the method used to produce PRP, the cellular composition of PRP, the conditions in which PRP was stored, the method of injection, the dose and frequency of injection and the setting of the control group. The scoring criteria and methods used in the included studies also differed.

This study was unable to analyze PRP in different subgroups due to the heterogeneous nature of PRP production and application techniques and the absence of an standardized classification system. Consequently, a comprehensive investigation into the effectiveness and safety of a specific form of PRP therapy in treating tendinopathies was not feasible.

CONCLUSION

This study showed no significant efficacy of PRP injection alone in patients with ATR and AT. Thirteen high-quality RCT articles were reviewed to reach this conclusion. Future studies should focus on completing RCTs with large sample sizes and standardizing the preparation/procedure of PRP injections. As well as exploring the clinical efficacy of PRP injections combined with minimally invasive AT techniques.

ARTICLE HIGHLIGHTS

Research background

Achilles tendon rupture (ATR) and Achilles tendinopathy (AT) are commonly seen in orthopaedic outpatient clinics. These conditions have serious complications and are treated clinically, mainly by conservative treatment. However, this treatment is ineffective and prone to recurrence. Along with the deep investigation of research, it is found that growth factors promoted Achilles tendon repair. The use of Platelet-Rich Plasma (PRP) was indicated to treat Achilles tendon diseases.

Research motivation

But the effectiveness of PRP in the treatment of patients with ATR and AT has been controversial.

Research objectives

To determine whether PRP injection is viable for patients with AT and to inform the decisions of physicians faced with challenges when making treatment choices.

Research methods

This study conducted a comprehensive review of relevant literature was conducted utilizing multiple databases such as Cochrane Library, PubMed, Web of Science, Chinese Science and Technology Journal, EMBASE, and China Biomedical CD-ROM. The present investigation integrated randomized controlled trials that assessed the effectiveness of platelet-rich plasma injections in managing individuals with ATR and AT. The eligibility criteria for the trials encompassed publications that were published within the timeframe of January 1, 1966 to December 2022. The statistical analysis was performed utilizing the Review Manager 5.4.1. The Victorian Institute Ankle Function Scale (VISA-A), Visual Analogue Scale (VAS) and Achilles tendon thickness were used to assess outcomes.

Research results

This meta-analysis included 13 randomized controlled trials, 8 of which were randomized controlled trials of PRP for AT and 5 of which were randomized controlled trials of PRP for ATR. PRP for AT at 6

wk, at 3 mo, and 6 mo after which there was no significant difference in VISA-A scores between the PRP and control groups. There was no significant difference in VAS scores between the PRP group and the control group after 6 wk and 6 mo of treatment, and at mid-treatment at 3 mo after mid-treatment, the PRP group demonstrated better outcomes than the control group. Post-treatment patient satisfaction, Achilles tendon thickness and return to sport were not significantly different between the PRP and control groups. There was no significant difference between the PRP and control groups for VISA-A score improvement at 3 mo, 6 mo, and 12 mo for ATR patients. Additionally, no significant difference was observed between the PRP and the control groups in improving heel lift height respectively at 6 mo and 12 mo for ATR patients. There was no significant difference in calf circumference between the PRP group and the control group after 6 mo and 12 mo of treatment. There was no significant difference in ankle mobility between the PRP and control groups at 6 mo of treatment and after 12 mo of treatment there was a significant improvement in ankle mobility between the PRP and control groups. There was no significant difference in the rate of return to exercise after treatment and the rate of adverse events between the PRP group and the control group.

Research conclusions

This study showed no significant efficacy of PRP injection alone in patients with ATR and AT. Thirteen high-quality RCT articles were reviewed to reach this conclusion. Future studies should focus on completing randomized controlled trials with large sample sizes and standardizing the preparation/procedure of PRP injections. As well as exploring the clinical efficacy of PRP injections combined with minimally invasive AT techniques.

Research perspectives

This meta-analysis reviewed 13 high-quality randomized controlled trials articles and the result suggested that there is no significant efficacy of PRP injection alone in patients with ATR and AT.

FOOTNOTES

Author contributions: Huang D, Arthur Vithran DT and Gong HL contribute equally to this study, they share co-first author; Wen J conceived and coordinated the study, designed; Xiao S performed and analyzed the experiments; Tang ZW wrote the paper; Zeng M, Arthur Vithran DT and Gong HL did the data analysis and carried out the data collection; Zeng M revised the paper; and all authors approved the final version of the manuscript.

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CORRECTION

Erratum: Rates of readmission and reoperation after operative management of midshaft clavicle fractures in adolescents

Laura A Carrillo, Hao Hua Wu, Matt Callahan, Aman Chopra, Toshali Katyal, Ishaan Swarup

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Abstract

This is an erratum to an already published paper. We found an error in the results section and Table 1. Specifically, we have revised results with $n \leq 10$ to be reflected as such, which is consistent with the reporting instructions by the Agency for Healthcare Research and Quality. Please note, these changes do not affect our results, and we had previously listed this requirement in the results section. We apologize for our unintentional mistake.

Key Words: Adolescent; Clavicle fracture; Reoperation; Readmission; Correction

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Core Tip: This is an erratum to an already published paper. We found an error in the results section and Table 1. Specifically, we have revised results with $n \leq 10$ to be reflected as such, which is consistent with the reporting instructions by the Agency for Healthcare Research and Quality. Please note, these changes do not affect our results, and we had previously listed this requirement in the results section. We apologize for our unintentional mistake.

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TO THE EDITOR

This is an erratum to an already published paper[1]. We found an error in the results section and Table 1. Specifically, we have revised results with $n \leq 10$ to be reflected as such, which is consistent with the reporting instructions by the Agency for Healthcare Research and Quality. Please note, these changes do not affect our results, and we had previously listed this requirement in the results section. We apologize for our unintentional mistake.

Table 1 Adolescent fracture demographics: Reoperation *vs* no reoperation

Predictor variables		Cohort proportion, %	Cohort total, *n*	Cohort proportion, %	Cohort total, *n*	*P* value
Sex	Male	0.68	36	0.83	229	0.01
	Female	0.32	17	0.17	47	
Race	White	0.79	42	0.78	209	0.86
	Hispanic	-	≤ 10[1]	0.12	31	
	Black	-	≤ 10[1]	0.05	14	
	Other	-	≤ 10[1]	0.05	13	
Payer type	Commercial	0.74	39	0.62	175	0.47
	Medicaid	-	≤ 10[1]	0.24	67	
	Self-pay	-	≤ 10[1]	0.06	17	
	Other	-	≤ 10[1]	0.08	22	
State	CA	-	≤ 10[1]	0.20	55	< 0.01
	FL	0.98	52	0.80	226	
Median income quartile	0-25th %	-	≤ 10[1]	0.20	42	0.64
	26th-50th %	0.34	16	0.34	70	
	51st-75th %	0.28	13	0.29	61	
	76th-100th %	0.23	11	0.16	34	
Hospital type	Academic	-	≤ 10[1]	0.07	19	0.07
	Children's	-	≤ 10[1]	-	≤ 10[1]	
	Community	0.75	40	0.77	215	
	County	-	≤ 10[1]	0.14	38	
	Outpatient	-	≤ 10[1]	-	≤ 10[1]	
Age	Mean	15.87 ± 1.8	53	16.08 ± 1.7	281	0.41

[1]Please note that data with ≤ 10 patients is not reported due to database reporting restrictions.
CA: California; FL: Florida.

FOOTNOTES

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MINIREVIEWS

Role of platelet-rich plasma in the treatment of rotator cuff tendinopathy

Ausberto Velasquez Garcia, Liborio Ingala Martini, Andres Franco Abache, Glen Abdo

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Abstract

Shoulder pain is a common musculoskeletal complaint, and rotator cuff (RC) pathologies are one of the main causes. The RC undergoes various tendinopathic and avascular changes during the aging process. Other degenerative changes affecting its healing potential make it an appealing target for biological agents. Platelet-rich plasma (PRP) has demonstrated the potential to deliver a high concentration of several growth factors and anti-inflammatory mediators, and its clinical use is mainly supported by experiments that demonstrated its positive effect on muscle, ligaments, and tendinous cells. This review aimed to specify the role of PRP and its future applications in RC tendinopathies based on the current clinical evidence. Due to the different characteristics and conflicting outcomes, clinicians should use PRP with moderate expectations until more consistent evidence is available. However, it is reasonable to consider PRP in patients with contraindications to corticosteroid injections or those with risk factors for inadequate healing. Its autologous origin makes it a safe treatment, and its characteristics make it a promising option for treating RC tendinopathy, but the efficacy has yet to be established.

Key Words: Rotator cuff; Tendinopathy; Platelet-rich plasma; Shoulder pain; Nonoperative

treatment; Injectables

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Core Tip: Platelet-rich plasma may be a promising treatment option for rotator cuff tendinopathy, but more consistent evidence is needed to establish its effectiveness. Therefore, clinicians should approach its use with moderate expectations and consider it a potential treatment option for patients who cannot receive corticosteroid injections or have risk factors for poor healing.

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INTRODUCTION

Shoulder pain and disability are common musculoskeletal complaints caused mainly by rotator cuff (RC) lesions[1]. Aging can promote the development of many tendinopathic and avascular changes in RC, altering its intrinsic healing capacity and increasing failure rates after surgical or non-surgical treatment[2]. RC lesions include a wide range of pathological states, beginning with acute tendinitis and progressing to tendinosis, degeneration, partial-thickness, and full-thickness tears[2,3]. Full-thickness RC tears represent the end stage of RC pathology and have an incidence of approximately 20% in adults. The prevalence of these tears increases to over 50% after the age of 60 years[4-6].

To ensure accurate management and effective communication among clinicians, it is necessary to establish a clear definition for tendinitis and tendinosis[7,8]. Tendinitis is associated with inflammation, stress, degeneration, and poor mechanics and is generally caused by overuse[9]. Tendinosis encompasses tendon degeneration with or without histological signs of inflammation, including impaired and disorganized collagen, increased vascularity, and cellularity[9, 10]. In general, tendinopathy is a term attributed to different tendons pathologies with various etiological factors, mainly caused by overuse, that can cause discomfort when the tissue does not regenerate[7,11].

New biological therapies aim to improve tendon healing as part of the ongoing development for the treatment of RC tendinopathy. These therapies include platelet-rich plasma (PRP) injections, growth factors, mesenchymal stem cells (MSCs), adipose-derived, and bone marrow aspirate concentrate. These have been proposed to speed up tendon recovery based on encouraging results from experimental models and clinical trials[12,13]. Therefore, a wide range of the states of RC tendinopathy may be effectively treated with nonoperative treatment, particularly in those where the structural integrity of the tendon has not been fully involved[14]. This review aimed to summarize the current evidence for the effectiveness of PRP as a non-surgical treatment method for RC tendinopathy.

ETIOLOGY AND SYMPTOMS OF RC TENDINOPATHY

Several theories have described possible pathophysiological routes for RC tendinopathy. Intrinsic and extrinsic mechanisms have traditionally been associated with the development of RC tendinopathy[2]. Widely studied, the intrinsic pathway describes degeneration due to hypoperfusion of the RC tendons, cell degeneration, and apoptosis, and some authors state that these create the main link in the establishment of tendinopathy[2]. Extrinsic factors are related to mechanical theories, in which microtears occur due to overuse or repetition[15]. Disorders associated with biomechanical causes, such as chronic impingement, superior humeral head translation, and overuse, have been associated with progressive degeneration of the RC tendons[2]. Since the underlying mechanism or tendon pathology cannot be determined in routine clinical practice, tendinopathy is a common term that involves many different clinical diagnoses [16].

RC tendinopathy, including partial-thickness tears, could cause limited shoulder motion, discomfort at rest, a painful arc of motion, and external rotation weakness. It is common to cause symptoms with painful overhead and positive special testing[16]. Furthermore, sleep disturbances may be characterized by discomfort in the mid-lateral region of the humerus or the anterolateral aspect of the acromion[7,8]. Indeed, partial tears are usually more painful than full-thickness [17].

TENDON HEALING

Regardless of the type of treatment applied, tendon healing occurs in three overlapping phases: Inflammatory, proliferative, and remodeling[18]. The inflammatory process produces cytokines near the injury site in the first 24 to 48 h,

attracting neutrophils, macrophages, and red blood cells. The healing process continues with hematoma formation and cellular invasion into the surrounding areas of the tendon. Growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor, are released by platelets during this phase[19-21].

During the proliferative phase, MSCs migrate and differentiate, influenced by PDGFs[18]. The cells involved in tissue repair, such as fibroblasts and MSCs, proliferate and synthesize extracellular matrix (ECM) proteins[19-23]. Fibroblasts that migrate during this phase generate type III collagen and glycosaminoglycans, which enhances the tissue's tensile strength, elasticity, and lubrication[24,25]. Tenocytes become the primary cell type responsible for producing and maintaining the ECM proteins that provide the necessary structure and mechanical properties to form new tissue[19].

Collagen cross-linking increases during the remodeling phase, and collagen type III is reabsorbed and replaced, resulting in an improved organization[25]. During this stage, tenocytes produce ECM proteins and other signaling molecules that amplify the upregulation of collagen type I gene expression and optimize the structure and function of the newly formed tissue[19,20,22,23]. However, complete tendon regeneration is not achieved, and the complex remodeling process usually leads to a steady decrease in tendon biomechanical strength[18,24]. Figure 1 illustrates the role of PRP in different stages of tendon healing.

CLINICAL EVIDENCE OF PRP INJECTIONS

Overall, clinical findings suggest that PRP injections for musculoskeletal pathologies, including supraspinatus tendinopathy, are safe[26], cost-effective, and easily administered outpatient procedures providing promising results compared to other treatment options[3]. The efficacy of various types of PRP is currently being evaluated in the shoulder and other joints[27]. Previous reports have shown inconsistent outcomes, with superior results in the PRP-treated group compared to the control groups, while others have shown similar or even inferior results[28-31]. The variability in the preparation techniques for PRP may explain the wide range of effectiveness among various studies[32]. Furthermore, factors such as the number of platelets available and the presence of anticoagulants and activators can significantly impact the growth factors present in the final PRP composition. As a result, it is difficult to compare research studies that differ substantially in design and methodology[33-35]. Furthermore, the intrinsic heterogeneity in the final composition of PRP and the various elements involved have been recognized as the main limitation of PRP injections for their wide recommendation in clinical practice[36-40].

Since these studies used different procedures to obtain the final PRP and varied the concentration of platelets and other components, the clinical results are inconsistent. This compositional variation can affect the advantages of a hypothetical healing effect[41]. Furthermore, factors such as concurrent physical therapy, exercise programs, and the impact of needle stimulation can contribute to some bias, which could also affect outcomes[42].

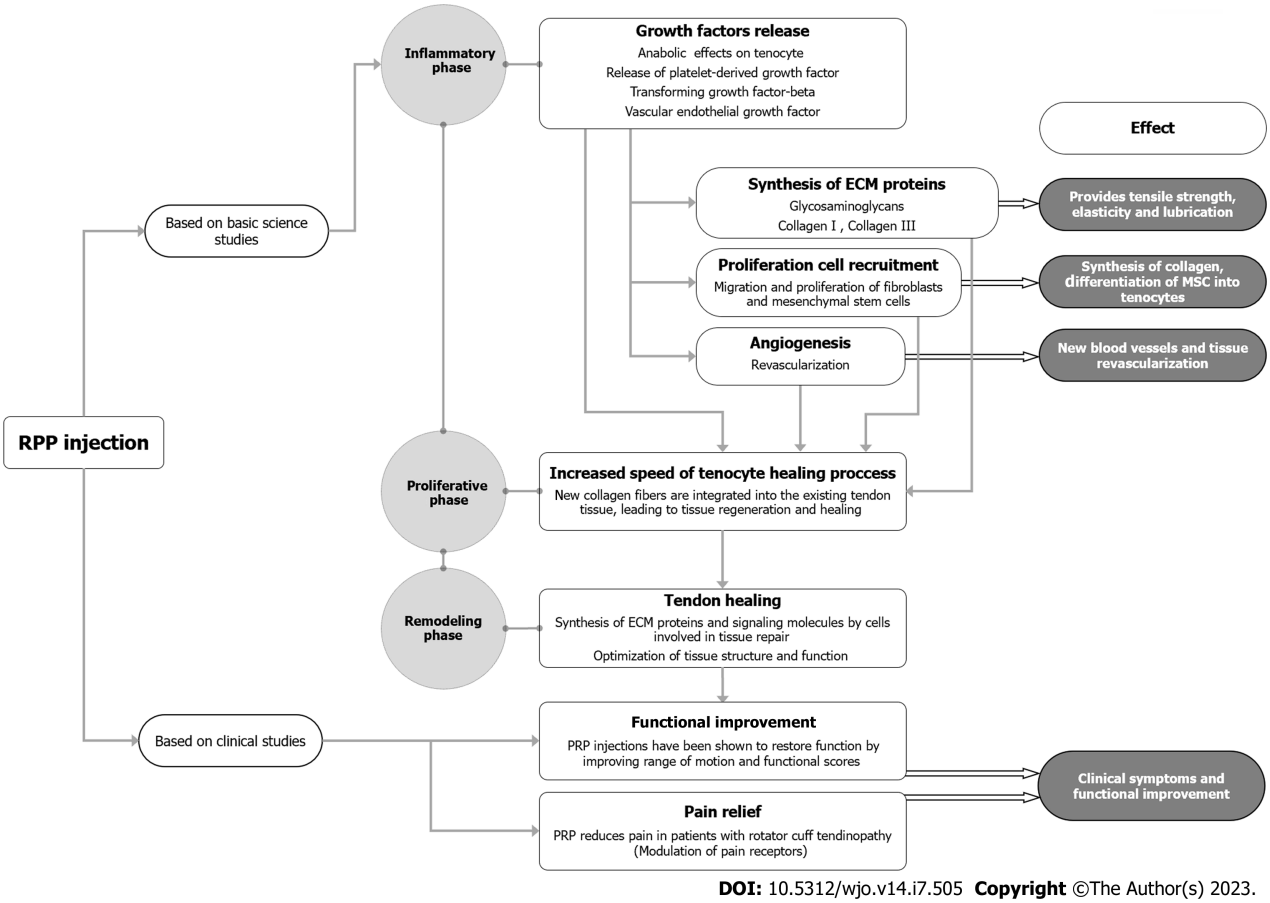
PRP IN TENDINOPATHIES

Natural growth factors, cytokines, and anti-inflammatory mediators are used in orthopedics to treat and recover tissues involved in diseases. As a result, a significant increase in the use of biological agents to treat common musculoskeletal injuries has been observed in recent years[43]. Different disorders have been treated with PRP, MSCs obtained from bone marrow aspirates, and adipose tissue[43]. PRP has gained recent popularity for treating shoulder disorders in clinical practice and as a viable method to enhance the surgical treatment of RC tears[44]. However, due to conflicting results, clinicians are still skeptical about the actual benefit and optimal use of these treatments in common shoulder diseases[43].

The clinical use of PRP is mainly supported by *in vitro* experiments that demonstrated its positive effect on muscle and tendinous cells[45]. Tenocytes exhibit enhanced proliferation and ECM production, improving tendon recovery. Additionally, when exposed to PRP, stem cells are stimulated to differentiate into tenocytes[45-48]. These characteristics show that PRP might enhance human tenocyte healing through cell proliferation and encourage ECM production[49]. Consequently, PRP could be a highly appealing therapy option for RC tendinopathy[49].

Authors in recent years have encompassed a wide range of preparations, presentations, and formulations under the term PRP. From a bioanalytical point of view, PRP consists of a fraction of whole blood with a supraphysiological concentration of platelets and other components[44]. The PRP therapy preparation process involves the separation of platelets from whole blood by centrifugation. In addition, platelet-activating chemicals can be added to enhance the effectiveness of the therapy. The growth factors released from the platelet alpha granules, approximately 7-10 d after PRP administration, coincide with the inflammation and healing phases of the tendon, promoting cellular differentiation and the healing process[32,50,51].

Growth factors, inflammatory mediators, and proteins that promote stromal and MSCs growth, including those derived from tendons, multiply once activated and hinder the repair process by creating fibrous scar tissue instead of healthy tissue[44]. Studies have shown that PRP injections can improve the structure of the ECM of tendons in the short term when injected directly into the tissue and administered through a matrix scaffold. This tendon healing and regeneration mechanism may be responsible for the clinical and structural improvements of the tendons after PRP therapy[28,33,44,52].



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Figure 1 The potential role of platelet-rich plasma in different stages of tendon healing. PRP: Platelet-rich plasma; ECM: Extracellular matrix.

PRP FOR RC TENDINOPATHY

PRP vs placebo injections, dry needling, or exercise

The comparative clinical efficacy of PRP, placebo (saline), autologous whole blood, and dry needling for ligament and tendon injury is unclear (Table 1). Lin *et al*[53] conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the effectiveness of PRP therapy in patients with RC tendinopathy compared to sham injection, no injection, or physical therapy alone. The study found that PRP therapy produced significant long-term pain relief (> 24 wk) but did not show significant differences in functional results compared to the control groups. Notably, the study included trials using various numbers of injections, ultrasound-guided and non-guided injection techniques, and different injection approaches, but it found no specific approach to be more effective than others.

Chen *et al*[26] conducted a systematic review and meta-analysis that evaluated the efficacy of PRP therapy in the healing of tendons and ligaments. The study analyzed 37 articles and included 1937 patients without restrictions on the tendons or ligaments studied. The authors found a wide variety of preparation methods used in the studies, and half of the studies did not use platelet activation or did not report the specific kit used. Despite this, the authors found no significant adverse events, highlighting the safety of PRP therapy. Overall, the PRP groups in the studies showed significantly less long-term pain than the control groups, particularly in lateral epicondylitis and RC injuries.

A randomized controlled study by Kesikburun *et al*[54] evaluated the effectiveness of PRP therapy in patients with RC tendinopathy who were treated with an exercise program. The study found that PRP was less effective than a placebo injection in several aspects, which can be attributed to leukocyte-rich PRP and shorter follow-up periods. However, another prospective open-label comparative trial compared a PRP group with an exercise group and found that PRP showed better American Shoulder and Elbow Surgeons Score (ASES) and Constant Murley Score (CMS) at 6 and 12 wk. However, at 24 wk, PRP was not superior to exercise. The PRP group had better rates of decreasing tendon thickness, but the concentration of leukocytes was not analyzed. Furthermore, the study found that higher levels of TGF-β1 and interleukin-1β growth factors were related to the clinical efficacy of PRP. This suggests that PRP provided more remarkable results than exercise alone, but exercise showed a cumulative positive effect in the long term, suggesting that more than a single injection may be necessary[55].

Wesner *et al*[56] reported results in a RCT that included 9 participants with RC tendinopathy receiving 4 mL of PRP injected into the supraspinatus or infraspinatus, and patients in the placebo group were injected with 4 mL of saline. All participants completed a 3-mo standardized home-based daily exercise program. The primary outcome measures were evaluated 3 and 6 mo after injection in RCT[56]. The study showed that patients who underwent PRP injections reported considerable improvements in pain and disability[56]. The authors concluded that intratendinous ultrasound-guided PRP

Table 1 Single or double-arms trials assessing effectiveness of platelet-rich plasma *vs* placebo injections, dry needling, or exercise

Ref.	Level of evidence	Design	Groups (*n*)	Injections/dosis	Outcomes measure	Follow-up	Conclusions
Kesikburun *et al*[54], 2013	I	Ultrasound-guided PRP injections *vs* saline injections	40 patients PRP (20), placebo (20)	1/5 mL	VAS, WORC, and SPADI	3, 6, 12, 24 wk. 1 yr	PRP is not more effective in improving shoulder quality of life, pain, disability, and range of motion than placebo
Rha *et al*[57], 2013	I	PRP injections *vs* dry needling	39 patients. PRP (20), dry needling (20)	1/3 mL	SPADI, passive ROM, global rating scale, ultrasound measurement	24 wk	PRP leads to a progressive reduction in pain and disability compared to dry needling
Scarpone *et al* [59], 2013	III	Ultrasound guided PRP injection at the lesion and surrounding tendon	18	1/3.5 mL	MRI, VAS and three-item patient satisfaction scale	8, 12, 52 wk	Improvement in MRI, pain and function with PRP
Lee *et al*[62], 2019	III	PRP injection *vs* exercise treatment; leukocyte-poor *vs* leukocyte-rich PRP	60. PRP (27), exercise (33)	1/1.5 mL	ASES, CMS, and NRS	12 wk, 24 wk	PRP is more effective than exercise therapy for the first 3 mo
Kim *et al*[55], 2019	II	PRP injection *vs* exercise treatment	30 patients. PRP (15), exercise (15)	1/2 mL	ASES, CMS, and NRS	12 wk, 24 wk	PRP had an advantage over exercise; improvement until 12 wk, slight decrease at 24 wk
Rossi *et al* [71], 2021	II	Subacromial PRP injections	50 patients	1/5 mL	ASES, CMS, and VAS	1 yr	PRP decreased pain, improved functional outcomes, and resolved sleep disturbances. Return to sports for most athletes
Oudelaar *et al* [77], 2021	I	NACD + PRP *vs* NACD + CI	88 patients. NACD + PRP (41), NACD + CI (47)	1/5 mL	VAS, CMS, DASH, OSS, EQ-5D	6 wk, 3 mo, 6 mo, 12 mo, 24 mo	NACD + PRP was worse at the 6-wk follow-up but better at the 6-mo follow-up. Comparable results at 12 and 24 mo

ASES: American Shoulder and Elbow Surgeons score; CMS: Constant Murley Score; CI: Corticosteroid injection; DASH: Disability of Arm-Hand-Shoulder score; PRP: Platelet-rich plasma; ROM: Range of motion; SPADI: Shoulder Pain and Disability Index; SST: Simple Shoulder Test; UCLA: University of California Los Angeles score; VAS: Visual analog scale; WORC: Western Ontario Rotator Cuff; MRI: Magnetic resonance imaging; NACD: Needle Aspiration of Calcific Deposits; OSS: Oxford Shoulder Score.

injection could improve tendon pathology as documented by magnetic resonance imaging (MRI). This finding provides information for future studies examining PRP effectiveness[56]. However, the study's limited sample size restricts the generalization of the results, and larger-scale studies are required to validate the findings.

A clinical trial compared the effectiveness of dry needling *vs* ultrasound-guided injection of PRP to treat RC tendinopathy[57]. The study found similar levels of effectiveness in reducing pain and improving function between dry needling and PRP injection. However, patients who received PRP injections experienced a steady decrease in pain and impairment six months after treatment, suggesting that PRP may have long-term benefits[57].

A recent systematic review and meta-analysis pooled the results of previous studies on the efficacy of PRP injections *vs* other treatments for patients with RC tendinopathy[58]. The study included 8 RCTs and found no significant differences between the PRP and control groups after three weeks of follow-up[58]. PRP was compared to saline injection in 4 trials, while rehabilitation programs and dry needling were control interventions in the other 4. PRP therapy's medium- and long-term outcomes were superior, except for the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire. The most common adverse effect was mild and temporary pain[58].

In another long-term trial, 18 patients who had not responded to previous physical treatment but received a single 3.5 mL ultrasound-guided intralesional injection of PRP showed steady improvement on the Visual Analog Scale (VAS)[59]. At one year of follow-up, the median VAS dropped from 7.5 ± 0.3 before injection to 0.4 ± 0.2, and MRI alterations and functional outcomes similarly improved[59].

PRP vs corticosteroid injections

Subacromial corticosteroid injections (CI) or PRP have both seen an increase in comparative investigations in recent years [60-63] (Table 2). Some evidence supports that PRP could be a suitable substitute for patients who cannot use CIs, as suggested in a RCT of 40 patients with symptomatic partial-thickness RC tears, where PRP injections and CI were compared for pain control and patient-reported outcomes (PROs)[60]. Although both groups showed a significant improvement over the pre-injection condition at 12 wk, the PRP group showed a statistically significant improvement in pain and PROs at 24 wk. MRI at 6 mo of follow-up did not show significant differences between groups[60].

Table 2 Randomized controlled trials comparing platelet-rich plasma *vs* corticosteroid injections for rotator cuff tendinopathy

Ref.	Level of evidence	Design	Groups (*n*)	Dosis/quantity	Outcomes measure	Follow-up	Conclusions
Barreto *et al* [66], 2019	I	Subacromial PRP injections *vs* CI	51 patients. PRP (26), CI (25)	1/about 3 mL	DASH, UCLA-SRS, CMS	3mo, 6 mo	No statistically significant differences
Dadgostar *et al* [63], 2021	I	Ultrasound guided PRP injections *vs* CI	58 patients. (30) PRP, (28) CI	1/3 mL intra-articular, 3 mL intratendinoeus	VAS, ROM, WORC, DASH, US supraspinatus thickness	3 mo	PRP with similar results to CI
Kwong *et al* [70], 2021	I	Ultrasound-guided leokocyte-poor PRP injection *vs* CI	99 patients. PRP (47), CI (52)	1/(3-5) mL intratendineous (non-specific) and the rest at the subacromial space	VAS, ASES score, and WORC	6, 12, 48 wk	The PRP group showed superior improvement in pain and function at short-term follow-up, without benefit at long-term follow-up
Ibrahim *et al* [68], 2019	I	Ultrasound guided subacromial PRP *vs* CI	30 patients. PRP (15), CI (15)	1/2 mL	VAS, SDQ, ROM Clnical tests, US findings	8 wk	Both groups showed significant improvement. PRP is safe and can be used for PRCT
Jo *et al*[78], 2020	I	Ultrasound guided allogenic PRP *vs* CI	60 patients. PRP (30), CI (30)	1/4 mL	VAS, CMS, ASES, DASH, RC strength, ROM	1, 4, 12, 24 wk	PRP reduced pain and improved overall function at 6 mo. DASH score, overall function, and external rotation were significantly better in the PRP group
Pasin *et al*[79], 2019	I	PRP *vs* CI *vs* exercise	60 patients. PRP (30), CI (30)	1/4 mL	VAS, quick DASH, UCLA SRS, SF-36	3, 8 wk	PRP had better scores than CI and Physical Therapy even in a long time
Sabaah *et al* [80], 2020	I	Prolotherapy *vs* CI and PRP	40 patients. PRP (20), CI (20)	2/5 mL	VAS, WORC-Index, ROM and US findings	12 wk	Prolotherapy was superior. PRP improve tendon healing
Sari *et al*[81], 2020	I	Ultrasound guided PRP *vs* CI, prolotherapy and lidocaine	60 patients. PRP (30), CI (30)	1/5 mL	VAS, ASES and WORC	3, 12, 24 wk	CI were better at 3 wk. NO difference at 12 wk. PRP had better outcomes at 24 mo
Thepsoparn *et al*[82], 2021	I	Ultrasound guided leukocyte-poor PRP *vs* CI	31 patients. PRP (15), CI (16)	1/5 mL	VAS and OSS	4, 24 wk	No difference at 4 wk. PRP had better results at 24 wk for PRCT. No complications

ASES: American Shoulder and Elbow Surgeons score; CMS: Constant Murley Score; CI: Corticosteroid injection; DASH: Disabilities of the Arm, Shoulder and Hand score; PRP: Platelet-rich plasma; ROM: Range of motion; SPADI: Shoulder Pain and Disability Index; SST: Simple Shoulder Test; UCLA: University of California Los Angeles score; UCLA-SRS: University of California Los Angeles Shoulder Rating Score; VAS: Visual analog scale; WORC: Western Ontario Rotator Cuff; MRI: Magnetic resonance imaging; SDQ: Shoulder Disability Questionnaire; PRCT: Partial rotator cuff tears; SF-36: Short Form 36; OSS: Oxford Shoulder Score.

PRP has proven advantages, such as the possibility of repeat injections if symptoms worsen. It could even be administered 1 to 6 mo before surgery due to its safety, which contrasts with CI, and its recognized risk of perioperative complications[64,65]. However, the cost-effectiveness of PRP has not been established. Other reports have shown similar effectiveness between PRP and CI. In a randomized, double-blind trial, patients were evaluated using the DASH score, the University of California Los Angeles (UCLA) shoulder rating scale, and CMS at baseline and 1, 3, and 6 mo after treatment. Results showed no statistically significant differences ($P < 0.05$) between the PRP and CI groups in any outcome measures at any time. Both groups showed a significant improvement in DASH and UCLA scores ($P < 0.05$) compared to baseline, but the CMS score 6 mo after corticosteroid treatment was lower than baseline. These findings suggest that PRP is a safe treatment option for RC impingement syndrome and may be a valuable alternative, as it was found to be equally effective as corticosteroids[66]. Similar results were found in a prospective study with 60 patients with RC tendinosis or partial tendon tear. The authors used 2.5 mL of activated PRP or 40 mg methylprednisolone during the trial. The CMS improved from 41 to 53 points at 6 mo in the PRP group and from 38 to 66 points in the CI group[67].

In a study of 30 patients with RC tendinopathy, two groups of 15 were randomly chosen to receive a subacromial ultrasound-guided injection of PRP or corticosteroids. Pain in patients was evaluated using the VAS, shoulder function using the Shoulder Disability Questionnaire, and range of motion (ROM) before and 8 wk after injection. The study found that PRP and CI were similarly effective in the treatment of RC tendinopathy, showing significant improvements in pain, function, and ROM. These results suggest that PRP is a safe alternative to CI, decreasing inflammation and improving

outcomes[68].

In another double-blind clinical trial, 58 patients with RC tendinitis were randomized to receive 3 mL of PRP or 1 mL of Depo-medrol 40 mg. The study found that both treatments resulted in similar significant improvements in pain, ROM, Western Ontario Rotator Cuff scores, DASH scores, and supraspinatus thickness during follow-ups[63]. A recent systematic review and meta-analysis of RCTs that included 639 patients revealed that at short-term follow-up, CI was more effective than PRP in the short term, but, in the mid-term, PRP was superior to CI in DASH and ASES scores. However, both treatments achieved minimal clinical important difference for each score, indicating no significant clinical differences between the two treatment modalities in managing RC disease[69].

A double-blind, randomized controlled study compared ultrasound-guided PRP injection with conventional CI in patients who had completed a detailed physical therapy protocol. Ninety-nine patients with MRI or ultrasound documented partial-thickness RC tears or tendinopathy were included. Patients treated with leukocyte-poor PRP ultrasound-guided injections showed superior improvement in pain and function at short-term follow-up. However, at 12 mo, there was no persistent effect of PRP over CI and no variations in the incidence of failure or conversion to surgery [70]. Ultrasound-guided injection of PRP potentially improves the precision and safety of the infiltration method, thus leading to improved effectiveness of the treatment[3,68]. However, the benefit has not been demonstrated extensively.

In contrast, a recent systematic review and meta-analysis of 12 RCTs have shown that while CI may have better short-term outcomes in treating RC tendinopathy, PRP therapy may have superior medium-term outcomes. These results suggest that while CI may provide faster pain relief, PRP therapy may be more effective in promoting long-term healing and tissue regeneration[69]. However, it should be noted that the studies included in the review had significant heterogeneity in their preparation of PRP (such as using the buffy-coat method *vs* the tube method and using one *vs* two centrifugation steps) and their treatment protocols after injection[69].

Similarly, a prospective cohort study included 50 patients with MRI-diagnosed tendinopathy, no tendon rupture, and 3 mo of failed conservative treatment. Two spin protocols were performed, and 5 mL of leukocyte-rich PRP was used to treat patients in combination with physical therapy. Results included pain relief, positive clinical results, and a return to sports at the pre-injury level at high rates[71].

FUTURE PERSPECTIVE

Kieb *et al*[72] introduced an innovative method to standardize PRP growth factor concentrations using allogeneic lyophilized PRP powder. This technique involves creating a powder using twelve pooled platelet concentrations from various donors and comparing the growth factor concentration achieved using this technique to that found in whole blood. Theoretically, this approach allows the precise composition of the PRP to be chosen to provide a specific amount of growth factors based on the treated pathology. This advantage may provide a more controlled and efficient way to use the benefits of PRP therapy.

In a separate study, 17 patients with RC tendinopathy were treated with an injection of allogeneic PRP, while a control group received CI. Both groups experienced a significant reduction in pain and improved outcomes, with the CI group showing a faster recovery. No adverse effects were reported. The results of this trial suggest that allogeneic PRP may be a safe and potentially beneficial treatment option for RC tendinopathy, but further research is needed to confirm these findings and establish its long-term effectiveness[73].

High-quality evidence supports the use of PRP after RC repair[74]. However, the clinical evidence on the benefits of PRP in the nonoperative treatment of RC disorders is inconsistent. This makes it difficult to draw firm conclusions about PRP's advantages in treating RC disorders. Although some *in vitro* studies have shown promising results for PRP, clinical studies have not consistently supported its therapeutic impact.

Additionally, the effectiveness of PRP can depend on the type and concentration of the specific components used. Therefore, more research is needed to fully understand PRP's potential benefits and limitations in treating RC disorders. This situation highlights the need for a detailed investigation to define the optimal composition, efficient dose, and mechanism of action of PRP[73,75,76].

CONCLUSION

PRP therapy has been proposed as a treatment option for RC tendinopathy, but the available evidence is conflicting due to variability in settings, indications, and clinical outcomes. As a result, clinicians should approach PRP therapy with moderate and realistic expectations until more reliable evidence is available. While the basic science literature supports the potential of PRP to manage RC tendinopathy, there is not yet enough clinical data to support its effectiveness. However, PRP therapy is considered a safe treatment option because it uses a patient's blood, decreasing the risk of allergic reactions or other complications associated with the use of foreign substances. Therefore, it is reasonable to consider PRP injections in patients with a contraindication to CI or patients with risk factors for inadequate healing as a promising treatment option for RC tendinopathy.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Effectiveness of an early operating room start time in managing pediatric trauma

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Abstract

BACKGROUND

The timing of operative treatment for pediatric supracondylar humerus fractures (SCHF) and femoral shaft fractures (FSF) remains controversial. Many fractures previously considered to be surgical emergencies, such as SCHF and open fractures, are now commonly being treated the following day. When presented with an urgent fracture overnight needing operative treatment, the on-call surgeon must choose whether to mobilize resources for a late-night case or to add the case to an elective schedule of the following day.

AIM

To describe the effect of a program allowing an early operating room (OR) start for uncomplicated trauma prior to an elective day of surgery to decrease wait times for surgery for urgent fractures admitted overnight.

METHODS

Starting in October 2017, patients were eligible for the early slot in the OR at the discretion of the surgeon if they were admitted after 21:00 the previous night and before 05:00. We compared demographics and timing of treatment of SCHF and FSF treated one year before and after implementation as well as the survey responses from the surgical team.

RESULTS

Of the 44 SCHF meeting inclusion criteria, 16 received treatment before imple-

mentation while 28 were treated after. After implementation, the mean wait time for surgery decreased by 4.8 h or 35.4% (13.4 h *vs* 8.7 h; $P = 0.001$). There were no significant differences in the operative duration, time in the post anesthesia care unit, and wait time for discharge. Survey results demonstrated decreased popularity of the program among nurses and anesthesiologists relative to surgeons. Whereas 57% of the surgeons believed that the program was effective, only 9% of anesthesiologists and 16% of nurses agreed. The program was ultimately discontinued given the dissatisfaction.

CONCLUSION

Our findings demonstrate significantly reduced wait times for surgery for uncomplicated SCHF presenting overnight while discussing the importance of shared decision-making with the stakeholders. Although the program produced promising results, it also created new conflicts within the OR staff that led to its discontinuation at our institution. Future implementations of such programs should involve stakeholders early in the planning process to better address the needs of the OR staff.

Key Words: Pediatrics; Trauma; Supracondylar humerus fractures; Operating room

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Core Tip: This study describes the effect of a program allowing an early operating room start for uncomplicated trauma prior to an elective day of surgery to decrease wait times for surgery for urgent fractures admitted overnight. After implementation, the mean wait time for surgery decreased by 4.8 h or 35.4%. Survey results demonstrated decreased popularity of the program among nurses and anesthesiologists relative to surgeons. Our findings demonstrate significantly reduced wait times for surgery for uncomplicated pediatric supracondylar humerus fractures presenting overnight while discussing the importance of shared decision-making with the stakeholders.

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INTRODUCTION

The timing of operative care for pediatric orthopedic injuries is a subject of controversy. Recent studies comparing early *vs* delayed intervention for supracondylar humerus fractures (SCHF) in children have challenged the conventional wisdom that postponing cases leads to unsatisfactory results[1-3]. Many fractures that were previously considered to be surgical emergencies, such as SCHF and open fractures, are now commonly being treated the following day. This avoids potentially inefficient provision of care by an on-call team who may not be as well-rested or as familiar with pediatric orthopedic care as a day team[4,5]. Despite this shift away from overnight care, a safe and expeditious provision of care remains in the best interest of the patient and family. The timely provision of care for urgent fractures thus presents a logistical challenge to hospitals.

SCHF and femoral shaft fractures (FSF) are among the most common surgically treated pediatric fractures, with SCHF accounting for 60% of pediatric elbow fractures and FSF being the most common diaphyseal fracture in children[6-10]. Given their high incidences, the timeliness of their treatment continues to be a metric used for United States News and World Report's ranking of children's hospitals[8]. This presents a challenge for hospitals with moderate trauma volume that is insufficient to justify a daily trauma room. When presented with an urgent fracture overnight needing operative treatment, the on-call surgeon must choose whether to mobilize resources for a late-night case or to add the case to an elective schedule of the following day.

Here we describe the effect of the 6 AM start quality improvement program implemented at a suburban level I trauma center. This program was designed to decrease wait times for urgent trauma cases while minimizing surgeon fatigue, thereby increasing the efficiency of care and improving compliance with United States News and World Report's standard for timely management.

MATERIALS AND METHODS

Implemented at our facility in October 2017, the 6 AM start program allowed the orthopedic surgeon on call overnight to book an uncomplicated case for an early start in the operating room (OR) at 06:00 prior to the start of a typical elective surgery weekday (Monday through Friday, excluding holidays) at 07:30. Patients with SCHF and FSF were eligible if they were admitted to the ED after 21:00 the prior day and indicated for surgical treatment at the discretion of the surgeon.

Surgeon-controlled time in the OR also had to be projected at less than 75 min.

We received IRB approval (IRB #46989) which granted a waiver of consent and assent. We queried our electronic medical record system for all pediatric patients who underwent surgical fixation for closed isolated SCHF (CPT codes: 24538, 24545, 24546) or FSF (CPT codes: 27502, 27506, 27507) from October 2016 to October 2018. We included patients who were admitted to the ED between 19:00 and 05:00 as the program was often applied to patients technically admitted earlier than 21:00 who had a long wait for an orthopedic consult. Patients admitted on Friday or Saturday nights as well as on the eve of a holiday were excluded. Those over age 12 for SCHF and eight for FSF were excluded since they were more likely to have adult or transitional fracture patterns indicating fixation methods that exceed the projected-surgeon control time of 75 min. Complicated cases including open fractures, threatened vascular status, concurrent ipsilateral fractures, and pathological fractures were excluded.

Patient charts were screened for patient and fracture characteristics. The outcome measure of this study was the wait time for surgery, defined as the time between ED admittance and the patient's arrival at the OR. Balancing measures included the operative duration (time between start and end of the procedure), post anesthesia care unit (PACU) length-of-stay (LOS), time between arrival and departure from the PACU, and wait time for discharge (time between departure from the PACU and discharge). Cases were further classified as overnight cases, 6 AM start cases, and add-on cases based on their scheduled start time as more than 1.5 h prior, 1.5-1 h prior, and after the start of the elective surgery weekday, respectively. The percentage of eligible cases that utilized the 6 AM start program served as the process measure for this study.

For additional balancing measures, all OR staff received an anonymous electronic survey through the internal hospital distribution lists. The survey asked respondents to score their level of agreement on a Likert scale with five statements regarding the beneficiaries of the program and the effectiveness of the program. Additional text boxes allowed providers to explain their responses and provide general feedback.

Statistical analyses were performed with RStudio (Boston, MA) using a two-sided level of significance of 0.05. Baseline characteristics among groups were tested using two-sample *t*-tests, Mann-Whitney *U*-tests, and Fisher's exact tests. Wait time for surgery, operative duration, PACU LOS, and wait time for discharge were compared between patients admitted before and patients admitted after the implementation of the program using two-sample *t*-tests or Mann-Whitney *U*-tests. The same outcome variables were compared among patients whose surgeries were scheduled at the three aforementioned time points (overnight cases, 6 AM start cases, and add-on cases) using one-way ANOVA tests and Kruskal-Wallis tests, with Tukey-adjusted *P* values and Dunn's test for pairwise comparisons. For the survey analysis, responses to the five survey items were compared between various roles in the surgical team using one-way ANOVA tests with Bonferroni-adjusted *P* values for pairwise comparisons.

RESULTS

We initially identified 118 pediatric patients with SCHF and 23 with FSF treated during the study period. After applying the exclusion criteria, 44 SCHF and six FSF were included in the study (Figure 1). For SCHF, 16 patients received operative treatment before the program's implementation and the other 28 were treated after. There were no significant differences in patient and fracture characteristics between the two groups (Table 1). After the implementation of the 6 AM start program, the mean wait time for surgery for patients presenting overnight with uncomplicated SCHF decreased by 4.8 h or 35.4% (13.4 h *vs* 8.7 h; $P = 0.001$). There were no significant differences in the operative duration, PACU LOS, or wait time for discharge (Table 2). The before-implementation group for SCHF included one (6%) overnight case and 15 (94%) add-on cases. The after-implementation group was composed of four (14%) overnight cases, 14 (50%) 6 AM start cases, and 10 (36%) add-on cases. Other than the significantly decreased wait time for surgery, the three subgroups in the after-implementation group showed no differences in demographics and subsequent phases of patient care (Tables 3 and 4).

This study identified five FSF cases treated before the program's implementation and one case treated after. A case in the former group had an incorrectly recorded time of discharge and was thus excluded from the calculation for the wait time for discharge. All patients in the before-implementation group were add-on cases, while the one case in the after-implementation group was a 6 AM start case. Although sample size precludes a meaningful statistical analysis, the 6 AM start case had a shorter wait time for surgery by 4.2 h or 30.2% [13.9 (12.7-19.6) h *vs* 9.7 h] than the before-implementation group. Otherwise, it had a longer operative duration (61 ± 42 min *vs* 138 min), PACU LOS (1.6 ± 1.1 h *vs* 3.2 h), and wait time for discharge [12.4 (4.4-42.9) h *vs* 51.1 h].

There were a total of 24 survey respondents which was composed of 11 (46%) anesthesiologists, seven (29%) surgeons, and six (25%) nurses. 17 (70.8%) respondents directly participated in a 6 AM surgery while five (20.8%) respondents did not; two (8.4%) respondents did not answer the prompt. Since many of the OR staff are involved in scheduling cases without directly participating in the surgery or may have participated in other surgeries that were affected by the program's policy, all 24 respondents were included in the analysis.

Univariate analysis showed a significant difference in responses among anesthesiologists, nurses, and surgeons for all five survey questions. Further pairwise comparisons revealed that anesthesiologists reported more dissatisfaction than surgeons for all five items. Furthermore, nurses reported lower opinions on the program's benefit to the patient, ease of placing urgent trauma cases, and overall effectiveness than surgeons (Figure 2). Seven (29%) providers cited that the program benefited patient care because of the efficiency, stating that "patients received surgical care more quickly". However, four (17%) providers disagreed as they "felt that the timing of the 6 AM cases typically did not end at an appropriate time" and "caused delays for scheduled patients". Regarding the program's benefit to the staff, eight (33%)

Table 1 Demographics of uncomplicated supracondylar humerus fractures treated before and after implementation of the 6 AM start program

	Total (*n* = 44)	Before implementation (*n* = 16)	After implementation (*n* = 28)	*P* value
Female, % (*n*)	61 (27)	56 (9)	64 (18)	0.182
Age	5.1	5.1	5.1	0.912
Gartland classification, % (*n*)				0.686
Type I	0 (0)	0 (0)	0 (0)	
Type II	38.6 (17)	31.3 (5)	42.9 (12)	
Type III	52.2 (23)	56.3 (9)	50 (14)	
Type IV	9.09 (4)	12.5 (2)	7.14 (2)	
Reduction, % (*n*)				0.732
Closed	95.5 (42)	100 (16)	92.9 (26)	
Open	4.6 (2)	0 (0)	7.14 (2)	

Table 2 Length of time within phases of patient care for supracondylar humerus fractures

	Total (*n* = 44)	Before implementation (*n* = 16)	After implementation (*n* = 28)	*P* value
Wait time for surgery, h	10.4 ± 9.3	13.4 ± 8.6	8.6 ± 7.9	0.001
Operative duration, min	31.5 (24.5-35.3)	30.5 (21.5-37.5)	31.5 (24.5-35.3)	0.817
PACU LOS, h	1.34 (1.2-1.6)	2 ± 1.6	1.4 (1.2-1.6)	0.060
Wait time for discharge, h	4.96 (3.5-9.7)	3 (0.01-7.21)	5 (3.5-9.7)	0.924

PACU: Post anesthesia care unit; LOS: Length-of-stay.

Table 3 Demographics of supracondylar humerus fractures treated after the implementation of the 6 AM start program, stratified by scheduled surgery time

	Overnight cases (*n* = 4)	6 AM cases (*n* = 14)	Add-on cases (*n* =10)	*P* value
Female, % (*n*)	100 (4)	57.1 (8)	60 (6)	0.271
Age	6	4	6.3	0.310
Gartland classification, % (*n*)				0.514
Type I	0 (0)	0 (0)	0 (0)	
Type II	50 (2)	42.9 (6)	40 (4)	
Type III	25 (1)	50 (7)	60 (6)	
Type IV	25 (1)	7.1 (1)	0 (0)	
Reduction, % (*n*)				0.210
Closed	75 (3)	100 (14)	90 (9)	
Open	25 (1)	0 (0)	10 (1)	

providers commented that the early hours were an issue with reports of being "frustrated having to come back to the hospital for a 6 AM start" and concluding that it was "a horrible time to do a case". In the feedback section, seven (29%) providers expressed their dislike of the program while seven (29%) providers liked the program as "it gave a time for patients to be scheduled in a timely manner" and "benefited patient care". Six (25%) providers suggested that either "starting at 7:30 (or) having a bump room for quick ortho cases is preferred". Regarding the program's benefit to the hospital, while four (17%) providers believed that the program positively impacts the United States News and World Report scores, four (17%) staff members expressed that "the intangible negative effects on nursing and anesthesiologists far outweighed any USNWR points it got (the hospital)".

Table 4 Length of time within phases of patient care for supracondylar humerus fractures, stratified by scheduled surgery time

	Night cases (*n* = 4)	6 AM cases (*n* = 14)	Add-on cases (*n* = 10)	*P* value
Wait time for surgery, h	2.3 ± 0.2	8.2 ± 2.4	11.8 ± 3.1	1.19e-06
Operative duration, min	30.5 (27.5-71.5)	33.5 ± 7.7	25.5 (19-35)	0.229
PACU LOS, h	1.2 ± 0.3	1.4 (1.2-1.6)	1.5 (1.1-1.6)	0.681
Wait time for discharge, h	8.9 ± 6.6	6.5 ± 3.6	3.6 (0.9-3.9)	0.410

PACU: Post anesthesia care unit; LOS: Length-of-stay.

DISCUSSION

The provision of consistent and timely pediatric orthopedic trauma care can present logistical challenges when available OR space and patient volumes render a daily trauma or add-on room inefficient. Our study evaluated the effectiveness of a program that made available an earlier slot in the OR for uncomplicated fractures presenting to the ED overnight, thus facilitating timely care without disrupting the daily elective schedule or mobilizing resources for an urgent case at night. Before the implementation of this program, it was not uncommon for an urgent case presenting overnight to wait until the end of a scheduled day of elective cases in the following afternoon or evening. Our findings suggest that the 6 AM start program facilitated more timely care for patients with uncomplicated fractures presenting overnight without significant consequences to subsequent phases of patient care.

The timeliness of operative treatment for SCHF and FSF continues to be in dispute in the medical community. Furthermore, studies use different standards for what is considered early and delayed intervention[11-13]. For the ranking of children's hospitals, United States News and World Report defines timely management as the treatment for SCHF and FSF within 18 h of presentation to the ED. For SCHF, hospitals receive one point for ≥ 75% and < 90% of cases that meet this definition and two points for ≥ 90%; for FSF, hospitals are awarded one point for ≥ 60% and < 80% of cases and two points for ≥ 80%[8]. A review of the literature calls into question the wisdom of rewarding hospitals for expedited care and in absence of literature support any improved patient outcomes with expedited care. For example, a study in Texas of 399 SCHF demonstrated that a delay in surgery of greater than 24 h did not result in increased rate of complications for type II SCHF[14].

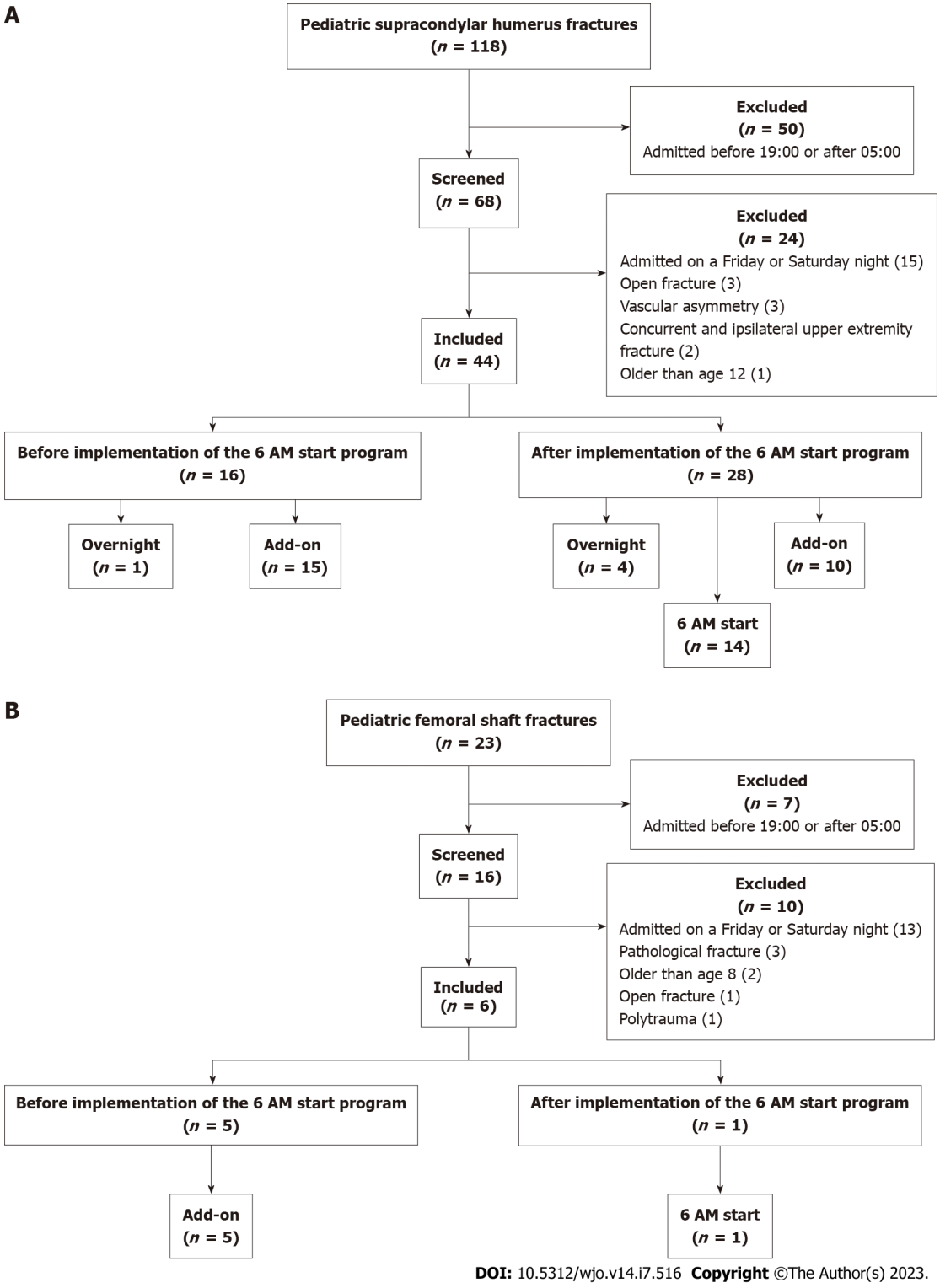
At our own institution we previously published a review of 153 patients with SCHF and we found no significant differences in outcomes among SCHF operated on overnight *vs* daytime surgery however surgery between midnight and 6 AM was associated with slightly a higher rate of malunion[15].

The treatment of type III SCHF is perhaps more controversial. A retrospective review of 172 patients spanning different severities of from the United Kingdom found no increasing complications when supracondylar fractures arriving after hours are managed the following day *vs* overnight[16].

Similarly, a recent report from Japan including 244 patients found that delaying treatment more than 12 h did not affect the rate of complications after surgery for Gartland type II or III SCHF[17]. A recent paper from Boston Children's Hospital demonstrated that at that institution 35% of type III and IV SCHF presenting overnight are operated on the night they presented while the remainder were treated the following day. No difference in complication rate was found based on timing of treatment. Based on their existing practice patterns they suggested that patients with potential neurovascular compromise or displacement of any cortex by greater than 25 mm should be considered for treatment overnight[18]. Despite the lack of any clinically demonstrable threshold for a delay in care that predicts poor outcomes, expediting care may have other benefits to families and patients. Furthermore timeliness of care continues to be a benchmark process metric of quality.

In this study, the percentage of cases with wait times for surgery within 18 h of ED admittance increased from 81% to 100% for SCHF and 56% to 100% for FSF after the implementation of the program. This translates to an additional award of two points to achieve the maximum of four points in this category. These findings support the 6 AM start program as an effective alternative to designated trauma rooms for reducing wait times for operative treatment for uncomplicated fractures, benefiting both patients and the institutions that do not have the OR space or trauma volume to render a trauma room cost-effective.

However, the survey responses highlight issues to address for future attempts at implementation of similar programs. The survey uncovered a significant disparity in opinions about the program amongst the staff, in particular those of surgeons *vs* those of anesthesiologists and nurses. This is partly attributed to the time of transition from overnight calls to daytime shifts at our institution. Surgeons typically take a home call followed by a clinic or OR day. In contrast, the on-call anesthesiologist has a 24-h shift from 07:00 to 07:00, making the 6 AM start case the 24th h of their shift. Nurses also change shifts at 07:00. Thus surgeons would take on the 06:00 fracture cases as their first or only surgery of the day while overnight anesthesiologists and nurses would have to either come in from home or stay until the last hour of their shift. This led nurses and anesthesiologists to feel that the program took advantage of OR staffing to facilitate the surgeon's schedule. Several nurses and anesthesiologists voiced concerns that the elective schedule was often delayed if the 06:00 case did not start on time or ran over the expected time. The nursing staff also felt that mobilizing for an urgent case at 06:00 was inefficient because the 06:00 h is typically spent preparing the following day's cases. Several nurses questioned the logic of waiting until 06:00 if the OR and staff were available to do the case sooner.

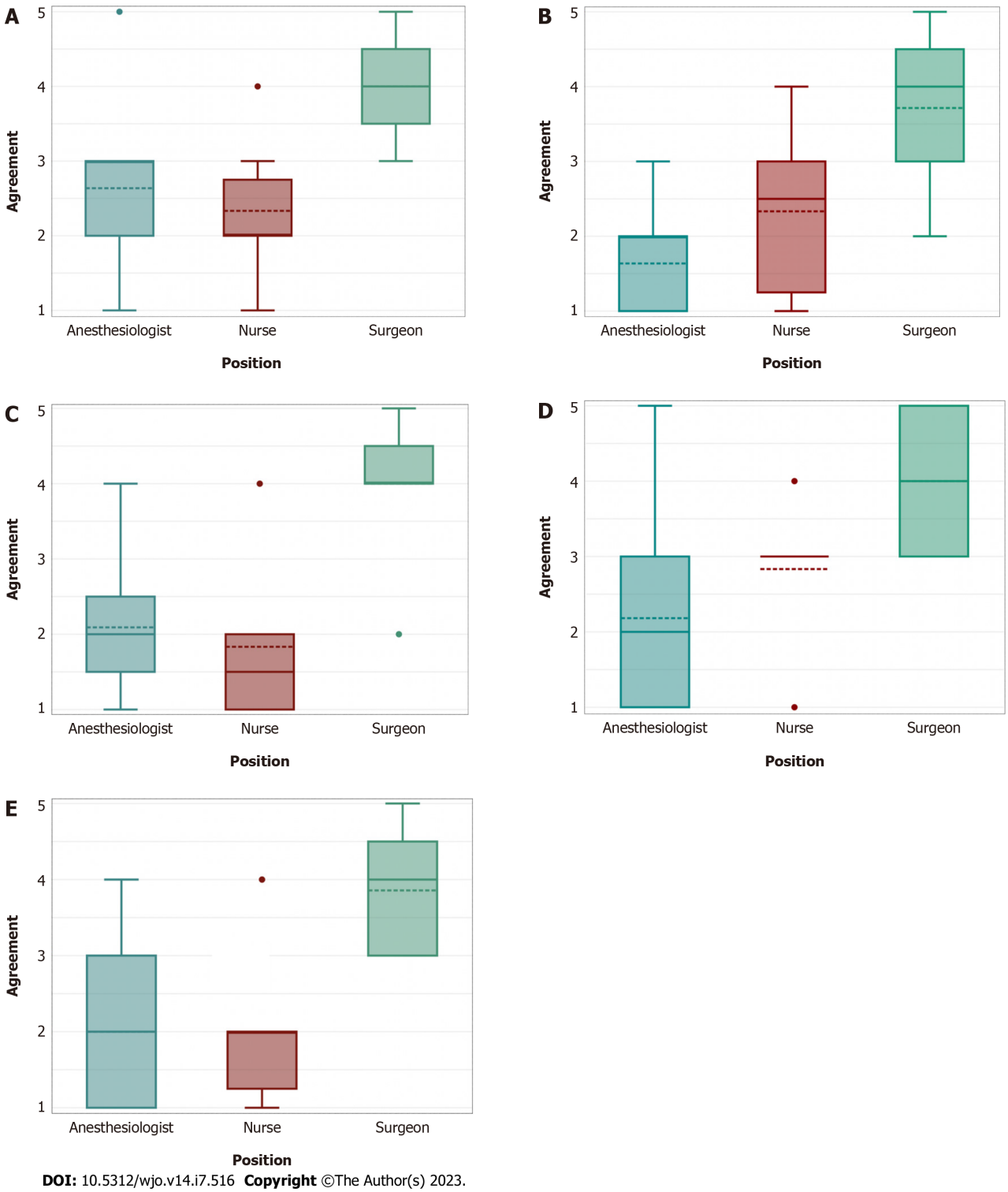


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Figure 1 Flow chart of the inclusion and exclusion criteria for supracondylar humerus fractures patients. A: Pediatric supracondylar humerus fractures; B: Pediatric femoral shaft fractures.

While the 6 AM start program was effective in reducing wait times for surgery, it was ultimately discontinued at our institution after one year, based in large part on the aforementioned inefficiencies and the extreme unpopularity of the program with non-surgeons. This outcome could potentially have been mitigated had anesthesiologists, nurses, and surgical technologists been invited earlier to plan and facilitate the implementation of the program. Many authors have stressed the importance of multidisciplinary teams in the success of quality improvement initiatives[19]. We recommend other institutions consider adopting similar programs to engage stakeholders early in the planning process to minimize the risks of unintended consequences and customize the program to best fit the structure of each institution.

With this study's retrospective design, we were also unable to ensure adherence to the protocol of scheduling eligible cases and starting the case on time which influenced the opinions of some OR staff. Factors other than the imple-



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Figure 2 Survey responses on 6 AM start program effectiveness. A: The 6 AM start program benefited patient care; B: The 6 AM start program benefited my service; C: The 6 AM start program made it easier to place urgent trauma cases; D: Supracondylar humerus fractures benefited from the 6 AM Start program; E: The 6 AM start program was an effective way to manage uncomplicated elbow and femur fractures presenting at night.

mentation of the early start time may influence the amount of time it takes for child to get to the OR. For example, individual decision making of attendings and residents on-call. By sampling patients for 1 year before and after we hope to have a good distribution of attendings and residents to eliminate individual decision making is a significant confounder. There are also large scale time variations that affect volume of these type of fractures. By using a sample size of 1 year before and 1 year after the implementation of the policy we hope to eliminate the effect of seasonal variation in volume and fracture type/saverity on the timing of surgical treatment. This study is also limited by its smaller sample size, in particular, the FSF given that they are often complicated by polytrauma or pathology. The 6 AM start program was discontinued at our institution after a year, thus we were unable to expand the time window to capture more cases for the study.

CONCLUSION

We have demonstrated that our 6 AM start program was effective in reducing the wait time for operative treatment for uncomplicated SCHF presenting overnight. This is of interest and benefit to institutions as United States News and World Report uses timeliness of operative treatment for SCHF and FSF as a metric for ranking children's hospitals. Although the program produced promising results, it also created new conflicts within the OR staff that led to its discontinuation at our institution. This information may be useful to surgeons and hospital administrators as they undertake quality improvement programs to enhance the timeliness of care. Future implementations of such programs should involve stakeholders early in the planning process to better address the needs of the OR staff.

ARTICLE HIGHLIGHTS

Research background

This study describes the effect of a program allowing an early operating room (OR) start for uncomplicated trauma prior to an elective day of surgery to decrease wait times for surgery for urgent fractures admitted overnight.

Research motivation

The timing of operative treatment for pediatric supracondylar humerus fractures (SCHF) and femoral shaft fractures (FSF) remains controversial.

Research objectives

We present the impact of the quality improvement program initiated at a suburban level I trauma center, aiming to enhance the efficiency of care and adhere to United States News and World Report's standard for timely management. The program specifically focuses on reducing wait times for urgent trauma cases and mitigating surgeon fatigue by implementing a 6 AM start.

Research methods

From October 2017 onwards, patients admitted between 21:00 the previous night and 05:00 were considered for the early slot in the OR, subject to the surgeon's judgment. To evaluate the effects of this change, we analyzed the demographic characteristics and treatment timelines of patients with SCHF and FSF, comparing data from one year before and one year after the implementation. Additionally, we gathered survey responses from the surgical team for further insights.

Research results

Out of the 44 SCHF cases that met the inclusion criteria, 16 underwent treatment prior to the program's implementation, while 28 received treatment afterward. Following the implementation, the average wait time for surgery decreased by 4.8 h or 35.4% (from 13.4 h to 8.7 h; $P = 0.001$). However, no significant differences were observed in operative duration, post anesthesia care unit stay, or discharge wait time. Survey responses indicated a decline in the program's popularity among nurses and anesthesiologists compared to surgeons. While 57% of surgeons believed the program was effective, only 9% of anesthesiologists and 16% of nurses shared the same opinion. Due to the overall dissatisfaction, the program was eventually discontinued.

Research conclusions

The results of our study highlight a significant decrease in surgery wait times for uncomplicated SCHF cases admitted overnight. Additionally, we emphasize the significance of engaging stakeholders in shared decision-making. While the program yielded promising outcomes, it also gave rise to conflicts among the OR staff, ultimately leading to its discontinuation at our institution. Moving forward, it is essential to involve stakeholders early on during the planning phase of similar programs to effectively address the OR staff's requirements and concerns.

Research perspectives

Surgeons and hospital administrators engaging in quality improvement initiatives to improve the timeliness of care can find value in this information. It is recommended that future implementations of such programs involve stakeholders from the outset of the planning process to ensure better alignment with the needs of the OR staff.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Low risk of postoperative ulnar nerve affection in surgically treated distal humeral fractures when the nerve is released *in situ*

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Abstract

BACKGROUND

Adult distal humeral fractures (DHF) comprise 2%-5% of all fractures and 30% of all elbow fractures. Treatment of DHF may be technically demanding due to fracture complexity and proximity of neurovascular structures. Open reduction and internal fixation (ORIF) are often the treatment of choice, but arthroplasty is considered in case of severe comminution or in elderly patients with poor bone quality. Ulnar nerve affection following surgical treatment of distal humerus fractures is a well-recognized complication.

AIM

To report the risk of ulnar nerve affection after surgery for acute DHFs.

METHODS

We retrospectively identified 239 consecutive adult patients with acute DHFs who underwent surgery with ORIF, elbow hemiarthroplasty (EHA) or total elbow arthroplasty (TEA) between January 2011 and December 2019. In all cases, the ulnar nerve was released *in situ* without anterior transposition. We used our institutional database to review patients' medical records for demographics, fracture morphology, type of surgery and ulnar nerve affection immediately; records were reviewed after surgery and at 2 wk and 12 wk of routine clinical outpatient follow-up. Twenty-nine percent patients were excluded due to pre- or postoperative conditions. Final follow-up examination was a telephone interview in which ulnar nerve affection was reported according to the McGowen Classification Score. A total of 210 patients were eligible for interview, but 13 patients declined participation and 17 patients failed to respond. Thus, 180 patients were included.

RESULTS

Mean age at surgery was 64 years (range 18-88 years); 121 (67.3%) patients were women; 59 (32.7%) were men. According to the AO/OTA classification system, we recorded 47 patients with type A3, 55 patients with type B and 78 patients with type C fractures. According to the McGowen Classification Score, mild ulnar nerve affection was reported in nine patients; severe affection, in two. A total of 69 patients were treated with ORIF of whom three had mild temporary ulnar nerve affection and one had severe ulnar nerve affection. In all, 111 patients were treated with arthroplasty (67 EHA, 44 TEA) of whom seven had mild ulnar nerve affection and one had severe persistent ulnar nerve affection. No further treatment was provided.

CONCLUSION

The risk of ulnar nerve affection after surgical treatment for acute DHF is low when the ulnar nerve is released *in situ* without nerve transposition, independently of the treatment provided.

Key Words: Humeral fracture; Arthroplasties; Internal fixation; Ulnar nerve affection; *In situ* release

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Core Tip: Ulnar nerve affection after surgery for distal humerus fractures (DHF) is a known complication. We retrospectively reviewed a consecutive series of 180 patients with acute DHF treated either with open reduction and internal fixation (ORIF), total elbow arthroplasty (TEA) or elbow hemiarthroplasty (EHA). According to the McGowan Classification Score, 11 patients reported ulnar nerve affection symptoms (nine patients with mild affection and two patients with severe affection). The risk of ulnar nerve affection after surgery for acute DHF is low when the ulnar nerve is released *in situ* without transposition, independently of the treatment provided (*i.e.*, ORIF, EHA, or TEA).

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INTRODUCTION

Adult distal humeral fractures (DHF) comprise approximately 2%-5% of all fractures and 30% of all elbow fractures[1,2]. Open reduction and internal fixation (ORIF) is often the treatment of choice, but arthroplasty [elbow hemiarthroplasty (EHA) or total elbow arthroplasty (TEA)] may be considered in case of severe comminution or in elderly patients with poor bone quality[3-5]. Ulnar nerve affection is a known complication associated with surgical treatment of distal humerus fractures[6]. The development of ulnar affection has many potential aetiologies[7]. The ulnar nerve may be contused or lacerated at the time of the initial trauma or at the time of the surgical intervention, particularly from excessive retraction during fracture exposure or fixation. Swelling in the immediate posttraumatic or postoperative setting may also contribute to ulnar nerve affection. Postoperatively, soft tissue scar formation, heterotopic ossification and prominent hardware may represent aetiologic factors for ulnar nerve affection. During surgery, mobilisation of the ulnar nerve is often necessary for protection and to reduce and fixate the fracture or to perform a joint arthroplasty. Most injuries are described to give temporary paraesthesia without motoric affection[8,9]. In some rare cases, severe ulnar affections are seen with weakness and atrophy of one or more of the ulnar intrinsic muscles, leading to claw hand deformity, which compromises the outcome[10]. Some surgeons perform anterior transposition of the ulnar nerve, which has theoretical advantages including moving the nerve away from the implants, preventing kinking of an incompletely released nerve, avoiding subluxation over the medial epicondyle, limiting entrapment in scar tissue and allowing nerve-free excursion[11-13]. On the other hand, transposition requires further nerve dissection with a potential risk of additional trauma, devascularisation and prolonged operative time[12,14]. How the ulnar nerve is best protected during surgery is still debated[9].

This study aimed to report the risk of ulnar nerve affection after surgery for acute DHF with in situ release and protection of the ulnar nerve without anterior transposition. The secondary outcome was to investigate if the type of surgery performed is a risk factor for postoperative ulnar nerve affection.

MATERIALS AND METHODS

Study design

This was a retrospective study conducted within a consecutive cohort of patients surgically treated for distal humerus fracture. The study was conducted in accordance with the STROBE guidelines[15].

Study population

We used our institutional database to identify all adult patients surgically treated for acute DHF during the nine-year period from 2011 to 2019. A total of 239 patients were identified (Figure 1). Twenty-nine percent patients were excluded due to pre-operative nerve affection, postoperative infection and reoperation, other fractures adjacent to the elbow and pathological fractures. Additionally, we excluded patients whose data could not be retrieved due to immigration and cognitive impairment. Thus, 210 patients were eligible for the final telephone interview. In all, 13 patients opted out of participating, and 17 patients failed respond to the phone calls. According to the medical records, four of these 30 patients had mild paraesthesia without motoric affection in the immediate postoperative period, which resolved spontaneously during the first 12 postoperative weeks. Thus, 180 patients were included in the study.

Participants included 121 (67.3%) women and 59 (32.7%) men. The mean age was 64 years (18-88 years). The mean follow-up was six years (3-11 years). According to the OTA/AO Classification, we recorded 47 patients with type A (7 type A2 and 40 type A3), 55 patients with type B (15 type B1, 18 type B2, and 22 type B3) and 78 patients with type C (19 type C1, 30 type C2, and 29 type C3). The fractures were classified by the first author using conventional X-rays supplied with computed tomography (CT) if available. A total of 69 patients were treated with ORIF, 67 with EHA and 44 with TEA.

Treatment, surgical technique and rehabilitation

According to our treatment algorithm, conservative treatment is indicated for non-displaced fractures and in patients with severe comorbidities where the risk of surgery outweighs its benefit. Arthroplasty is considered for comminuted intra-articular fractures unamenable for ORIF. EHA is preferred in active patients, whereas TEA is preferred in elderly and low-demanding patients and patients with radiographic signs of osteoarthritis. Conventional radiographs were performed in all cases, and CT was used for preoperative planning in selected cases.

All patients were operated in the lateral decubitus position with a standard posterior midline approach. All operations were performed in general anaesthesia. Tourniquets were used in all cases. All patients were operated within two weeks from their injury (range 2-14 d). The ulnar nerve was identified, released *in situ* and protected. The ulnar nerve was not transposed. All procedures were performed using a triceps split with a reverse Y-shaped incision in the triceps[16] except for OTA/AO type 13A fractures where a triceps-sparing approach with medial and/or lateral windows was adopted at the surgeon's discretion and the fracture comminution. In the ORIF group, all patients were operated with double plates [Synthes Locking Plate System (West Chester, PA, United States), VariAx Locking Plate System (Stryker, Kalamazoo, MI, United States), or Acumed Elbow Plating System (Hillsboro, OR, United States)]. The Latitude (WRIGHT, Memphis, TN, United States) was used as EHA and the Coonrad-Morrey elbow arthroplasty (Zimmer Biomet, Rochester, MN, United States) as TEA.

All patients performed oedema prophylactic exercises of the hand and fingers during the time of immobilisation. In ORIF and EHA groups, a posterior splint was used for two weeks. Passive exercises were allowed from week two to week six, and light weight bearing was permitted after six weeks. Full weight-bearing exercises were allowed after three months. In TEA, group mobilisation was initiated on the first postoperative day or as soon as discomfort allowed, with retention of the bulky dressing. Mobilisation was proceeded incrementally according to the patient's level of discomfort. Patients were instructed to keep the arm in a sling, except when they were exercising it. They were also instructed specifically to avoid resisted extension and lifting during the first six postoperative weeks. Thereafter, they were advised to stretch the elbow into full extension and full flexion daily, progressively increasing their level of activity as their discomfort decreased. They were advised to indefinitely refrain from strenuous manual activities such as carrying more than 5 kg loads with the treated arm.

Outcome

Medical records were reviewed for demographics, fracture morphology, type of surgery and ulnar nerve affection immediately after surgery and at 2 wk and 12 wk of routine clinical outpatient follow-up. All patients participated in a final telephone interview, and ulnar nerve conditions were reported. Ulnar nerve affection was categorised according to the McGowan Classification Score[17]. Mild affection was identified as paraesthesia in the 4th and 5th fingers aggravated by elbow flexion (grade 1). Paraesthesia with additional weakness and clumsiness of the interossei was graded as moderate (grade 2); and severe symptoms in form of interossei paralysis and marked hypoesthesia in the 4th and 5th fingers were identified as severe affection (grade 3). Routine electromyographic studies were not performed.

Statistical analysis

Descriptive statistics for continuous variables were presented as mean, minimum and maximum values. Categorical variables were presented by frequencies and percentages. A binary logistic regression model was used to compare the risk of ulnar nerve affection for different types of surgery. The results were presented as odds ratio (OR) with 95% confidence intervals (CI) and *P* values. The ORIF group was used as a reference. *P* values < 0.05 were considered statistically significant. The analyses were performed using SPSS software (version 25.0, IBM, Armonk, NY, United States).

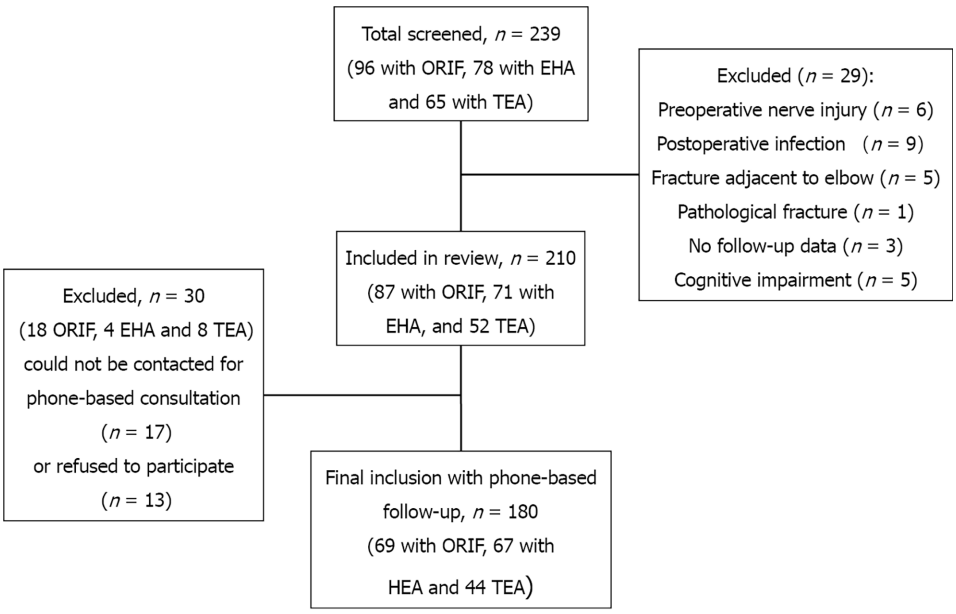
RESULTS

Eleven patients (6%) had post-operative ulnar nerve affection during the follow-up period; seven women and four men. Four of these patients were treated with ORIF, four with EHA and three with TEA (Table 1).

Table 1 List of patients with ulnar nerve affection

Patient number	AO fracture classification	Gender	Age at surgery	Surgery type	The onset of affection postoperatively	McGowan grade
1	A3	F	67	ORIF	Two weeks	3
2	C3	F	73	EHA	Two years	3
3	C3	F	63	EHA	Immediately	1
4	C2	M	61	EHA	Immediately	1
5	C3	F	70	TEA	Immediately	1
6	C2	F	79	EHA	Two weeks	1
7	C3	M	68	TEA	Two weeks	1
8	C1	F	66	ORIF	Immediately	1
9	A3	M	53	ORIF	Immediately	1
10	B1	M	48	ORIF	Two weeks	1
11	B3	F	82	TEA	Immediately	1

AO: Arbeitsgemeinschaft für osteosynthesefragen; ORIF: Open reduction and internal fixation; EHA: Elbow hemiarthroplasty; TEA: Total elbow arthroplasty.



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Figure 1 Study flowchart summarizing screening, inclusion, exclusion and final phone-based patient follow-up. ORIF: Open reduction and internal fixation; EHA: Elbow hemiarthroplasty; TEA: Total elbow arthroplasty.

Six patients had ulnar nerve affection immediately after surgery. The symptoms were mild paraesthesia in the 4th and 5th fingers (McGowan grade 1, which resolved spontaneously before the 12-wk follow-up examination.

Four patients had ulnar nerve affection with onset around the two-week follow-up. Three of these patients had mild symptoms with paraesthesia in the 4th and 5th fingers (McGowan grade 1), which resolved spontaneously before the 12-wk follow-up examination. The fourth patient had persistent severe symptoms in the form of interossei paralysis and marked hypoesthesia in the 4th and 5th fingers (McGowan grade 3).

One patient had persistent, severe symptoms (McGowan grade 3) in the form of interossei paralysis and marked hypoesthesia in the 4th and 5th fingers with onset during the second year.

No difference was observed in the risk of ulnar nerve affection between patients treated with ORIF or EHA (OR = 1.03, 95%CI: 0.25, 4.31, P = 0.97) or between patients treated with ORIF or TEA (OR = 1.19, 95%CI: 0.25, 5.59, P = 0.83).

DISCUSSION

In this study, 11 out of 180 patients (6%) had ulnar nerve affection after surgery for distal humerus fractures. However, only two patients (1%) had severe and persistent ulnar nerve affection (McGowan grade 3). Ulnar nerve affection may occur due to excessive retraction during exposure, or the nerve may become affected after surgery due to hardware irritation or scar tissue formation. This may explain the late symptom onset in some patients. In this study, we focused on per- and post-operative nerve affection. We excluded patients with pre-operative ulnar nerve affection and patients complicated by postoperative infection. Surgery of the ulnar nerve may consist of either subcutaneous anterior transposition or *in situ* release retaining the nerve in its original position. However, which method should be preferred is debatable. Several retrospective studies have reported a risk of ulnar nerve affection after surgery for DHF where the nerve was either anteriorly transposed or released *in situ*, but they have drawn different conclusions[6]. We used the McGowan Classification Score[17] to evaluate the postoperative ulnar nerve affection and to grade the severity of the nerve affection. We chose this classification system to ensure the comparability of our results to the results of those previously published studies.

However, the true prevalence of ulnar nerve affection after elbow injury remains unknown as studies have not successfully differentiated between acute injury-related, acute surgery-related and delayed (subacute or chronic) ulnar affections. Furthermore, in most of these retrospective case series, careful evaluation of ulnar nerve function was not reported[18].

Wiggers *et al*[19] retrospectively analysed a cohort of 107 consecutive adult patients with surgically treated distal humerus fractures to determine risk factors for development of ulnar affection. These risk factors included age, sex, implant over or below the medial epicondyle and total number of surgeries. They found that columnar fracture and application of a medial plate were the only potential risk factors for iatrogenic postoperative ulnar affection.

To identify factors related to ulnar nerve affection, Vazquez *et al*[20] retrospectively evaluated 69 DHF treated with or without ulnar nerve transposition. They reported 14 patients with documented ulnar nerve affection either in the immediate postoperative period or at the final evaluation; and the prevalence of post-operative affection reached 16%. They concluded that transposition of the nerve did not significantly decrease the risk of iatrogenic ulnar affection. However, the optimal handling of the ulnar nerve remains uncertain even though anterior transposition in the acute surgical treatment of displaced distal humerus fractures seems to be associated with a high risk of ulnar nerve affection [20].

Chen *et al*[21] retrospectively investigated the risk of ulnar nerve affection in 170 patients who underwent ORIF for acute distal humeral fracture. The study groups consisted of patients who did not undergo ulnar nerve transposition at the time of fracture fixation and a control group of patients who did undergo ulnar nerve transposition during fracture fixation. They reported that the risk of ulnar nerve affection was four times higher after transposition (33%) than (9%) in the in situ release group. They suggested three explanations for this observation. The first was devascularisation of the nerve during transposition, the second was iatrogenic compression resulting from an overlying tight transposition and the third was an inadequate proximal release of the arcade of Struthers or the medial intermuscular septum. The study was limited by selection bias that was potentially introduced by the surgeon's decision to perform a transposition. Even so, the decision to transpose was based on a best practice scenario.

Likewise, in a retrospective series of 83 total elbow arthroplasties, Dachs *et al*[22] observed a lower incidence of ulnar nerve affection when they used in situ release of the nerve than when they used transposition. They recommended that transposition of the nerve should be reserved for cases with marked limitation of preoperative elbow flexion or when deemed necessary at intraoperative assessment, like abnormal tracking or increased tension on the nerve after insertion of the prosthesis.

Ahmed *et al*[12] conducted a retrospective cohort study of 97 consecutive patients with distal humerus fractures who underwent ORIF where subcutaneous ulnar nerve anterior transposition was compared with no transposition at the time of ORIF. They found a five-fold increase in ulnar nerve affection following transposition (35.7% for transposition; 14.5% for no transposition). However, this study may suffer from selection bias because nerve transposition was not conducted systematically.

In the present study, we found that in situ release and protection of the ulnar nerve without transposition produced a low prevalence of postoperative ulnar nerve affection for both ORIF and arthroplasty surgery following distal humerus fracture. The potential advantage of in situ management of the ulnar nerve is less manipulation of the nerve and its vascularity. In contrast, the potential disadvantages of transposition are a higher risk of nerve affection, devascularisation and scar formation.

The present study is primarily limited by its retrospective design. Additionally, the data collection process depended on the accuracy of follow-up reports from the outpatient clinic during the initial follow-up period. Another limitation is that electromyographic examination was generally not used to confirm ulnar nerve affection. This may lead to information bias due to, *e.g.*, misclassification of ulnar nerve affection.

In addition, the study comprised initial follow-up examinations only at two and 12 wk, which makes it difficult to report the exact time of onset and when the symptoms resolved. Furthermore, we had no information about the length of tourniquet time, which may possibly have influenced ulnar nerve affection.

The main strength of this study is its large sample. Further strengths include that all eligible patients were reviewed, that the surgeries were performed by speciality-trained surgeons in a single centre, that the follow-up period was mean seven years and that an independent reviewer conducted the final telephone interview. In contrast to the previously published studies, we were able to compare the risk of ulnar nerve affection after ORIF, EHA, and TEA.

CONCLUSION

The risk of ulnar nerve affection after surgery for acute DHF is low when surgeons use in situ ulnar nerve release without nerve transposition, regardless of the treatment provided (*i.e.*, ORIF, EHA, or TEA).

ARTICLE HIGHLIGHTS

Research background

Ulnar nerve affection following surgical treatment of distal humerus fractures (DHF) is a well-recognized complication. Surgery of the ulnar nerve may consist of either subcutaneous anterior transposition or *in situ* release retaining the nerve in its original position. However, which method should be preferred is debatable. We believe that in situ release and protection of the ulnar nerve without transposition produced a low prevalence of postoperative ulnar nerve affection for both Open reduction and internal fixation (ORIF), Total elbow arthroplasty, (TEA) and elbow hemiarthroplasty (EHA) surgeries of distal humerus fracture. In contrast to the previously published studies, we were able to compare the risk of ulnar nerve affection after ORIF, EHA, and TEA.

Research motivation

Several retrospective studies have reported a risk of ulnar nerve affection subsequent to surgery for distal humeral fractures (DHF), where either the nerve was anteriorly transposed or released *in situ*. However, these studies have arrived at differing conclusions. As a result, we were motivated to conduct a detailed investigation into the prevalence of per- and post-operative ulnar nerve affection when the nerve is released *in situ*. To this end, we excluded patients who were presented with pre-operative ulnar nerve affection, as well as those who were afflicted with postoperative infection.

Research objectives

To report the risk of ulnar nerve affection after surgeries (ORIF, TEA, and EHA) for acute DHF when the ulnar nerve is in situ released without transposition.

Research methods

We retrospectively reviewed a consecutive series of 180 patients with acute DHF treated either with ORIF, TEA, or EHA.

Research results

Our study found a low risk of ulnar nerve affection following surgical treatment for acute DHF when the ulnar nerve was released *in situ* without nerve transposition. Of the 180 patients included in the study, only nine reported mild ulnar nerve affection and two reported severe affection according to the McGowen Classification Score. The study also found that the type of surgery (ORIF, EHA, or TEA) did not significantly affect the risk of ulnar nerve affection. Three out of 69 patients treated with ORIF had mild temporary ulnar nerve affection, while seven out of 111 patients treated with arthroplasty (67 EHA, 44 TEA) had mild ulnar nerve affection and one had severe persistent affection.

Research conclusions

The findings of our study suggest that releasing the ulnar nerve *in situ* without transposition during surgical treatment of acute DHF may help minimize the risk of ulnar nerve affection, regardless of the type of surgery performed.

Research perspectives

Further research may be needed to confirm these results and explore other potential risk factors for ulnar nerve affection in DHF patients.

FOOTNOTES

Author contributions: Al-Gburi M, Al-Hamdani A, Rasmussen JV, and Olsen BS made substantial contributions to the conception and design, the analysis and interpretation of data, and the drafting and revising of the article; and all authors approved the final version of the manuscript for publishing.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Excision of trochanteric bursa during total hip replacement: Does it reduce the incidence of post-operative trochanteric bursitis?

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Abstract

BACKGROUND

Trochanteric bursitis is a common complication following total hip replacement (THR), and it is associated with high level of disability and poor quality of life. Excision of the trochanteric bursa prophylactically during THR could reduce the occurrence of post-operative trochanteric bursitis.

AIM

To evaluate whether synchronous trochanteric bursectomy at the time of THR affects the incidence of post-operative trochanteric bursitis.

METHODS

This retrospective cohort study was conducted in the secondary care setting at a large district general hospital. Between January 2010 and December 2020, 954 patients underwent elective primary THR by two contemporary arthroplasty surgeons, one excising the bursa and the other not (at the time of THR). All patients received the same post-operative rehabilitation and were followed up for 1 year. We reviewed all cases of trochanteric bursitis over this 11-year period to determine the incidence of post-THR bursitis. Two proportion Z-test was used to compare incidences of trochanteric bursitis between groups.

RESULTS

554 patients underwent synchronous trochanteric bursectomy at the time of THR whereas 400 patients did not. A total of 5 patients (incidence 0.5%) developed trochanteric bursitis following THR; 4 of whom had undergone bursectomy as part of their surgical approach, 1 who had not. There was no statistically significant difference between the two groups (Z value 1.00, 95%CI: -0.4% to 1.3%, $P = 0.32$). There were also 8 other patients who had both trochanteric bursitis and hip osteoarthritis prior to their THR; all of whom were treated with THR and synchronous trochanteric bursectomy, and 7 had resolution of their lateral buttock pains but 1 did not.

CONCLUSION
Synchronous trochanteric bursectomy during THR does not materially affect the incidence of post-operative bursitis. However, it is successful at treating patients with known trochanteric bursitis and osteoarthritis requiring THR.

Key Words: Total hip replacement; Trochanteric bursectomy; Trochanteric bursitis; Greater trochanteric pain syndrome

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Core Tip: We investigated a plausible theory of prophylactic trochanteric bursectomy at the time of total hip replacement (THR) to reduce the incidence of post-operative bursitis. Our retrospective study included 954 patients over an 11-year period operated by two contemporary surgeons, one excising the bursa and the other not. From our analysis, we found no significant difference in the incidence of post-THR bursitis between the two groups. However, our series did demonstrate that synchronous trochanteric bursectomy during THR is successful at treating the lateral buttock pain component for patients with known trochanteric bursitis and osteoarthritis requiring THR; and therefore, we recommend the procedure in these patients.

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INTRODUCTION

Hip osteoarthritis is a common painful condition of the groin and anteromedial thigh. It is one of the leading causes of elderly disability worldwide[1]. In fit patients, where medical treatment has been exhausted, total hip replacement (THR) offers the best chance of symptomatic relief and functional recovery. Trochanteric bursitis, on the other hand, is a condition of localised lateral buttock pain that can radiate down the lateral thigh, or into the posterior buttock, or both. Trochanteric bursitis is the most common cause of Greater Trochanteric Pain Syndrome (GTPS) in the literature. It is estimated to affect 17.6% of adults aged between 50-79 years[2], and associated with similar level of disability and poor quality of life as in severe osteoarthritis[3]. Trochanteric bursitis can occur primarily from repetitive stress or secondary to various hip, knee, or lower back pathologies. It is also common following THR, with an incidence of 4%-8%[4-8]. When sub-analysed according to surgical approach, several studies have reported lower incidence in those operated by posterior approach, as low as 1.2%[8], compared to anterior or lateral approaches[7-9].

For a decade, our lead author has performed trochanteric bursectomy as part of the surgical approach for all his THR. The rationale being that the bursa is likely to fibrose following surgery, losing its functional properties as friction buffer but still have the potential of developing bursitis at a later date. Therefore, its prophylactic excision seemed logical. This is a unique series based on a plausible supposition (that excision of the trochanteric bursa during THR would be preventative of later trochanteric bursitis) carried out by a single surgeon continuously for a decade and collecting outcome data contemporaneously. There are no similar papers in the literature.

This study compares the outcomes between patients who underwent THR with synchronous trochanteric bursectomy and those without (within the same department, and with the same post-operative rehabilitation protocol), looking in particular at the incidence of post-THR bursitis that required secondary care treatment. As part of the study, the overall incidence of trochanteric bursitis, the incidence of post-THR bursitis, and the incidence of symptomatic bursitis and hip osteoarthritis prior to THR were also investigated. In addition, for the latter subgroup (symptomatic bursitis and hip osteoarthritis), we assessed whether the bursectomy at the time of THR abolished the lateral buttock pains as well as the groin pains.

MATERIALS AND METHODS

Study population

This is a single-centre retrospective cohort study conducted within a secondary care setting. 954 consecutive patients who underwent elective primary THR by either of two consultant hip arthroplasty surgeons, one who performed THR with synchronous trochanteric bursectomy (Surgeon A) and the other without bursectomy (Surgeon B), between January 1, 2010 and December 31, 2020, were identified and included in the study. There are no exclusion criteria. Research ethics approval was not sought as the study was purely observational, and only included anonymised and non-sensitive data.

Total hip replacement

Both surgeons use the same posterior approach to the hip joint. Surgeon A routinely excises the trochanteric bursa as part of the surgical approach while Surgeon B does not. The bursa is left open at the end of the procedure without repair.

Both surgeons perform a curvilinear skin incision centred on the greater trochanter, followed by fascia lata incision in this line. At this point, Surgeon A excises the bursa using electrocautery and tension from forceps, whereas Surgeon B incises into the bursa to expose the trochanter and posterior structures to continue with the posterior approach to the hip. The remaining procedure follows the same logical sequence of a standard total hip replacement. Both surgeons perform a standard capsulotomy and detach the short external rotators to visualise the acetabulum, and femoral head and neck. The hip replacement is then performed. The short external rotators are re-attached using sutures, closing the capsule, and subsequent soft tissue structures closed in layers.

Anaesthesia and post-operative variables

Patients in the cohort had a combination of different anaesthetic techniques at the time of surgery, dependent on individual anaesthetist's decision-making-process. 70% of the patients received a spinal anaesthetic (with propofol or midazolam sedation) containing fentanyl with either a low dose diamorphine, or fentanyl as an adjunct. The remaining 30% had either both spinal and general anaesthetic (GA), or a straight GA in the form of Total Intravenous Anaesthesia. All patients had 0.125% Bupivacaine (no adrenaline) injected as Local Infiltration of Anaesthesia into the periarticular tissues, generally 100 mL, but a lower volume used for patients with a low body weight.

All patients were managed under the same enhanced recovery programme. Patients are mobilised either on the same day of surgery, or the following day, and are permitted full weight bearing. The mean length of stay has fallen over this 11-year period from 4.4 d to 2.5 d at the time of writing. The discharge criteria have not changed in this time. Patients must be able to independently walk 20 m on flat surface with crutches, safely get into and out of bed, safely get into and out of a chair, and pass the stairs test. A dry dressing is mandated before discharge. All patients were then followed up with the primary surgeon in an elective clinic 6 wk after the operation, and with the physiotherapist at 3 mo, 6 mo and 1 year. Any patients, at any stage, with problematic symptoms of hip or lateral buttock pain were booked back into the clinic of the operating surgeon as a matter of course.

Trochanteric bursitis

We used our institution's electronic patient records to identify any patient coded as having a diagnosis of trochanteric bursitis, injection into the trochanteric bursa, and/or trochanteric bursectomy. From this list, each patient's electronic patient record was reviewed to confirm the finding. The resulting list of confirmed cases of trochanteric bursitis (managed within the secondary care setting) was then compared with the list of total hip replacements by either of the two surgeons to generate a list of patients who had both a diagnosis of trochanteric bursitis and total hip replacement over the 11-year period. It also permitted the investigators to document the incidence of trochanteric bursitis independent of having a THR during this study period.

Statistical analysis

Data was collected and analysed in Microsoft Excel. Continuous variables with normal distribution were expressed in mean ± SD. Two proportion Z-test was performed to compare the incidences of trochanteric bursitis between Surgeon A and Surgeon B. Continuity correction was not applied. Logistic regressions were carried out in R software v4.2.2. Results were considered statistically significant at $P \leq 0.05$.

RESULTS

From January 2010 to December 2020, 954 patients underwent primary total hip replacement by either of two consultant hip arthroplasty surgeons. Six patients underwent simultaneous bilateral uncemented THR, thus increasing the number of procedures to 960. Among these, 556 procedures had synchronous trochanteric bursectomy by Surgeon A as part of the surgical approach. Demographic and operative data are displayed in Table 1. 10.5% of patients did not turn up at their post-operative follow up with the primary surgeon, and hence were deemed lost to follow up. There is no significant difference in lost to follow up between surgeons ($P = 0.06$). The mean follow-up time for the entire cohort was 291 ± 115 d.

We identified a total of 152 cases of trochanteric bursitis at our institution over the 11-year period (independent of having hip osteoarthritis or THR, so the raw incidence). There were 16 patients who, on coding, had diagnoses of both THR and trochanteric bursitis. Of these 16 patients, 3 were for bursitis on the *contralateral* hip, 8 were pre-existing diagnosis of bursitis *prior to* THR, and 5 were identified to have developed bursitis *after* their THR (Table 2). The incidence of post-operative bursitis that required secondary care treatment in our series was therefore 0.5%. The mean interval between THR and diagnosis of bursitis was 412 days. Of these 5 patients; 4 patients had undergone a trochanteric bursectomy as part of the surgical approach (by Surgeon A), and 1 had not (by Surgeon B), corresponding to incidences of 0.72% and 0.25% respectively. Comparison using two proportion Z-test showed that there is no significant difference between the incidences of trochanteric bursitis following primary THR between Surgeon A and Surgeon B (Z value 1.00, 95%CI: -0.4% to 1.3%, $P = 0.32$).

There were 8 cases of trochanteric bursitis diagnosed prior to THR, all of which had synchronous trochanteric bursectomy by Surgeon A. Of them, 7 reported resolutions of symptoms following their hip procedures. But the 8th patient suffered a periprosthetic infection requiring staged revision surgery, confounding his outcome in the context of

Table 1 Patient demographic and operative data

Demographic	Surgeon A	Surgeon B
	Synchronous trochanteric bursectomy	Trochanteric bursa preserved
Number of patients	554	400
Age, mean ± SD, yr	66 ± 11.9	69 ± 9.9
Gender		
Female	346	264
Male	208	136
Procedures		
Uncemented THR	329	195
Cemented THR	0	84
Hybrid THR (cemented femoral component)	227	125
Laterality		
Right	288	204
Left	264	192
Bilateral	2	4

Note that six patients underwent simultaneous bilateral total hip replacement, thus increasing the total number of procedures to 960. SD: Standard deviation; THR: Total hip replacement.

Table 2 Incidence of trochanteric bursitis

Trochanteric bursitis	Number of cases
Overall incidence (independent of osteoarthritis or THR)	152
Laterality	
Right	73
Left	53
Bilateral	26
Trochanteric bursitis *after* THR	
With synchronous trochanteric bursectomy	4
Trochanteric bursa preserved	1
Pre-existing diagnosis of bursitis *prior to* THR	
With synchronous trochanteric bursectomy	8
Trochanteric bursa preserved	0

THR: Total hip replacement.

this series.

DISCUSSION

Lateral buttock pain is a common presentation in orthopaedic practice. Historically, majority of these have been diagnosed as trochanteric bursitis. However, recent studies with use of modern imaging techniques have shown that not all had evidence of inflamed peri-trochanteric bursae[10,11]. Other diagnoses reported were abductor tendinosis, abductor tears, and thickened ilio-tibial bands. The overall diagnostic term for this cohort is Greater Trochanteric Pain Syndrome. GTPS is the current preferred term to describe tenderness over the greater trochanter, buttock, or lateral thigh. It is reported to affect between 10% and 25% of the general population[12], and 17.6% of adults aged between 50-79 years

[2].

Trochanteric bursitis, a subset of GTPS, is a common complication following primary total hip replacement. Our study reported an overall incidence of 0.5%, which is significantly lower than previous studies where incidences ranged from 4% to 8%[4-8]. However, it should be noted that the incidence of trochanteric bursitis varies with surgical approach. Vicar *et al*[5] and Schinsky *et al*[7] both reported highest incidence of post-THR bursitis with the historic trans-trochanteric approach. Iorio *et al*[8] compared direct lateral and posterior approaches, and found that the latter had lower incidence of post-THR bursitis, corresponding to 5.3% and 1.2% respectively. Interestingly, Shemesh *et al*[6] reported no significant difference in incidences of post-THR bursitis between direct anterior and posterior approaches. One study evaluated soft tissue changes following THR using magnetic resonance imaging and identified more frequent occurrence of fluid within the trochanteric bursa for direct lateral approach compared to anterior, anterolateral, and posterior approaches[13]. This may explain our low incidence of post-THR bursitis as the posterior approach appears to be 'protective' against trochanteric bursitis following THR.

Trochanteric bursectomy has been thoroughly examined in a recent systematic review[14]. Crutchfield *et al*[14] included 15 studies with a mean follow-up of at least 12 mo. Despite the variability in outcome measures, all reported outcomes indicate the same positive trend in post-operative improvement. Patient satisfactions were high at 95%, and rate of failure to improve pain were low, ranging from 0% to 8%. Among patients who underwent trochanteric bursectomy by arthroscopy, several studies[15-17], with minimum of 1 year follow-up, have reported similar positive outcomes ranging from 85% to 97%. In the study by Fox[17], one patient (3.7%) had recurrence of symptoms at 1 year and two additional patients (total 11%) had recurrence at 5 years. Van Hofwegen[18] evaluated arthroscopic bursectomy in 12 patients with trochanteric bursitis following THR and found significant improvement in pain scale. The positive outcomes of bursectomy were the reason that Surgeon A chose in 2010 to perform prophylactic trochanteric bursectomy, as part of the surgical approach, in all patients undergoing elective THR. The hypothesis being that without a trochanteric bursa, one would not go on to develop trochanteric bursitis later. This is a plausible hypothesis but would require large numbers in a consecutive series to demonstrate a difference given the low post-operative incidence of trochanteric bursitis.

In our series, trochanteric bursitis appeared to occur more frequently in patients who underwent THR with synchronous bursectomy (0.72%) compared to those without bursectomy (0.25%). This apparent difference is however not statistically significant. Even taking the confidence interval into account, we consider that the rates of trochanteric bursitis following THR is not materially different between the two groups. We therefore concluded that the procedure is unnecessary. Of note, however, our series did demonstrate that it is successful at treating the lateral buttock pain component for patients with known trochanteric bursitis and osteoarthritis requiring THR. We therefore recommend performing synchronous bursectomy in this specific patient group.

To check whether any differences in the two surgeons' bursitis rates were being masked by confounding by their cases having different characteristics, we carried out logistic regressions using the four factors in Table 1 (as covariates) and the identity of the surgeon as explanatory variables, and the outcome (post-THR bursitis) as the response. None of the logistic regression models, including possible combinations of these variables, had any statistically significant terms. This could be because there were too few post-THR bursitis cases to estimate the associations precisely enough, or it could be because in fact none of the covariates have an influence on the outcome.

There were a number of limitations to our study. This is a retrospective study where cases were identified using procedure codes. There is the potential for missed cases from uncoded diagnosis of trochanteric bursitis even though our lost to follow-up figures were only 10.5%. In addition, our study only included trochanteric bursitis managed within the secondary care setting. Patients who were solely managed in the primary care are not accounted for. The reported incidences in this series could therefore be underestimates, and the true incidence of post-THR bursitis may be higher than 0.5%. This study is also observational, and there may be other possible explanation for our conclusion as not all confounding factors have been accounted for, most notably confounding by surgeon. To improve on this, a prospective study randomising patients to bursectomy *vs* non-bursectomy at the time of planned THR, effectively a clinical trial, would be needed.

CONCLUSION

Synchronous trochanteric bursectomy at the time of THR does not materially affect the incidence of post-THR bursitis. It may therefore be considered unnecessary. However, our series did demonstrate that it is successful at treating the lateral buttock pain component for patients with known trochanteric bursitis and osteoarthritis requiring THR.

ARTICLE HIGHLIGHTS

Research background

Trochanteric bursitis is a common complication following total hip replacement (THR). It has a reported incidence of 4%-8% and is associated with high level of disability and poor quality of life.

Research motivation

For a decade, our lead author has performed prophylactic trochanteric bursectomy as part of the surgical approach for

THR. The rationale being that the bursa is likely to fibrose following THR, losing its functional properties as friction buffer but still have the potential of developing bursitis at a later date. The procedure, therefore, seems logical as it could reduce the occurrence of post-operative trochanteric bursitis.

Research objectives

The study was conducted to evaluate whether synchronous trochanteric bursectomy at the time of THR affects the incidence of post-operative trochanteric bursitis.

Research methods

This retrospective cohort study was conducted in the secondary care setting at a large district general hospital. Between January 2010 and December 2020, 954 patients underwent elective primary THR by two contemporary arthroplasty surgeons, one excising the bursa and the other not (at the time of THR). All patients received the same post-operative rehabilitation and were followed up for 1 year. We reviewed all cases of trochanteric bursitis over this 11-year period to determine the incidence of post-THR bursitis. Two proportion Z-test was used to compare incidences of trochanteric bursitis between groups.

Research results

554 patients underwent synchronous trochanteric bursectomy at the time of THR whereas 400 patients did not. A total of 5 patients (incidence 0.5%) developed trochanteric bursitis following THR; 4 of whom had undergone bursectomy as part of their surgical approach, 1 who had not. There was no statistically significant difference between the two groups (Z value 1.00, 95%CI: -0.4% to 1.3%, $P = 0.32$). There were also 8 other patients who had both trochanteric bursitis and hip osteoarthritis prior to their THR; all of whom were treated with THR and synchronous trochanteric bursectomy, and 7 had resolution of their lateral buttock pains but 1 did not.

Research conclusions

Synchronous trochanteric bursectomy at the time of THR does not materially affect the incidence of post-operative bursitis and may therefore be considered unnecessary. However, our series did show that it is successful at treating patients with known trochanteric bursitis and osteoarthritis requiring THR.

Research perspectives

Future research in the form of a clinical trial randomising patients to prophylactic trochanteric bursectomy *vs* non-bursectomy at the time of THR would be needed.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Locking plates for distal fibula fractures in young and elderly patients: A retrospective study

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Abstract

BACKGROUND

Ankle fractures are common injuries in the young and elderly populations. To prevent post-traumatic arthritis, an anatomic reconstruction of the ankle structure is mandatory. Open reduction and internal fixation is the treatment of choice among orthopaedics. Conventional plates allow stability of the fracture if bone quality is present. Locking plates might offer an advantage for the treatment of lateral malleolar fracture in patients with comminution, severe instability, distal fractures, or osteoporotic bone. Our hospital introduced a new locking plate for fracture of the distal fibula.

AIM

To evaluate locking plates in terms of outcomes and complications in young and elderly patients.

METHODS

We retrospectively reviewed a total of 67 patients treated for displaced distal fibula fractures. Demographic data, number of comorbidities, use of inter fragmentary screw, complication, time of fracture healing, partial or full weight bearing, and reoperation were recorded for all patients. Clinical outcome was assessed by the American Orthopedic Foot and Ankle Society clinical scoring

system. Radiographs were obtained at 4, 8, 12, 16, 20, and 24 wk until radiographic union was obtained.

RESULTS

All patients displayed complete bony union on radiographic assessment, and no patients developed any serious complications. We observed two superficial infections, one delayed wound healing, and two plate intolerances. Significant differences were observed between the two age groups in terms of radiographic healing (11.9 wk in younger patients *vs* 13.7 wk in older patients; $P = 0.011$) and in the American Orthopedic Foot and Ankle Society score at 6 mo after surgery (88.2 in younger patients *vs* 86.0 in older patients; $P = 0.001$) and at 12 mo after surgery (92.6 in younger patients *vs* 90.0 in older patients; $P = 0.000$).

CONCLUSION

Locking plates provide a stable and rigid fixation in multifragmentary and comminuted fractures or in the presence of poor bone quality.

Key Words: Ankle fracture; Locking plate; Distal fibula fracture; Outcome; Complications; Osteoporosis

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Core Tip: Ankle fractures are common injuries in the young and elderly populations. Fibula locking plate is used for the older population due to osteoporotic bone or for the younger population with multifragmentary and comminuted fractures. We introduced a new locking plate for fracture of the distal fibula and evaluated it for lateral malleolar fixation in terms of outcomes and complications in young and elderly patients. We were interested in determining whether the use of this locking plate would provide the same advantage and outcomes that were described in literature.

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INTRODUCTION

Ankle fractures are common injuries and represent 9% of all fractures[1,2]. These fractures, often due to low energy trauma, have an annual incidence of 122-184/100000 people[2,3] and represent the third most common fracture, after hip and wrist fractures[4]. The repair process of these fractures is classified into primary and secondary fracture healing. Primary healing is direct bone repair without cartilaginous callus formation where bone remodelling occurs with rigid fixation and no gap formation; secondary healing is typically characterised by callus formation due to the presence of movement at the fracture site. The key to the repair process is the appropriate stability of the fracture site to obtain a biological healing response.

Several fixation methods may be used including one-third tubular plate, dynamic compression plate, and locking plate. The treatment in the elderly population must consider the presence of osteoporosis as the decisive factor for the type of implant to be used. Conventional plates allow stability of the fracture if bone quality is present. Loosening or toggling of screws represent a failure of fixation due to loss of friction between the plate and the bone[1]. Locking plates might offer an advantage in patients with osteoporotic bone. The stability does not depend on bone-plate friction because the screw head locks into the threaded hole of the plate. These plates reduce periosteal compression and improve bone healing through increased blood supply[5]. Precontoured locking plates facilitate placement and fixation of fractures in elderly and young patients and must be reserved for distal fractures that have limited places available for distal screw insertion through multiple multidirectional metaphyseal locked screws. Unfortunately, locking plates form a stiffer screw-plate construct that can cause greater rigidity compared to conventional plates, affecting fracture healing and causing delayed union or non-union.

In February 2017, our unit introduced a new locking plate for the fracture of the distal fibula. The aim of this study was to evaluate the new locking plate for lateral malleolar fixation in terms of outcomes and complications in young and elderly patients. We were interested in determining whether the use of this locking plate would provide the same advantage and outcomes that were described in the literature.

MATERIALS AND METHODS

We retrospectively reviewed a consecutive cohort of patients admitted from February 2017 to September 2018 for fixation of a distal fibula fracture with a follow-up of 1 year. Permission for this study was obtained from our institutional ethics

committee for the use of patient data for publication purposes (n°161/2020/CA). The eligibility criteria were displaced distal fibula fractures classified as a Dannis-Weber type B or C after a low-energy trauma, minimum follow-up of 1 year, and patient ambulatory prior to injury. Open ankle fracture, pilon fracture, bilateral ankle fractures, pathologic fractures, paediatric fractures, previous malleolar fractures history, fracture treated temporarily with external fixator, fracture treated with syndesmotic screws, patients with cognitive impairment, and polytrauma were excluded from study.

A total of 67 patients treated for displaced Dannis-Weber type B or C distal fibula fractures were included in this study. The implant used was a 3.0/3.5 mm precontoured anatomical locking plate for the distal fibula, manufactured by Hofer Medical Italy (Inteos plate). This implant provides a unicortical locking system to allow fixation in metaphyseal bone with 3.0 mm distal screws. The plate has a low profile and multiple smaller screws distally to obtain adequate distal fixation through multiple multidirectional locked screws. The use of a lag screw was left to the discretion of the surgeon, depending on the pattern of fracture.

Patients were divided into two groups based on age: Group 1 patients were under 60-years-old; and group 2 patients were aged 60 years and over. Demographic data (age, sex, type of fracture), number of comorbidities (diabetes, history of deep venous thrombosis or limb vascular disease), use of inter fragmentary screws, complications (superficial or deep infection, loss of reduction, loose screw, non-union, nerve injury, delayed wound healing, skin irritation), time of fracture healing, partial or full weight bearing, and reoperation were recorded for all patients.

Clinical outcome was assessed by the American Orthopedic Foot and Ankle Society (AOFAS), with clinical scoring at 6 and 12 mo after surgery. The AOFAS score has a maximum value of 100 points (50 points for function, 40 for pain, 10 for alignment). Complications were recorded at every clinical and radiographic follow-up. Radiographs of the anterior-posterior, lateral, and mortise view were obtained at 4 wk postoperatively and then at 8, 12, 16, 20, and 24 wk until radiographic union was obtained. Fracture healing was defined by the identification of three of the four cortices to be bridged by visible callus on X-ray exam, determined by a single radiologist that was not involved in this study, and full weight bearing without pain.

All patients received antibiotic prophylaxis with a single dose of 2 g of a second-generation cephalosporin. In case of allergy, the patients received teicoplanin or levofloxacin according to hospital protocol. All patients received low-molecular-weight heparin for thrombo prophylaxis from 6 h postoperatively and for the duration of immobilisation (30 d). Possible syndesmotic injuries (talar tilt or increase in tibial medial space) were evaluated during the surgery with external rotation stress test under fluoroscopy. In the event of a syndesmotic injury, the patient was excluded from the study. A short leg cast was applied for the first 2 wk, and then a brace for another 2 wk. Full weight bearing with a brace was allowed at 4 or 6 wk after surgery, depending on the radiographic result, while full weight bearing without a brace was allowed about 8 or 10 wk after surgery.

Statistical analysis was conducted using the IBM Statistical Package for Social Sciences, version 26. Descriptive statistics were calculated. Depending on the variable analysed, χ^2 test and *t*-test were used to compare the two age groups. All *P* values ≤ 0.05 were considered statistically significant.

RESULTS

A total of 67 patients (55.2% females), mean age 58.5 ± 16.2 years, were included in the study since their data were available for complete analysis and comparison. Among them, 43.3% of patients were in group 1 (< 60-years-old), and 56.7% were in group 2 (≥ 60-years-old). The majority of patients (79.1%) had a Dannis-Weber type B distal fibula fracture. In 9 patients (13.4 %), there was at least one comorbidity at the time of surgery.

All 67 patients displayed complete bony union on radiographic assessment. Radiographic union was obtained in 8 patients (11.9%) at 8 wk, in 40 patients (59.7%) at 12 wk, in 15 patients (22.4%) at 16 wk, and in 4 patients (6.0%) at 20 wk. Plates with a lag screw were used in 26 fractures (38.8%) and without in 41 fractures (61.2%), suggesting that these fractures frequently do not require a lag screw due to stabile fixation of locking plates. Full weight bearing with a brace was allowed at 4 wk after surgery in 54 patients and at 6 wk in 13 patients. Full weight bearing without a brace was allowed at 8 wk in 54 patients and at 10 wk in 13 patients. No patients developed any serious complications, including non-union, malunion, loss of fixation, loose screws, deep infection, peroneal tendinitis, nerve injury, and post-traumatic osteoarthritis. We observed two (3%) superficial infections (1 case in group 1, 1 case in group 2), which completely resolved after antibiotic treatment, one (1.5%) delayed wound healing (1 case in group 2), which was treated with medications, and two (3%) plate intolerances (1 case in group 1, 1 case in group 2) due to incorrect positioning that required removal of the implant. Patients with superficial infection or delayed wound healing had at least one comorbidity at the time of surgery.

Table 1 reports results of the comparison between group 1 and group 2. Significant differences were observed between the two age groups in terms of radiographic healing (11.9 wk in younger patients *vs* 13.7 wk in older patients; $P = 0.011$) and in the AOFAS score at 6 mo after surgery (88.2 in younger patients *vs* 86.0 in older patients; $P = 0.001$) and at 12 mo after surgery (92.6 in younger patients *vs* 90.0 in older patients; $P = 0.000$).

DISCUSSION

Fibula locking plate is used for the older population due to osteoporotic bone or for the younger population in multifragmentary and comminuted fractures. Biomechanical studies have shown that locking plates in an osteoporotic fibula have greater torque and axial and angle resistance at failure than conventional plates[6]. The use of two distal unicortical

Table 1 Comparison between group 1 and group 2 (mean ± SD)

Feature	Total, *n* = 67	Group 1 < 60 yr, *n* = 29	Group 2 ≥ 60 yr, *n* = 38	*P* value
Age in yr	58.5 ± 16.2	42.4 ± 11.7	70.7 ± 2.9	NA
Female sex	55.2%	55.2%	55.3%	0.994
Weber classification				
B	79.1%	79.3%	78.9%	0.971
C	20.9%	20.7%	21.1%	
Radiographic healing in wk	12.9 ± 2.9	11.9 ± 3.1	13.7 ± 2.6	0.011
Partial load with brace in wk	4.4 ± 0.8	4.3 ± 0.8	4.4 ± 0.8	0.701
Total load without brace in wk	8.4 ± 0.8	8.3 ± 0.8	8.4 ± 0.8	0.701
AOFAS score at 6 mo after surgery	86.9 ± 2.8	88.2 ± 1.9	86.0 ± 3.0	0.001
AOFAS score at 12 mo after surgery	91.1 ± 2.7	92.6 ± 2.4	90.0 ± 2.3	0.000

AOFAS: American Orthopedic Foot and Ankle Society; NA: Not assessed; SD: Standard deviation.

screws was mechanically equivalent to three distal cortical screws of standard plate[1,6,7]. In conventional devices, the plate-bone construct is dependent on bone mineral density, while in locking devices, bone quality does not influence the biomechanical resistance of the implant because the plate produces stability through a fixed-angle structure without the need for contact between the bone and the plate[8]. Locking plates do not offer an advantage in stable fractures with normal mineral density[9,10]. In addition, the fixation of the distal fibula could be inappropriate with a standard plate because it depends on the mechanical strength of a single cortex and cancellous bone of the distal fragment. The locking plates produce a fixed-angle structure without the need for anchorage of the screws on both corticales; therefore, these plates are useful in multifragmentary and distal fractures in young patients.

Wound infection, delayed wound healing, and skin irritation are common postoperative complications of ankle fixation and sometimes require revision or removal of metalwork[11,12]. Other postsurgical complications described in the literature are non-union, malunion, loss of fixation, loose screws, peroneal tendinitis, nerve injury, and post-traumatic osteoarthritis[5].

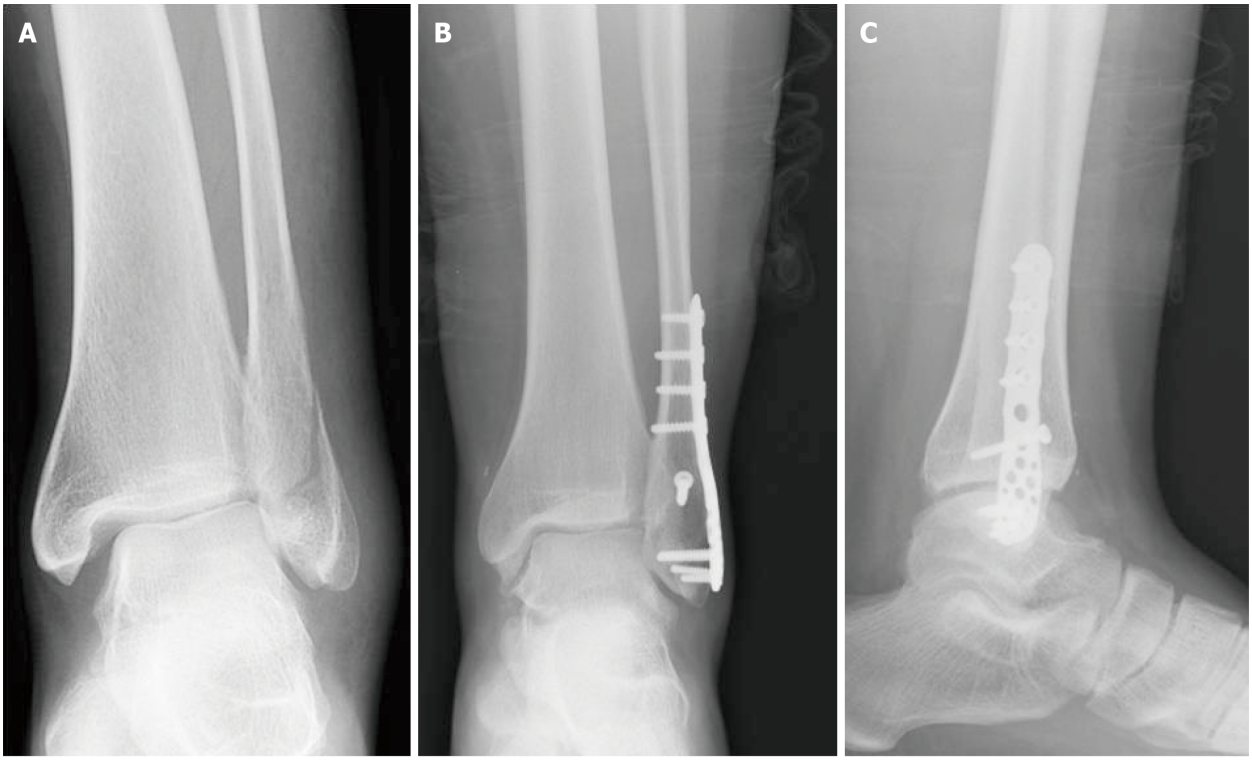
In the literature, there is a debate on clinical results, incidence of complications, and advantages on the use of locking plates. Generally, complications after locking plate osteosynthesis can reach 20%[1,13-15] and even 40% according to other authors[16]. Naumann *et al*[17] retrospectively reviewed 997 patients following surgery for ankle fractures and reported that 17.0% required implant removal and 2.6% required infection treatment. Lynde *et al*[18], through a retrospective study, found that there was no difference in the complication rates between locking *vs* non-locking plates used for distal fibula fracture. Lyle *et al*[1] and Tsukada *et al*[19] did not observe any clinical advantage in the use of locking plates and found no difference in complication rates between locking plates and conventional plates.

Huang *et al*[20] compared one-third tubular plates with locking compression plates and showed a higher functional score and less healing time in locking plates. Schepers *et al*[21], through a retrospective study, advised against the use of locking plates because of increased wound complication with respect to conventional plates (17.5% *vs* 5.5%). Herrera-Pérez *et al*[4] observed similar outcomes in both locking and conventional plates but recommended the use of locking plates in patients with concomitant soft tissue damage or who cannot tolerate prolonged immobilisation, as it reduces non-weight-bearing time. Takemoto *et al*[22] observed that in multifragmentary fractures, lag screws are used half as often with locking plates compared to conventional plates because locking plates provide the necessary fixation. Kim *et al*[7], using a biomechanical study, compared semitubular locking and non-locking plates and observed that both implants were similar. However, locking plates were independent of bone mineral density and were advantageous for elderly patients with osteoporosis.

In our study, we used locking plates in both young and elderly patients (Figures 1 and 2) and found no differences in the complication rates between the two groups. Moreover, the complication rates were in line with those found in the literature for the treatment of distal fibula fractures.

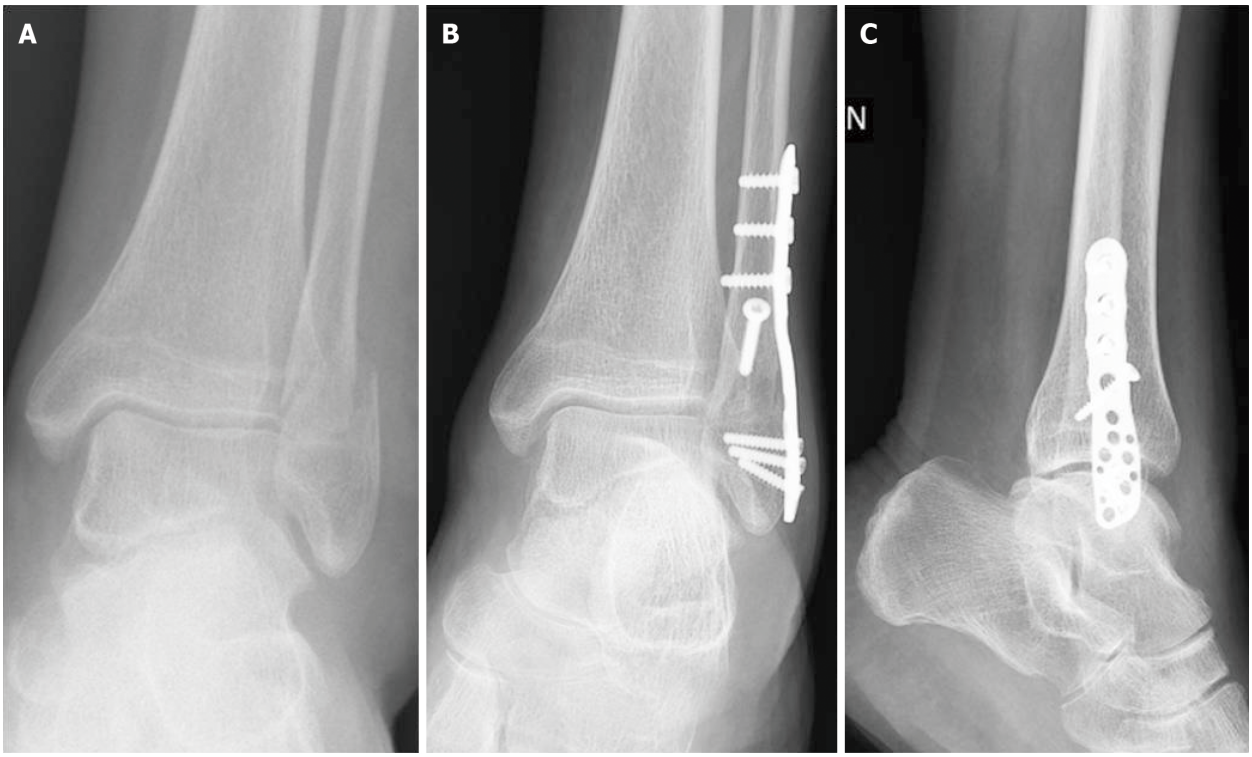
In this study, we observed a significant difference between the two groups in terms of radiographic healing (11.9 wk in younger patients *vs* 13.7 wk in older patients) and in the AOFAS score at 6 mo (88.2 in younger patients *vs* 86.0 in older patients) and at 12 mo (92.6 in younger patients *vs* 90.0 in older patients). Our findings indicated a high efficacy of these plates in lateral malleolar fixation. Therefore, in this study, locking plates seemed to offer an advantage in young patients with normal bone mineral density for the treatment of multifragmentary and comminuted fractures, permitting early rehabilitation and full weight bearing through a rigid fixation of the malleolar fracture. In elderly patients, this locking plate showed excellent results, as already known in the literature for the other devices.

The present retrospective study was limited because it was not randomised, did not have a control group, had a short follow-up, and had a limited sample of patients. Further studies, especially prospective, are needed to confirm clinical and radiological outcomes of locking plates in displaced malleolar fractures.



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Figure 1 Fixation of a lateral malleolus fracture with locking plate in a young patient. A: Preoperative X-ray; B: Anterior-posterior X-ray at follow-up; C: Lateral X-ray at follow-up.



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Figure 2 Fixation of a lateral malleolus fracture with locking plate in an elderly patient. A: Preoperative X-ray; B: Anterior-posterior X-ray at follow-up; C: Lateral X-ray at follow-up.

CONCLUSION

Locking plates provide a stable and rigid fixation in multifragmentary and comminuted fractures or in the presence of poor bone quality. The cost is greater than conventional plates but decreases the risk of displacement of fractures or further intervention of revisions in patients with osteoporotic bone or unstable fractures. In the young population, anatomical locking plates are useful to obtain stable fixation for distal fractures with comminution that have limited places available for distal screws. In the elderly population, locking plates offer an advantage in the presence of poor bone quality, avoiding screws loosening and subsequently coming out. Although locking plates have been associated with delayed union or non-union in the literature, we did not observe this in our study. However, the observation time was not very long and the overall included samples were limited. The locking plate utilised in this study showed few complications and complete bone union in all patients.

ARTICLE HIGHLIGHTS

Research background

Ankle fractures are common injuries in the young and elderly populations. Locking plates might offer an advantage for the treatment of these fractures in patients with comminution, severe instability, distal fractures, or osteoporotic bone.

Research motivation

The aim of this study was to evaluate our hospital's new locking plate for lateral malleolar fixation in terms of outcomes and complications in young and elderly patients.

Research objectives

We were interested in determining whether the use of a locking plate would provide the same advantage and outcomes that were described in literature.

Research methods

We retrospectively reviewed a consecutive cohort of patients for fixation of distal fibula fracture with a follow-up of 1 year.

Research results

Significant differences were observed between the two age groups in terms of radiographic healing and in the American Orthopedic Foot and Ankle Society score at 6 mo and at 12 mo after surgery.

Research conclusions

The locking plate utilized in this study showed few complications and complete bone union in all patients.

Research perspectives

Prospective studies with larger patient samples and longer follow-up are needed.

FOOTNOTES

Author contributions: All authors designed the study, acquired and interpreted the data, wrote the manuscript, and approved the final version of the article; Evola FR and Di Fede GF designed and performed the research; Evola FR and Evola G contributed to the literature research; Agodi A and Barchitta M analysed the data; Evola FR wrote the paper; Longo G revised the manuscript; All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Physiologic postoperative presepsin kinetics following primary cementless total hip arthroplasty: A prospective observational study

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Abstract

BACKGROUND

Presepsin is an emerging biomarker in the diagnosis of sepsis. In the field of orthopaedics, it could be useful in diagnosing and managing periprosthetic joint infections.

AIM

To define the normal postoperative presepsin plasmatic curve, in patients undergoing primary cementless total hip arthroplasty (THA).

METHODS

Patients undergoing primary cementless THA at our Institute were recruited. Inclusion criteria were: Primary osteoarthritis of the hip; urinary catheter time of permanence < 24 h; peripheral venous cannulation time of permanence < 24 h; no postoperative homologous blood transfusion administration and hospital stay ≤ 8 d. Exclusion criteria were: The presence of other articular prosthetic replacement or bone fixation devices; chronic inflammatory diseases; chronic kidney diseases; history of recurrent infections or malignant neoplasms; previous surgery in the preceding 12 mo; diabetes mellitus; immunosuppressive drug or corticosteroid assumption. All the patients received the same antibiotic prophylaxis. All the THA were performed by the same surgical and anaesthesia team; total operative time was defined as the time taken from skin incision to completion of skin closure. At enrollment, anthropometric data, smocking status, osteoarthritis stage according to Kellgren and Lawrence, Harris Hip Score, drugs assumption and comorbidities were recorded. All the patients underwent serial blood tests, including complete blood count, presepsin (PS) and C-reactive protein 24 h before arthroplasty and at 24, 48, 72 and 96 h postoperatively and at 3, 6 and 12-mo follow-up.

RESULTS
A total of 96 patients (51 female; 45 male; mean age = 65.74 ± 5.58) were recruited. The mean PS values were: 137.54 pg/mL at baseline, 192.08 pg/mL at 24 h post-op; 254.85 pg/mL at 48 h post-op; 259 pg/mL at 72 h post-op; 248.6 pg/mL at 96-h post-op; 140.52 pg/mL at 3-mo follow-up; 135.55 pg/mL at 6-mo follow-up and 130.11 pg/mL at 12-mo follow-up. In two patients (2.08%) a soft-tissue infection was observed; in these patients, higher levels (> 350 pg/mL) were recorded at 3-mo follow-up.

CONCLUSION
The dosage of plasmatic PS concentration is highly recommended in patients undergoing THA before surgery to exclude the presence of an unknown infection. The PS plasmatic concentration should be also assessed at 72 h post-operatively, evaluate the maximum postoperative PS value, and at 96 h post-operatively when a decrease of presepsin should be found. The lack of a presepsin decrease at 96 h post-operatively could be a predictive factor of infection.

Key Words: Presepsin; Periprosthetic joint infection; Total hip arthroplasty; Total hip replacement; Hip surgery; Postoperative care

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Core Tip: The dosage of plasmatic presepsin (PS) concentration is highly recommended in patients undergoing total hip arthroplasty before surgery to exclude the presence of an unknown infection. The PS plasmatic concentration should be also assessed at 72 h post-operatively, to evaluate the maximum postoperative PS value, and at 96 h post-operatively when a decrease of presepsin should be found. The lack of a presepsin decrease at 96 h post-operatively should be a predictive factor of infection.

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INTRODUCTION

Periprosthetic joint infections (PJIs) are a relevant cause of prosthetic surgery revision, accounting for 15% of failed total hip arthroplasties (THA)[1-3].

PJIs are fearsome complications in orthopaedics, as they might significantly affect the patient's quality of life. Therefore, in the last two decades, an increasing interest towards the prevention of these complications has developed[1-3]. In the meantime, several research groups have investigated the potential role of presepsin (PS) in this PJI prevention and diagnosis[1-3].

PS, from a molecular point of view, is the N-terminal fragment of the soluble cluster of differentiation 14-SubType[14]. It is released into circulation after the activation of defence mechanisms, mainly bacterial phagocytosis[4].

Yaegashi *et al*[5], in 2004, hypothesized for the first time that PS could be useful as a biomarker to predict clinical prognosis in septic conditions. In the following years, different studies have highlighted the potential of PS in several infectious diseases, including severe community-acquired pneumonia, severe acute pancreatitis, infections in patients with haematological malignancies, implantable cardioverter-defibrillator (ICD) pocket infections, neonatal sepsis, pacemaker and PJIs and surgical site infections (SSIs)[6-22].

Furthermore, PS has been also studied in the risk stratification in patients undergoing cardiac surgery and as a biomarker in the perioperative management of patients undergoing total knee arthroplasty (TKA) or THA[23-29].

In a previous preliminary study, our research group defined the normal perioperative plasmatic levels of presepsin at 96 h postoperatively in 50 patients undergoing primary cementless THA and primary cemented TKA[25].

The present study aims at depicting the normal postoperative PS plasmatic curve, in patients undergoing primary cementless THA, at 12-mo follow-up.

MATERIALS AND METHODS

Study population and data collection

Patients undergoing primary cementless THA at our Institute were recruited. Ethical clearance was obtained from our centre's Clinical Research Ethics Committee, as per the 1964 Declaration of Helsinki.

All the patients gave written informed consent before enrolment in the study. Inclusion criteria were: Primary osteoarthritis of the hip; urinary catheter time of permanence < 24 h; peripheral venous cannulation time of permanence < 24 h; no postoperative homologous blood transfusion administration and hospital stay ≤ 8 d.

Exclusion criteria were: The presence of other articular prosthetic replacement or bone fixation devices; chronic inflammatory diseases; chronic kidney diseases; history of recurrent infections or malignant neoplasms; previous surgery in the preceding 12 mo; diabetes mellitus; immunosuppressive drug or corticosteroid assumption.

All the patients received the same antibiotic prophylaxis with cephazolin 2 g. All the THA were performed by the same surgical and anaesthesia team; total operative time was defined as the time taken from skin incision to completion of skin closure. At enrolment anthropometric data, smocking status, osteoarthritis stage according to Kellgren and Lawrence, Harris Hip Score, drugs assumption and comorbidities were recorded.

All the patients underwent serial blood tests, including complete blood count, PS and C-reactive protein (CRP) 24 h before arthroplasty and at 24, 48, 72 and 96 h postoperatively and at 3, 6 and 12-mo follow-up. The complication rate was recorded during the 12-mo follow-up.

Statistical analysis

Statistical analysis was performed with SPSS v25.0 (SPSS Inc, Chicago, IL, United States). The Shapiro-Wilk Test was conducted. Pearson correlation test was performed to assess any relationship between non-modifiable risk factors and preoperative PS values at baseline.

Compared to the baseline, the paired t-student test was performed to assess PS and CRP modifications at 3, 6 and 12-mo follow-ups. *P* values below 0.05 were considered significant.

RESULTS

A total of 96 patients (51 females; 45 males; mean age = 65.74 ± 5.58) were recruited in the present study. The main data of the study are summarized in Table 1.

Table 2 shows the correlation between non-modifiable risk factors and preoperative PS values at baseline; a significant correlation was observed between patients' age and preoperative PS levels. Notably, no correlation was found between preoperative creatinine and preoperative PS levels, since patients with chronic kidney disease were excluded from the present study.

Figure 1 shows the mean postoperative PS levels (Figure 1A) and the mean PS levels at 12-mo follow-ups (Figure 1B). The PS plasmatic concentration showed an increasing trend until 72 h post-op and started decreasing 96 h after surgery. During the 12-mo follow-up, the plasmatic PS concentration showed a significant increase at the three-month follow-up, when three patients out of 96 (3.125%) reported a soft-tissues infection. Higher levels (> 350 pg/mL) were recorded in these three patients at a 3-mo follow-up. No PJIs were diagnosed during the 12-mo follow-up.

Figure 2 shows plasmatic CRP kinetics after surgery (Figure 2A) and at 12-mo follow-up (Figure 2B). The plasmatic CRP curve still showed an increasing trend at 96 h after surgery. During the 12-mo follow-up, plasmatic CRP showed a reducing trend and it was not influenced by the presence of soft-tissue infections.

DISCUSSION

PJIs are an emerging complication in prosthetic surgery, accounting for a relevant percentage of revision surgeries[27,28].

The pursuit of a biomarker able to improve the diagnosis and management of PJI, together with clinical findings and imaging modalities, is currently playing a central role in orthopaedics and traumatology[1].

Presepsin is an emerging biomarker studied in a wide range of infective conditions, including severe acute pancreatitis, neonatal sepsis, severe community-acquired pneumonia, pacemaker and ICD pocket infections, infections in patients with haematological malignancies, SSIs and PJIs. The present paper aims at depicting the normal postoperative plasmatic PS trend, in patients undergoing primary cementless THA, at 12-mo follow-up, to further depict a presepsin cut-off level for hip PJIs.

Our data showed PS has an increasing trend until 72 h post-op after THA surgery and starts decreasing 96 h after surgery. Furthermore, during the 12-mo follow-up, the plasmatic PS concentration showed a significant increase at the three-month follow-up, when three patients reported a soft-tissues infection. Hence, in the present study, plasmatic PS values are more sensitive to soft-tissues inflection, than CRP. Although the study sample is not so big and no cases of PJI have been observed in this trial, based on the study findings, the dosage of plasmatic PS concentration is recommended in patients undergoing THA before surgery, to exclude a concomitant unknown infection. However, future studies with a bigger sample size are needed to better define the limits of presepsin physiologic interval. The PS plasmatic concentration should be also assessed at 72 h after surgery, to assess the highest postoperative PS value, and at 96 h after surgery, when a decrease in plasmatic PS concentration is awaited. The lack of a plasmatic PS decrease, at 96 h after surgery could be a predictive factor of SSI or PJI.

These findings are consistent with the data reported by our research group in a preliminary report on perioperative presepsin levels in patients undergoing THA and TKA[25].

PS has been also studied in the assessment of PJIs by Marazzi *et al*[23], in a prospective multicentre study recruiting 100 patients who underwent revision surgery for aseptic loosening or PJI. These authors reported PS plasmatic levels were

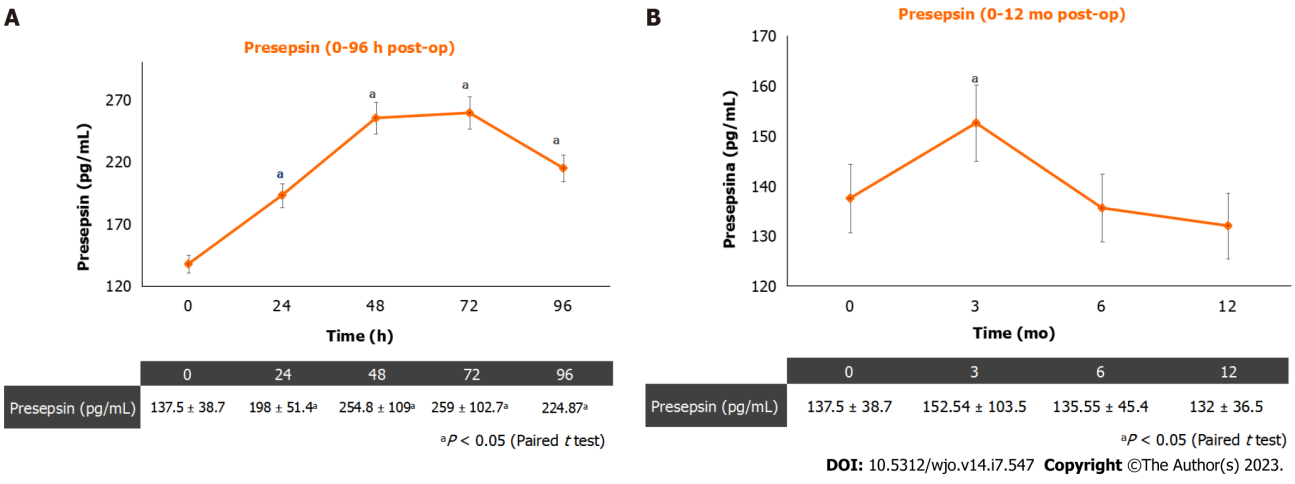
Table 1 Main data of the study

Characteristic	Values
Patients (*n*)	96
Gender, male, *n* (%)	45 (46.875)
Age, mean ± SD	65.74 ± 5.58
Range	54-77
BMI (kg/m^2), mean ± SD	26.34 ± 7.22
Total operative time (min), mean ± SD	86.54 ± 43.5
Hospital staying (d), mean ± SD	5.45 ± 1.76

Table 2 Non-modifiable risk factors and presepsin values at recruitment: Pearson correlation test

	Presepsin	
	R	*P* value
Age	0.74	0.018[a]
BMI (kg/m^2)	-0.259	0.734
Gender	0.19	0.44
KLS	0.287	0.16
HHS	-0.17	0.645
Creatinine	0.056	0.852

[a]$P < 0.005$.
HHS: Harris Hip Score.



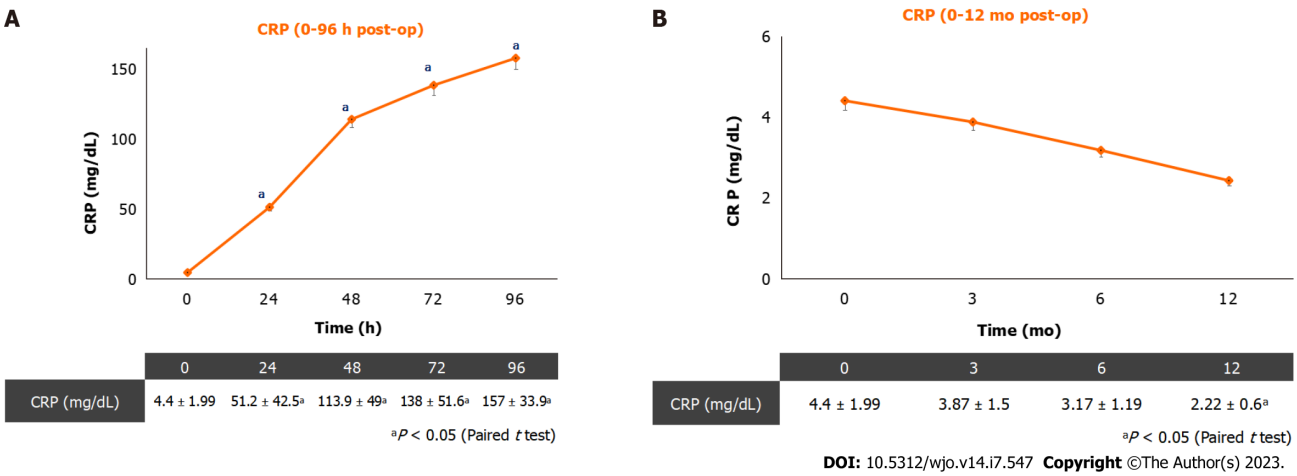
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Figure 1 Presepsin levels. A: Presepsin postoperative plasmatic concentration (0-96 h after surgery); B: Presepsin plasmatic levels during the 12-mo follow-up.

higher in the PJI group compared to the aseptic loosening group[23].

Koakutsu *et al*[30] have recently investigated the potential of PS in SSIs in a prospective observational study recruiting 118 patients who underwent elective major spine surgical procedures. These authors depicted an SSI in 3 patients out of 118; in these patients, higher levels (*i.e.*, > 300 pg/mL) were depicted in the first postoperative week[30].

Imagama *et al*[31] recently evaluated synovial fluid and serum PS, together with procalcitonin (PCT) serum levels, in 28 patients affected by osteoarthritis (OA), compared with 18 patients suffering from septic arthritis (SA). These authors observed that synovial fluid, plasmatic PS and plasmatic PCT were significantly higher in the SA group compared with the OA group[31]. Hence, Imagama *et al*[31] concluded that synovial fluid PS could be a useful biomarker to differentiate SA from OA.



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Figure 2 C-reactive protein levels. A: C-reactive protein postoperative plasmatic concentration (0-96 h after surgery); B: C-reactive protein plasmatic levels during the 12-mo follow-up. CRP: C-reactive protein.

On the other hand, Busch *et al*[32], in a prospective cohort study on 53 patients with aseptic painful total shoulder, knee and hip arthroplasty and 27 patients affected by PJI, reported synovial fluid PS was not significantly higher in the PJI group, compared with the aseptic group. Synovial fluid presepsin specificity was 51% and sensitivity was 29%, with a cut-off value above 0.06 ng/mL[32].

Considering the above-mentioned findings, further studies with larger samples are awaited to better define the potential of serum and synovial PS concentration in the diagnosis of PJI.

The present study has some limitations. First of all, the sample size is not so large and no cases of PJI were recorded in the recruited patients during follow-up, hence the findings of the present study should be validated in a study with a larger sample size. Moreover, no control group was included in the present study and presepsin accuracy was not compared to other emerging biomarkers.

CONCLUSION

The dosage of plasmatic PS concentration is highly recommended in patients undergoing THA, in the preoperative phase, to rule out any unknown infection.

The PS plasmatic concentration should be also assessed at 72 h after surgery, to assess the higher postoperative PS value, and at 96 h after surgery, when a PS decrease should be found. The lack of a presepsin decrease at 96 h after surgery might be a predictive factor of infection.

ARTICLE HIGHLIGHTS

Research background

Periprosthetic joint infections (PJIs) are a relevant cause of prosthetic surgery revision, accounting for 15% of failed total hip arthroplasties (THA).

Research Motivation

Presepsin (PS) is released into the circulation following bacterial phagocytosis and the activation of other innate defence mechanisms. In a previous preliminary study, our research group defined the normal perioperative plasmatic levels of presepsin at 96 h postoperatively in 50 patients undergoing primary cementless THA and primary cemented total knee arthroplasties.

Research objectives

This paper aims at depicting e normal postoperative PS plasmatic curve, in patients undergoing primary cementless THA, at 12-mo follow-up.

Research methods

Patients undergoing primary THA were prospectively recruited. All the procedures were performed by the same anaesthesia and surgical équipe. The recruited patients underwent serial blood tests, including complete blood count, PS and C-reactive protein 24 h before arthroplasty and at 24, 48, 72 and 96 h postoperatively and at 3, 6 and 12-mo follow-up.

Research results

Ninety-six patients (51 female; mean age = 65.74 years old) were included in the present study. The mean PS values were: 137.54 pg/mL before surgery, 192.08 pg/mL at 24 h post-op; 254.85 pg/mL at 48 h post-op; 259 pg/mL at 72 h post-op; 248.6 pg/mL at 96-h post-op; 140.52 pg/mL at 3-mo follow-up; 135.55 pg/mL at 6-mo follow-up and 130.11 pg/mL at 12-mo follow-up.

Research conclusions

The assessment of plasmatic PS concentration is highly recommended in patients undergoing THA in the preoperative phase, to rule out any unknown infection. The PS plasmatic concentration should be also assessed at 72 h after surgery, to quantify the higher postoperative PS value, and at 96 h after surgery, when a decrease in PS should be found. The lack of a presepsin decrease at 96 h after surgery might predict a local infection.

Research perspectives

Presepsin is an emerging biomarker in the diagnosis of PJIs. However, further studies with bigger samples are awaited to better define the role of serum and synovial PS in the diagnosis of PJI.

FOOTNOTES

Author contributions: Bizzoca D, Moretti B and Solarino G designed the research study; Bizzoca D and Vicenti G performed the research; Bizzoca D wrote the manuscript; Moretti L and Piazzolla A revised the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: The study was approved by the local Ethics Committee of AOU Policlinico di Bari (No. 6919).

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ORIGINAL ARTICLE

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Clinical outcome of open ankle fractures in patients above 70 years of age

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Abstract

BACKGROUND

Open fractures of the ankle are complex injuries requiring multidisciplinary input and are associated with significant morbidity and mortality. However, data on the clinical outcomes of open ankle fracture management in patients older than 70 is minimal.

AIM

To evaluate the clinical outcomes following open ankle fracture management in patients older than 70. Our secondary aim is to look at predictors of poor outcomes.

METHODS

Following local research and audit department registration, 22 years of prospectively collated data from an electronic database in a district general hospital were assessed. All patients older than 70 years of age with an open ankle fracture requiring surgical intervention were identified. Demographic information, the nature, and the number of surgical interventions were collated. Complications, including surgical site infection (SSI), venous thromboembolic events (VTEs) during hospital stay, and mortality rate, were reviewed.

RESULTS

A total of 37 patients were identified (median age: 84 years, range: 70-98); n = 30 females median age: 84 years, range: 70-97); n = 7 males median age: 74 years,

range: 71-98)) who underwent surgical intervention after an open ankle fracture. Sixteen patients developed SSIs (43%). Superficial SSIs (n = 8) were managed without surgical intervention and treated with antibiotics and regular dressing changes. Deep SSIs (n = 8; 20%) required a median of 3 (range: 2-9) surgical interventions, with four patients requiring multiple washouts and one patient having metalwork removed. VTE incidence was 5% during the hospital stay. Eight patients died within 30 d, and mortality at one year was 19%. The 10-year mortality rate was 57%. The presence of a history of stroke, cancer, or prolonged inpatient stay was found to be predictive of lower survivorship in this population (log-rank test: cancer P = 0.008, stroke P = 0.001, length of stay > 33 d P = 0.015). The presence of a cardiac history was predictive of wound complications (logistic regression, P = 0.045). Age, number of operations, and diabetic history were found to be predictive of an increase in the length of stay (general linear model; age P < 0.001, number of operations P < 0.001, diabetes P = 0.041).

CONCLUSION

An open ankle fracture in a patient older than 70 years has at least a 20% chance of requiring repeated surgical intervention due to deep SSIs. The presence of a cardiac history appears to be the main predictor for wound complications.

Key Words: Fragility fracture; Open fracture; Clinical outcome; Mortality; Infection; Survival

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Core Tip: There is no standard consensus on management of open ankle fractures in patients above 70 years of age. Cardiac issues are the main predictors of poor outcome. 1 in 5 patients above 70 years of age develop deep infection requiring further surgical intervention. High infection increases length of stay in the hospital and mortality.

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INTRODUCTION

Open fractures are complex injuries requiring multidisciplinary input[1] and are associated with significant morbidity and mortality[2]. Open ankle fractures account for about 2% of all ankle fractures[3]. About 187 per 100000 adults sustain ankle fractures every year[4]. Ankle fractures can be caused by various modes of trauma, *e.g.*, twisting, impact, and crush injuries. The degree of bony comminution and soft tissue damage is directly related to the energy of trauma[5]. In older patients with unstable ankle fractures, surgical intervention *vs* application of a contact cast is reported to have an equivalent functional outcome at six months[6]. Surgical intervention is still the first line of management for the elderly with open fractures to minimize the risk of infection[7]. Among the elderly, an open ankle fracture can reduce quality of life by more than half, sharing a similar characteristic to a fragility fracture[8]. Typically, fractures of the hip, pelvis, spine, humerus, wrist, rib, clavicle, scapula, or sternum are described as osteoporotic fractures[9,10]. The incidence of ankle fractures does not increase with age, excluding them from the osteoporotic fracture class[11,12]. Minimal data on the clinical outcome of open ankle fracture management in patients older than 70 is available[13].

The primary aim of this study is to describe the clinical outcomes following an open ankle fracture in patients older than 70. Our secondary aim is to look at predictors of poor outcomes in this age group.

MATERIALS AND METHODS

Following local research and audit department registration, 22 years of prospectively collated data from an electronic database in a district general hospital (DGH) were reviewed. All patients older than 70 years with an open ankle fracture requiring surgical intervention were identified. Demographic information, the nature, and the number of surgical interventions were collated. All open fractures were classified according to the Gustilo and Anderson classification[14] and the number of malleoli involved[15].

Complications, including surgical site infection (SSI), venous thromboembolic events (VTE) during hospital stay, and mortality rate at 30 d and one year, were reviewed. The presence of comorbidities, including diabetes mellitus, a history of cancer, and previous thromboembolic disease, and their relationship to poor outcomes, were evaluated.

Statistical analysis was performed using R 4.2.2 (R foundation). With patient factors as explanatory variables, logistic regression was used to predict any wound complication. A general linear model was chosen to identify variables that are predictive of an increased length of hospital stay. Survival analysis was performed with follow up time from admission

and death due to any cause as endpoint. The log-rank rest was used to compare variables influencing survival. For all statistical analyses, a P value < 5% was considered significant.

RESULTS

There were 37 patients older than 70 years who underwent surgical intervention after an open ankle fracture. The median age was 84 years (range: 70-98), with 30 females (median age: 84, range: 70-97 years) and seven males (median age: 74, range: 71-98 years).

Twenty-nine patients (78%) sustained bimalleolar ankle fractures; four patients had unimalleolar and another four had trimalleolar ankle fractures. An open wound over the medial malleolus was seen in 89% of the patients. Eight patients had a Gustilo-Anderson Type I fracture, and 24 patients had Type II, with the remaining five patients having Type III. The ankle joint was dislocated at initial assessment in 86% of cases (Table 1). There were no sex differences in the type of ankle fracture sustained or in the incidence of complications (Table 2).

Thirty-two patients (86%) had surgery within 24 h of injury, four underwent surgical intervention within 48 h, and one patient had surgery after six days due to a late presentation to the emergency department. Two patients were allowed to put partial weight on the surgical site following surgery.

The remaining 35 patients were advised to initially mobilize non-weight bearing on the operated site.

All 37 patients had wound washout and debridement at initial surgery. Twenty-one (57%) patients had primary closure, and 25 (68%) underwent definite fixation in the first sitting. Of the 37 patients, 16 wounds (43%) were left to heal by secondary intention. Of these, three patients later required a split skin graft, and seven required vacuum assisted closure (VAC) therapy application to achieve skin closure (Figures 1 and 2).

Out of 16 wound complications, eight were managed with regular dressing changes and antibiotics (superficial SSIs).

The other eight patients required further washout in the operating theatre (deep SSIs). Four patients with deep SSIs required multiple washouts. One of these patients needed to have the metalwork removed for the wound to heal. The maximum number of operations one patient had was nine (requiring washouts and VAC dressing changes). The median number of operations patients with deep SSIs had to undergo was three (range: 2-9). Table 3 describes the instances where either primary or secondary closure was chosen at the initial surgical intervention (Table 3).

The overall mortality rate in this study was 59%. Out of 37, seven (19%) patients died within one year of the open ankle injury. The 30-d mortality rate was 8%, with the 0-year mortality rate at 57%. The median length of stay in the hospital was 26 d (range: 3-84) (Table 4).

The overall mortality rate in this study was 59%. Out of 37, seven (19%) patients died within one year of the open ankle injury. The 30-d mortality rate was 8%, with the 0-year mortality rate at 57%. The median length of stay in the hospital was 26 d (range: 3-84) (Table 5).

DISCUSSION

This is a retrospective study that evaluates the outcome of patients older than 70 who had surgical treatment for an open ankle fracture. Previously, Schermann *et al*[16] looked at predisposing factors and associated mortality in patients older than 65 years with open ankle fractures. Wijendra *et al*[8] reviewed outcomes in low-energy open ankle fractures in patients aged 27-100 (mean: 73). We assessed the clinical outcome in this group of patients based on the rate of complications and the number of operations undertaken. Patients requiring multiple operations had a longer hospital stay (median: 26 d, range: 5-84 d). All these patients were initially managed per the BOA Standards for Trauma guidelines[7] for open fractures.

In our study, four out of five Type III open fractures required multiple operations due to wound complications. These results are similar to the meta-analysis by Kortram *et al*[17] who described the Gustilo-Anderson classification Type III open fracture as a statistically significant risk factor for developing infectious complications. Thangarajah *et al*[18] showed SSI after fixation to be higher in patients with bimalleolar fractures. However, our study did not show any such relationship. We found that two out of four trimalleolar ankle fractures had a primary closure at the initial operation, while three unimalleolar ankle fractures required multiple operations due to wound complications.

Forty-five percent of patients presenting with an open bimalleolar fracture had definite fixation and primary closure.

The outcome and complication rates after an open ankle fracture dislocation are multifactorial. Factors include multiple comorbidities, the patient's age, and wound contamination. These findings are similar to Frank *et al*'s work on dislocated ankles[19].

Comparing the clinical outcomes of patients who had primary closure *vs* delayed closure, none of the 21 patients with primary closure and definite fixation required a second operation. Eight patients in this group developed superficial wound infections that could be managed with antibiotics. All patients with external fixation as primary fixation required a split skin graft at a later setting. These patients had the longest length of stay in the hospital. Patients requiring VAC dressing to achieve skin closure were at high risk for deep infections and required multiple washouts in the operating theatre. These findings align with the work done by Ovaska *et al*[15] and Wijendra *et al*[8]. We did not find any influence of the fracture pattern or fixation type on clinical outcomes.

Mortality among patients who are older than 65 with open ankle fractures has been reported at about 23%-27% during the first year postoperatively[16]. The mortality rate in our study was 19% at 12 mo and 57% at 10 years. Patients with multiple comorbidities had poor survival. Patients on anticoagulants or antiplatelets medication or patients with a cardiac

Table 1 Description of clinical features of open ankle fractures in patients > 70 years old

Clinical feature	Number of patients, *n* (%)
1 Mechanism of injury	
Road traffic accident	4 (11)
Falls	33 (89)
2 Classification of ankle injuries[23]	
Unimalleolar	4 (11)
Bimalleolar	29 (78)
Trimalleolar	4 (11)
3 Site of open wound	
Medial	33 (89)
Lateral	1 (3)
Anterior	1 (5)
Medial + lateral + anterior	1 (3)
4 Gustilo-Anderson classification[24]	
Type I	8 (22)
Type II	24 (65)
Type III	5 (13)
5 Joint dislocation at initial assessment	
Yes	32 (86)
No	5 (13)

Table 2 Male *vs* female characteristics, *n* (%)

Gender	Number of patients (*n* = 37)	Open fracture classification	Number of operations	Complications
Male	7 (19)	Type I = 3; Type II = 3; Type III = 1	Range - 1 to 7; Median - 2	Superficial SSI - 2; Deep SSI - 3
Female	30 (81)	Type I = 21; Type II = 5; Type III = 4	Range - 1 to 9; Median - 2	Superficial SSI - 5; Deep SSI - 6

SSI: Surgical site infections.

Table 3 Type of wounds and joint congruency *vs* type of closure at initial surgical intervention

Type of wound	Total No. of patients (%)	Primary closure (%)	Secondary (%)	Closure
Gustilo-Anderson classification Type I	8 (22)	7 (87)	1 (13)	
Gustilo-Anderson classification Type II	24 (65)	13 (54)	11 (46)	
Gustilo-Anderson classification Type III	5 (13)	1 (20)	4 (80)	
Dislocated joint	32 (86)	20 (62)	12 (37)	
Congruent joint	5 (13)	1 (20)	4 (80)	
Medial wound	33 (89)	19 (57)	14 (42)	
Lateral wound	1 (3)	1 (100)	0	
Anterior wound	2 (5)	0	2 (100)	
Medial + lateral + anterior wound	1 (3)	1 (100)	0	

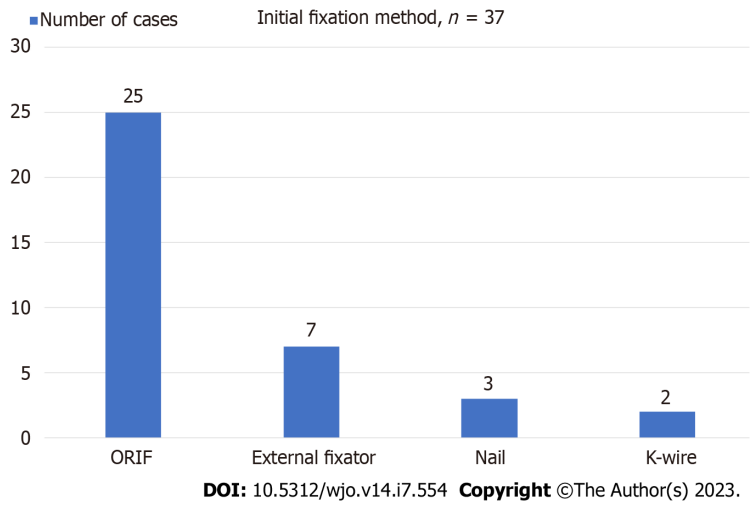
Table 4 Predictors of poor outcome in patients with open ankle fractures > 70 years old

No.	Predictors	Number of patients (%)	*P* value
1	Diabetes mellitus	9 (24)	0.041
2	Anticoagulants/Antiplatelets intake: Warfarin/Apixaban; Aspirin/Clopidogrel; Dual antiplatelet therapy	20 (54); 9 (45); 9 (45); 2 (10)	
3	Cardiac history (IHD, AF)	21 (57)	0.045
4	Chronic kidney disease	12 (32)	
5	Cancer history	8 (22)	0.008
6	History of thromboembolic disease	3 (8)	0.001
7	Steroids intake	9 (24)	0.75

IHD: Ischemic heart disease; AF: Atrial fibrillation.

Table 5 Male *vs* Female predictors of poor outcome (%)

Gender	Diabetes mellitus	Anticoagulants/Antiplatelets intake	Cardiac history	Chronic kidney disease	Cancer history	History of thromboembolic disease	Steroids intake
Male	2 (28)	3 (43)	3 (43)	1 (14)	4 (57)	0	0
Female	7 (23)	17 (57)	18 (60)	11 (37)	4 (13)	3 (10)	9 (30)



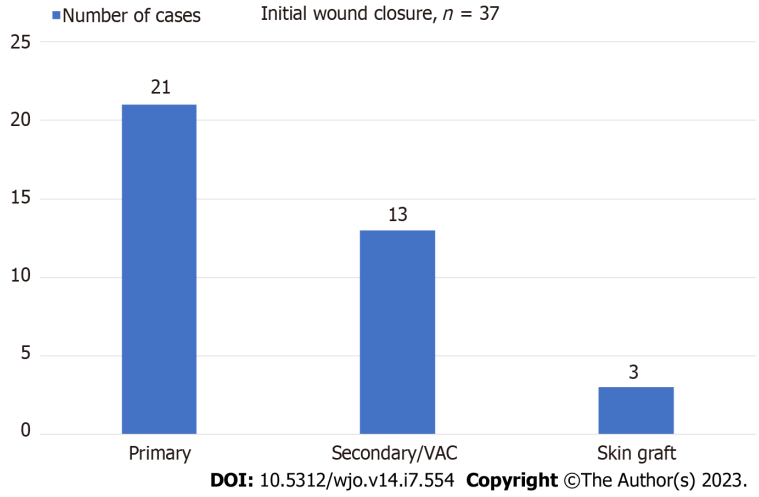
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Figure 1 Surgical Interventions performed in patients > 70 years old presenting with open ankle fractures.

history had a worse outcome. This is likely due to the poor blood supply to the limb, which disrupts the wound-healing process. In our study, 20 patients were on anticoagulation due to a history of ischemic heart disease or atrial fibrillation. Three patients had a history of pulmonary embolism or deep venous thrombosis. These outcomes are similar to the work done by Schermann *et al*[16] and Toole *et al*[20], who also concluded that ischemic heart disease, chronic kidney disease, diabetes, and peripheral vascular disease are variables for mortality in the elderly population. Deep infection (8%) and skin necrosis (14%) were the most common complications after immediate internal fixation in open ankle fractures. Minimal literature is available on the outcomes of definitive treatment in patients with open ankle fractures[16]. In our study, two patients had a thromboembolic event.

Our results are compatible with other studies that suggest that definite fixation in the initial operation is safe, has fewer complications, and leads to a shorter hospital stay[8,21,22]. An external fixator is best employed in patients with inadequate soft tissue coverage.

There are limitations to this study. First, the total number of patients is relatively small. We operated on nearly 2500 ankle fractures over this 22 year period. This is mainly because this study is undertaken in a DGH, not an orthoplastic center. Second, this study has some selection bias. The data was collected from a database, and medical notes were reviewed retrospectively. The database was used logistically in generating theatre lists and acted as an accurate source of data. However, the surgery description may not always have included an open wound, which could have led to underre-



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Figure 2 Soft tissue procedures performed in patients > 70 years old presenting with open ankle fractures. VAC: Vacuum assisted closure.

porting.

CONCLUSION

An open ankle fracture in a patient older than 70 years of age has at least a 20% chance of requiring repeated surgical intervention due to deep SSI. The presence of a cardiac history appears to be the main predictor for wound complications.

ARTICLE HIGHLIGHTS

Research background

There is no data on the clinical outcomes of patients older than 70 admitted with open ankle fractures. This study sets the foundation for future research trials in elderly population.

Research motivation

This is the only study looking at patients older than 70 with open ankle fractures. This study highlights the multiple factors which can predict the poor outcome in this age group with open ankle fractures. There is no consensus on the best management strategy for these injuries in this population.

Research objectives

The overall objective of this study is to look at the predictors of poor clinical outcome in patients older than 70 with open ankle fractures.

Research methods

This is a retrospective observational study performed on 22 years of prospectively collated data from an electronic database in a district general hospital. We used R 4.2.2 (R foundation) to perform statistical analysis.

Research results

We identified 37 patients above 70 years of age admitted over the period of 22 years with an open ankle fractures. Sixteen patients developed deep surgical site infections, with 4 requiring multiple wash outs. Eight patients developed superficial surgical site infections and were managed with antibiotics and regular dressing change. The 10 years mortality rate in this age group was 57%. The presence of a cardiac and stroke history, cancer, or prolonged inpatient stay were found to be the predictors of mortality.

Research conclusions

We concluded that there is a 20% risk of patients above 70 years of age with open ankle fracture requiring repeated surgical intervention. The need for repeated surgical interventions is mainly due to deep Surgical Site Infections. We identified multiple predictors for worse outcome. However, the presence of a cardiac history appears to be the main predictor for wound complications.

Research perspectives

This study sets the foundation for further research trials in patients above 70 years of age.

FOOTNOTES

Author contributions: Zahra W, Seifo M, and Cool P contributed to data collection; Zahra W and Cool P contributed to data analysis; Cool P and Ford D contributed to supervision; Ford D and Okoro T contributed to project idea; Zahra W contributed to writing the manuscript and literature review; Seifo M contributed to review the manuscript; Okoro T contributed to overall supervision.

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Informed consent statement: This study is registered with the local audit department and patients data has been used as per the local trust guidelines. This authorization has no expiration date.

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ORIGINAL ARTICLE

Prospective Study

Internal fixator *vs* external fixator in the management of unstable pelvic ring injuries: A prospective comparative cohort study

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Abstract

BACKGROUND

Reconstruction of the pelvic ring anatomy in unstable anterior pelvic ring injuries is a significant step to reduce the mortality rate associated with these injuries efficiently. There is a debate on using either an anterior subcutaneous pelvis internal fixator (INFIX) or an anterior supra-acetabular external fixator (EXFIX) to manage an unstable anterior pelvic ring fracture.

AIM

To compare the functional and radiological outcomes and complications of INFIX *vs* EXFIX in managing unstable pelvic ring injuries.

METHODS

A prospective cohort study included 54 patients with unstable pelvic ring fractures. The patients were divided into two groups; the INFIX group, in which 30 cases were fixed by INFIX, and the EXFIX group, in which 24 patients were treated by EXFIX. The average age in the EXFIX group was 31.17 years (16-57 years), while in the INFIX group, it was 34.5 years (17-53 years). The study included 20 (66.7%) males and 10 (33.3%) females in the INFIX group and 10 (41.7%) males and 14 (58.3%) females in the EXFIX group. The radiological outcomes were evaluated using Matta and Tornetta's score, and the functional outcomes using the Majeed score.

RESULTS

The results revealed a statistically significant difference between both groups (P = 0.013) regarding radiological outcomes, according to Matta and Tornetta's score in favor of the INFIX group. Sitting, standing, and walking abilities were measured at a 3-mo follow-up visit using Majeed score modules. It was significantly better

among the INFIX group than the EXFIX group in all three modules. At the final follow-up, both groups had no statistically significant difference according to the Majeed score; 92.35 in the INFIX group and 90.99 in the EXFIX group (P = 0.513). A lower surgical site infection rate was noticed in the INFIX group (P = 0.007).

CONCLUSION

Anterior subcutaneous pelvis INFIX is associated with better radiological outcomes and a lower infection rate than anterior supra-acetabular EXFIX in managing patients with unstable anterior pelvic ring fractures.

Key Words: Internal fixator; External fixator; Unstable; Anterior; Pelvic; Injuries

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Core Tip: Reconstruction of the pelvic ring anatomy in unstable anterior pelvic ring injures is considered to be a great step to efficiently reduce the mortality rate associated with these types of injures. There is a debate on the use of either anterior subcutaneous pelvis internal fixator (INFIX) or anterior supra-acetabular external fixator (EXFIX) in the management of anterior unstable pelvic ring fracture. This study aimed to compare the functional, radiological outcomes as well as complications of INFIX *vs* EXFIX in management of unstable pelvic ring injuries. This study showed that anterior subcutaneous pelvis INFIX is associated with better radiological outcome and less rate of infection than anterior supra-acetabular EXFIX in management of patients with anterior unstable pelvic ring fractures.

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INTRODUCTION

Unstable pelvic fractures represent a complex pathology that is often life-threatening and associated with significant morbidity[1]. Although stabilization of the injured pelvis is sustained by posterior ring fixation, concurrent anterior stabilization significantly improves biomechanical stability as the anterior ring provides about 30% of the pelvic stability [2,3].

The management of anterior ring injuries is still a matter of debate. Open reduction and internal fixation using plates and screws have been traditionally prescribed. While this has proven biomechanically superior for pure ligamentous disruption of the symphysis[4], it has the disadvantage of extensive soft tissue dissection, particularly when used for proximal ramus fractures[5].

Percutaneous external fixation in unstable pelvic ring injuries has also been used as an emergency treatment and a method for definitive fixation, which can be left in place until the consolidation of the injuries. This technique aims to stabilize anterior injuries of the pelvic ring, with posterior lesions being treated as required[6,7].

The two primary technical modalities for external fixation of the anterior pelvic ring are the iliac crest and supra-acetabular routes.

The main advantage of choosing the iliac crest route is its fast application without fluoroscopic imaging. However, iliac crest frames are more likely to be associated with primary or secondary reduction failure, particularly in obese patients [8]. In contrast to the iliac crest frame, supra-acetabular pins provide a large corridor of excellent quality bone stock, which allows for a solid purchase of a single Schanz pin; however, it needs fluoroscopically guided pin placement. This technique requires high expertise to find the perfect corridor[8].

Anterior pelvic external fixator (EXFIX) has some disadvantages as it can limit patient mobilization, particularly hip flexion and side rolling, and has a high rate of pin-track infection, fixator loosening, and skin problems[9]. To avoid some of these disadvantages associated with traditional external fixation, a subcutaneous anterior pelvic internal fixator (INFIX) was described[10-12].

Technically, in the anterior pelvic INFIX, two pedicle screws are fixed into the ilium and connected to a curved subcutaneous rod. It had been reported that INFIX is associated with less pin tract infection and loosening than the anterior pelvic EXFIX, but transient neuropraxia of the lateral cutaneous nerve of the thigh and discomfort were reported as complications[11,13-15].

This study aimed to compare both fixation methods regarding the radiological quality of fracture reduction, functional outcomes, and rate of complications.

MATERIALS AND METHODS

From December 2018 to December 2021, a prospective comparative cohort study included skeletally mature patients presenting with rotationally and/or vertically unstable pelvic ring fractures (Tile-type B and C) at our level 1 trauma center.

The ethical committee approved the study on December 8, 2018 with the number "N-147-2023". Exclusion criteria included stable pelvic ring fractures (Tile-type A), fractures with anterior injuries in the form of pure ligamentous symphysis pubis injuries, and pathological fractures. Furthermore, patients aged < 16 or > 65 years and those with incomplete follow-up records were also excluded.

Fifty-four patients were divided into two groups: 30 had an INFIX for anterior pelvic stabilization (the INFIX group), while the remaining 24 were treated using a supra-acetabular EXFIX group.

Standard preoperative radiographic evaluation included anteroposterior, inlet, and outlet X-ray views and computed tomography scans of the pelvis with coronal and 3-D reconstruction. Prophylaxis against deep venous thrombosis using low-molecular-weight heparin was started upon admission, stopped 12 h before surgery, and resumed for 28 d post-operation.

Surgical technique

Proper fixation of the posterior pelvic ring injury was performed first, as dictated by the patho-anatomy of the fracture. For both techniques, patients were placed supine on a radiolucent table, and fluoroscopy was adjusted to identify the anterior inferior iliac spine (AIIS) as an osseous entry on the obturator outlet view (teardrop) before starting (Figure 1). In addition, fluoroscopy was used to obtain anteroposterior, inlet, outlet, iliac, and obturator inlet views.

A 3-cm longitudinal incision was then centered over the AIIS. The AIIS is not easily palpable in obese patients but generally lies 3 to 4 cm distal and 2 cm medial to the anterior superior iliac spine.

In the INFIX group, blunt dissection was performed medially to the sartorius and tensor fascia lata muscles to gain access to the AIIS. A starting awl was placed in the middle of the AIIS (the center of the teardrop) and used to open the cortex. Next, a pedicle finder was used to establish a bony tunnel toward the posterior superior iliac spine. The obturator inlet view was utilized to confirm that the tunnel had not penetrated the inner or outer tables of the iliac bone. The iliac oblique view was used to ensure the pedicle finder was clear of the hip joint and greater sciatic notch (Figure 1).

The 6.5-7.3 mm diameter and 70-100 mm length U-shaped-headed polyaxial pedicular screws (local manufacture; EgyFix spinal system: EgyFix, Cairo, Egypt) were inserted bilaterally in supra-acetabular bone. Screw heads were left proud at the level of the sartorial fascia to avoid compression of neuromuscular structures. A subcutaneous 6 mm diameter pre-contoured (short lateral transverse limbs and curved central parts with an anteroinferior bow) connecting rod was maneuvered into the screw heads to connect the screws. The screw caps were then fixed to retain the rod in place (Figure 2). Polyaxial screw heads greatly facilitate rod placement.

In the EXFIX group, a similar approach was used until the AIIS, with the difference of using the interval between the sartorius and tensor fascia lata muscles. 6 mm pins were inserted bilaterally in supra-acetabular bone with an extracorporeal connecting rod system (pins connected to each other by either one or two extracorporeal connecting rods with clamps) (Figure 3).

Reduction of the pelvis was achieved using C-rings, laminar spreaders, compression or distraction using pins in the ASIS, or even injured leg traction, according to the characteristics and morphology of the fracture. The final reduction and fixation device positions were checked with fluoroscopy.

Anteroposterior, inlet, and outlet X-ray views of the pelvis were obtained on the first postoperative day and used to grade reduction quality according to Matta and Tornetta's score[16].

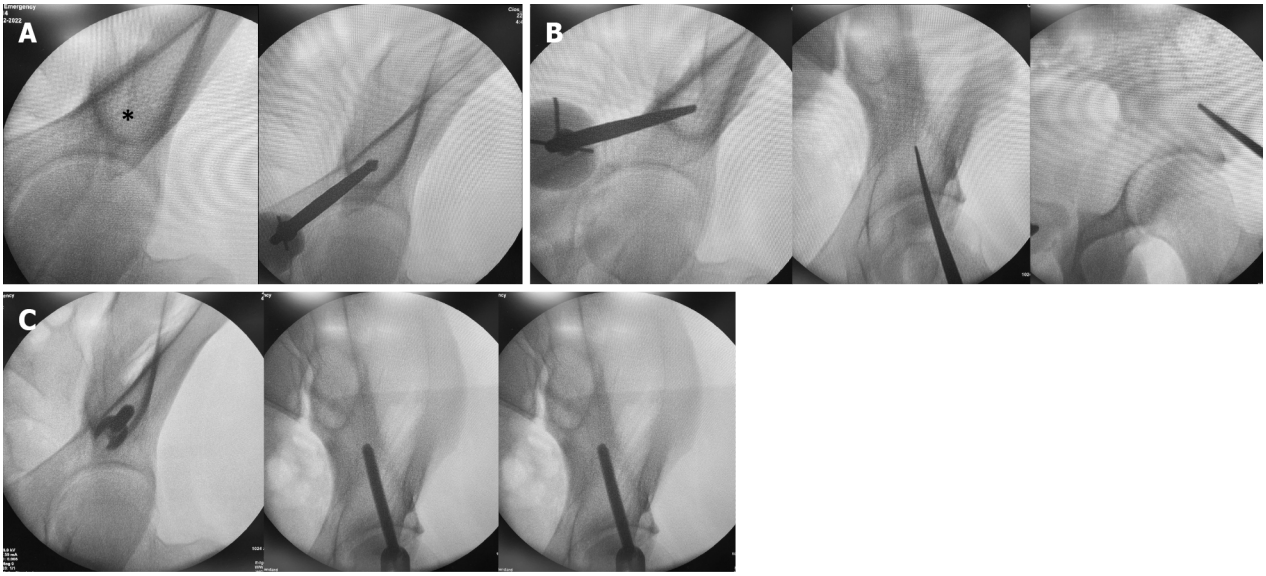
Bed-to-chair mobilization was allowed from the first postoperative day, guided by the injury pattern and associated injuries. Moreover, touch weight-bearing was allowed immediately from the 2nd day up to the 6th week. Partial weight-bearing was allowed from the 6th week. After achieving full union, full-weight bearing was allowed.

Follow-up evaluations were performed at 2 and 6 wk, 3 and 6 mo, and then yearly after the operation. Sitting, standing, and walking abilities were measured at a 3-mo follow-up visit (before implant removal) using Majeed score modules[17]. The total Majeed score[17] was measured among the two groups using its six questionnaire parameters, starting at six months and at the final follow-up.

In both groups, implant removal was scheduled starting in the 12th postoperative week, guided by fracture union and a non-painful straight leg raising test. While removal of the EXFIX was usually an outpatient procedure performed in the clinic, removing the INFIX required a second anesthetic session to remove the implants. This was achieved using the same incisions as implantation.

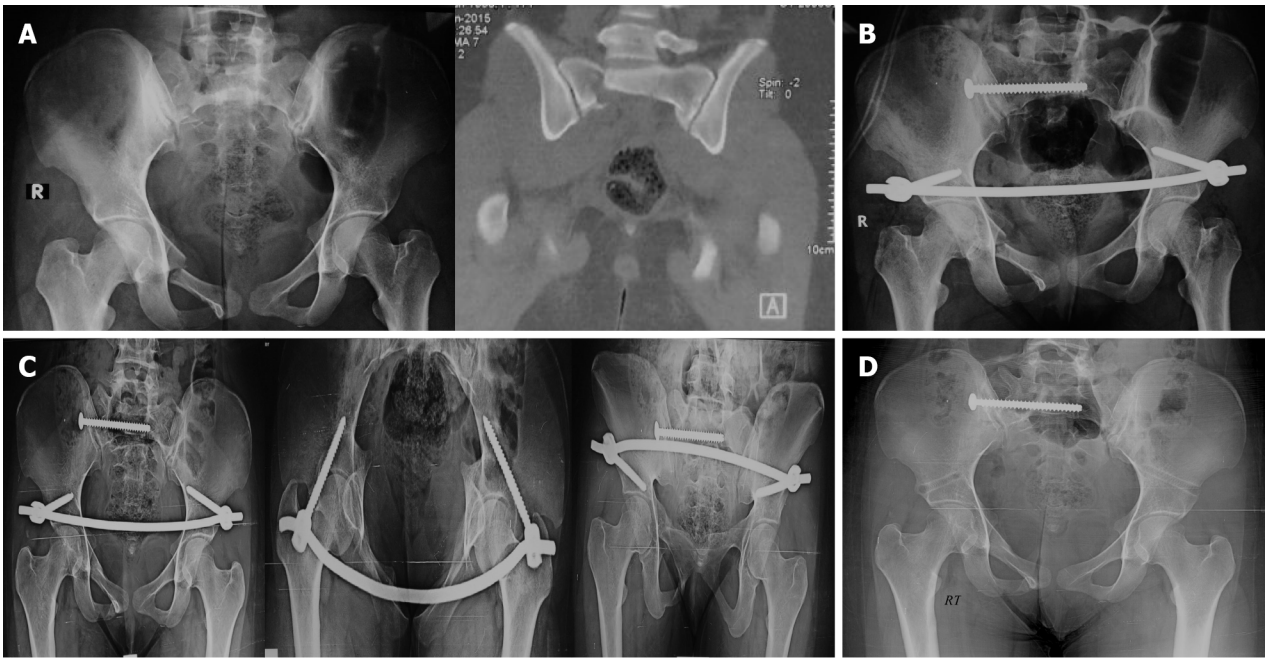
Statistical analysis

Data were analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp.). Qualitative data were described using frequency and percent. Furthermore, quantitative data were described using the range, mean, standard deviation, median, and interquartile range. The Kolmogorov-Smirnov test was used to verify the normality of the distribution. For comparing groups, quantitative variables were analyzed using a student *t*-test or Mann-Whitney test, as appropriate. Chi-square and Fisher's exact tests were used for categorical data. The significance of the obtained results was judged at the 5% level.



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Figure 1 Intraoperative fluroscopy images used to insert the internal fixator screws. A: Obturator outlet view showing the teardrop (*). A sharp starting awl was used to open the cortex for screw insertion; B: Pedicle finder was then used to establish the bony tunnel. Correct screw trajectory was checked in the obturator outlet, obturator inlet and iliac views; C: After screw insertion the three views checked agin to ensure that the screw did not penetrate the cortex and was placed totally intraosseous.



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Figure 2 17-year-old girl sustained a Tile C type pelvic fracture after fall from a height of 6 m. A: Pelvis antero-posterior (AP) X-ray view and sagittal computed tomography scans showing sacral and ramus fractures on the Rt. Side; B: The pelvic fracture was fixed using a fully threaded sacroiliac screw and an internal fixator (INFIX); C: 3-mo follow-up pelvic X-ray (AP, inlet and outlet) views showing complete union. The INFIX was removed 2 mo later in the OR; D: One-year follow-up X-ray. The patient had excellent function with complete return to her prefracture activity level.

RESULTS

Fifty-nine patients were recruited for the study; five were lost during follow-up and were excluded. Fifty-four patients were left for analysis; 30 for the INFIX and 24 for the EXFIX groups. These were 30 (55.6%) males and 24 (44.4%) females with a mean follow-up of 15.4 mo (range: 12-20 mo). The average age in the INFIX group was 34.5 years (range: 17-53 years) while in the EXFIX group, it was 31.2 years (range: 16-57 years). Patients' demographics and fracture characteristics are shown in Table 1. No significant differences in age, gender, associated comorbidities, ASA score, injury mechanism, fracture classification, fracture side, preoperative displacement, operative delay and intra-operative blood loss were

Table 1 Patient's demographics and fracture characteristics

	EXFIX group (*n* = 24)	INFIX group (*n* = 30)	*P* value
Age (years, mean ± SD)	31.2 ± 10.95	34.5 ± 8.35	0.205
Sex			0.066
M, *n* (%)	10 (41.7)	20 (66.7)	
F, *n* (%)	14 (58.3)	10 (33.3)	
Follow-up (months)			0.0468
Range	12-18	12-20	
mean ± SD	14.8 ± 0.8	15.9 ± 2.4	
Mode of trauma			0.873
Falling from height	10	12	
Road traffic accident	13	17	
Train accident	1	0	
Heavy object	0	1	
Tile classification			0.650
B1	2	0	
B2	8	8	
B3	3	7	
C1	9	12	
C2	1	2	
C3	1	1	
ASA score			0.978
ASA1	13	17	
ASA2	7	8	
ASA 3	4	5	

SD: Standard deviation; ASA: American society of anesthesiologists; EXFIX: External fixator; INFIX: Internal fixator.

noticed between both groups. However, operative time was significantly shorter among the EXFIX group (mean = 20.9 ± 2.6 min, range: 16-25 min) compared to the INFIX group (mean = 41.2 ± 7.7 min, range: 28-60 min) ($P < 0.001$) (Table 2). The INFIX group had significantly better quality of fracture reduction scores with 93% of the patients having excellent to good reduction (compared to 70% in the EXFIX group) ($P = 0.022$). All fractures united by an average of 13 wk (range; 10-16 wk) with no significant difference among the two groups ($P = 0.536$). Implants were removed in both groups starting at 3 mo postoperatively. However, patients tended to retain INFIX for longer periods ($P < 0.001$) which was in-part related to better tolerance of the implant as well as logistics related to hospital surgical schedule. Moreover, 2 patients were even reluctant to remove the implant and had them retained for more than 18 mo. Lateral femoral cutaneous nerve (LFCN) injury (22%) and surgical site infection (11%) were the most common complications reported. LFCN injury was equally observed among both the INFIX and the EXFIX groups with a frequency of 23.3 and 20.8 % respectively ($P = 0.826$). There was a transient nerve irritation that usually improved after implant removal except for two patients (one in each group) that experienced no improvement of their symptoms. Nevertheless, these patients had mild to moderate symptoms that were medically controlled and required no further intervention. On the contrary, surgical site infection was significantly higher among the EXFIX group ($P = 0.007$). Eight (33.4%) patients experienced pin-track infections that were classified according to Meléndez and Colón system[18]. Fortunately, five of these were grade I infections that responded well to daily wound dressing. In addition, two patients had grade III infection that needed intravenous antibiotic therapy together with surgical wound debridement during removal of the implants after union was achieved. One patient had a severe surgical site infection (grade V) causing loosening of the pins and very early fixation failure after 2 wk. EXFIX had to be prematurely removed with wound debridement and intravenous antibiotics for two weeks. After infection clearance, revision fixation of the anterior ring fractures was done using a 3.5 mm reconstruction plate and screws. The fracture eventually united with good function at last follow-up. As regards the INFIX group, there was a single case (3.3%) of superficial surgical site infection that was treated by intravenous antibiotics and local wound dressing. No implant loosening, loss of reduction and/or fixation failures were noted for this group. In a trial to assess patients' function before implant removal, sitting, standing, and walking abilities were measured at the 3-mo follow-up

Table 2 Results

	EXFIX group	INFIX group	*P* value
Operative time (minutes)			< 0.001[a]
Range	16-25	28-60	
mean ± SD	20.9 ± 2.6	41.2 ± 7.7	
Quality of reduction (Matta and Torrenta score)			
Excellent	10	14	0.022[a]
Good	7	14	
Fair	6	0	
Poor	1	2	
Duration of fixation till removal (months)			< 0.001[a]
Range	3-4	3-18	
Median (IQR)	3 (3-4)	5 (3-6)	
Function before removal			
Sitting abilities (*n*)			
Painful	0	0	< 0.001[a]
Painful if prolonged or awkward	8	0	
Uncomfortable	15	29	
Free	0	1	
Standing abilities (*n*)			
Bedridden or almost	1	0	0.008[a]
Wheelchair	1	0	
Two crutches	8	2	
Two sticks	4	2	
One stick	6	18	
No sticks	3	8	
Walking abilities (*n*)			
Cannot walk or almost	0	0	0.042[a]
Shuffling small steps	9	4	
Gross limp	6	4	
Moderate limp	5	7	
Slight limp	2	8	
Normal	1	7	
Total Majeed score at the end of the follow-up			
Range	75-100	71-100	0.513
mean ± SD	91 ± 7.8	92.4 ± 7.2	
LFCN affection, *n* (%)	5 (20.8)	7 (23.3)	0.826
Surgical site infection, *n* (%)	8 (33.3)	1 (3.3)	0.007[a]

[a]*P* < 0.05, Statistically significant.

SD: Standard deviation; IQR: Interquartile range; LFCN: Lateral femoral cutaneous nerve; EXFIX: External fixator; INFIX: Internal fixator.

visit using Majeed score modules. INFIX group was found to have significantly better scores in all modules (Table 2). Nevertheless, patients' function at the time of final follow-up showed no significant difference between both groups. The total Majeed score had an average of 92.3 (range: 71-100) and 91 (range: 75-100) for the INFIX and the EXFIX groups, respectively.



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Figure 3 57-year-old male patient sustained a Tile B type pelvic fracture after fall from a 3 meter height on his Rt. side. A: Pelvis antero-posterior (AP) X-ray view and axial computed tomography cuts showing Rt. sacral and bilateral rami fractures. The patient has an associated Rt. pertrochanteric fracture; B: The pelvic fracture was fixed using a fully threaded sacroiliac screw and an external fixator (EXFIX). The pertrochanteric fracture was also fixed at the same session using a long femoral nail; C: 3-mo follow-up pelvic X-ray (AP, inlet and outlet) views showing complete union. The EXFIX was removed in the outpatient clinic on the same day; D: 9-mo follow-up X-ray showing consolidation of the fractures. The patient had excellent function with complete return to his prefracture activity level.

DISCUSSION

Injuries of the pelvic ring represent 3%-8% of all fractures and are usually associated with high-energy trauma[19,20]. Combined anterior and posterior fixation is usually needed to restore pelvic stability; anterior pelvic fixation adds stability and protects the posterior fixation[2,21,22]. Open reduction and plate fixation of anterior ring fractures usually require extension lateral to the hip joint with extensive soft tissue dissection and a high risk of damaging the neurovascular structures[5]. EXFIX and, more recently, INFIX have been used for less invasive surgical options for anterior pelvic fixation.

Both techniques have provided adequate fixation, high fracture union rates, and ultimate good functional recovery[2,5,11,12,23-25]. In our series, except for one early failure due to pin-track infection, all fractures united by an average of 13 wk, and patients had good functions at the final follow-up in both groups.

However, several authors have argued that INFIX has been better tolerated than EXFIX in the postoperative period, particularly in obese patients[12]. Patients could sit, stand, lie prone, and lie on their sides normally. In addition, Vaidya *et al*[11] reported that nursing care for INFIX patients was easier than for EXFIX patients, especially in the intensive care unit setting, with more patient independence.

Nevertheless, these have been largely subjective opinions of treating surgeons and intensive care unit nursing staff. We measured sitting, standing, and walking abilities using Majeed score modules at the 3-mo follow-up visit for a better and more objective assessment of the patients' early functional recovery. The INFIX group showed significantly better scores in all modules. Similarly, Gardner *et al*[12] assessed hip flexion before INFIX removal. They found the mean hip flexion among their patients to be 96° (range: 60-120°), with 60% of them achieving flexion of 90° or more.

Moreover, better implant tolerance is reflected in the fact that patients tended to keep the INFIX for longer periods after fracture union, with some of them even declining the removal surgery. Vaidya *et al*[13] even reported on a patient conceiving twice (she even had normal vaginal deliveries) with the device in place. This observation, however, should be taken cautiously, as INFIX (contrary to EXFIX) requires removal inside the operating room.

Owing to its extracorporeal location, the main disadvantage of EXFIX, besides being cumbersome and limiting patient mobility, is a very high incidence of infection[9,26,27]. This is especially evident in obese patients with larger surgical wounds and greater soft tissue mobility around the transcutaneous pins[11]. This is the main selling point for INFIX. Our study highlights this fact with a highly significant difference between study groups regarding infection rates. Besides, infection with EXFIX is often associated with pin loosening, which may even lead to premature fixation failure and loss of reduction[21,26].

Moreover, EXFIX stability is affected by the distance between the bar and the bone-pin interface. In this regard, INFIX benefits from its subcutaneous location, with improved biomechanics superior to EXFIX in overall stiffness[4]. This might partially explain the better reduction quality achieved with INFIX.

However, failures were reported with INFIX. These were mostly related to the posterior fixation (mostly iliosacral screws) rather than the INFIX[5]. Nevertheless, unfamiliarity with the INFIX technique with improperly secured screw caps was reported to result in a loss of reduction requiring revision[11].

LFCN injury is a known complication with EXFIX using supra-acetabular Schanz pins. However, its incidence is usually low. On the contrary, the reported incidence of cutaneous nerve affection with INFIX was usually higher, reaching up to 55%[5]. This could be explained by the increased nerve irritation caused by the subcutaneous location of the implants, particularly the screw-rod junction. Moreover, excessive lateral rod overhang may be another contributor to nerve irritation. Several authors recommended a more medial soft tissue dissection to protect the nerve[15,21,28]. We believe that the low incidence in our series (comparable between the two groups) could be explained by the technique we adopted using the intermuscular interval between the sartorius and psoas muscles.

Femoral nerve palsy is another devastating condition; however, rare complications were reported to occur after INFIX use for pelvic fractures. Patients usually complain of delayed quadriceps weakness with gait affection in addition to anterior thigh pain and altered sensations[29]. Nevertheless, acute cases of postoperative palsy, sometimes associated with vascular compression, were reported[21,29]. It is thought that this neural affection is usually the result of the too-deep insertion of the pedicle screw heads, leading to nerve compression within the psoas muscle fascia. Despite the more medial approach we used, we had no cases of femoral nerve affection, and we believe this highlights the importance of paying careful attention to the technique and leaving the screw heads and the screw-rod junctions above the sartorial fascia. We did not use routine postoperative sonographic examination. Nevertheless, there have been reports on the safety of the INFIX with no femoral vessel compression and up to 90 degrees of hip flexion[11,15].

One last point is that INFIX is a relatively time-consuming procedure (up to one hour in some reports) requiring full fluoroscopic control[12]. Although there is a learning curve with improvements in the INFIX operative time towards the end of our study, we still found EXFIX to be a significantly more rapid procedure. Similar results were reported by Bi *et al* [21] comparing EXFIX to a modified three-screw INFIX technique. Thus, we strongly recommend against INFIX use for hemodynamically unstable patients. EXFIX is still the recommended technique in emergencies to rapidly reduce pelvic volume and allow for hematoma stabilization. Strengths of the study include being prospective, utilizing a similar approach for all patients, and using the Majeed score to determine the function between fixation and implant removal. Limitations of the current study include a small sample size, heterogenicity of posterior pelvic ring fractures, which may affect the failure rate of the fixation, including cases from a single trauma center, and a lack of randomization of cases in each group.

CONCLUSION

Both INFIX and EXFIX can provide anterior pelvic ring fracture stability to achieve comparable good functional and radiological outcomes. This study suggests that the anterior subcutaneous pelvis INFIX is associated with better radiological outcomes and a lower infection rate than the anterior supra-acetabular EXFIX in the management of patients with unstable anterior pelvic ring fractures. Benefits of INFIX use include easiness of sitting, standing, and walking with the implant and a low incidence of surgical site infection. On the other hand, the operative time of EXFIX is shorter, making it more suitable for emergencies.

ARTICLE HIGHLIGHTS

Research background

Reconstruction of the pelvic ring anatomy in unstable anterior pelvic ring injures is considered to be a great step to efficiently reduce the mortality rate associated with these types of injures. There is a debate on the use of either anterior subcutaneous pelvis internal fixator (INFIX) or anterior supra-acetabular external fixator (EXFIX) in the management of anterior unstable pelvic ring fracture.

Research motivation

This is one of the very few studies comparing the INFIX *vs* EXFIX in management of unstable anterior pelvic ring injuries.

Research objectives

The objective of this study was to compare the functional, radiological outcomes as well as complications of INFIX *vs* EXFIX in management of unstable pelvic ring injuries.

Research methods

A prospective cohort study was carried including 54 patients with unstable pelvic ring fractures. The patients were divided into two groups: INFIX group in which 30 cases were fixed by INFIX and EXFIX group in which the 24 patients were treated by EXFIX. The average age in the EXFIX group was 31.17 years (16-57 years) while in the INFIX group, it was 34.5 years (17-53 years). The study included 20 (66.7%) males and 10 (33.3%) females in the INFIX group and 10 (41.7%) males and 14 (58.3%) females in the EXFIX group. Evaluation of the radiological outcomes was done using Matta and Tornetta score and functional outcomes using Majeed score.

Research results

Fifty nine patients were recruited for the study; five were lost during follow-up. Fifty-four patients were left; 30 for the INFIX and 24 for the EXFIX groups. Operative time was shorter among the EXFIX group compared to the INFIX group ($P < 0.001$). INFIX group had significantly better quality of fracture reduction scores ($P = 0.022$). All fractures united by an average of 13 wk (range; 10-16 wk) ($P = 0.536$). Implants were removed in both groups starting at 3 mo postoperatively. Lateral femoral cutaneous nerve injury and infection were the most common complications reported. Infection was significantly higher among the EXFIX group ($P = 0.007$). Eight (33.4%) patients experienced pin-track infections that were classified according to Meléndez and Colón system. One patient had a severe surgical site infection (grade V) causing loosening of the pins and fixation failure after 2 wk. As regards the INFIX group, there was a single case (3.3%) of superficial infection that was treated by intravenous antibiotics and wound dressing. INFIX group was found to have significantly better Majeed scores in all modules. The total Majeed score had an average of 92.3 and 91 for the INFIX and the EXFIX groups, respectively.

Research conclusions

This study suggests that anterior subcutaneous pelvis INFIX is associated with better radiological outcome and less rate of infection than anterior supra-acetabular EXFIX in management of patients with anterior unstable pelvic ring fractures. Benefits of INFIX use include easiness to sit, stand and walk with the implant and low incidence of surgical site infection. On the other hand, operative time of EXFIX is shorter which makes it more suitable for emergency situations.

Research perspectives

Further research studies that would have more sample size, and randomization of the patients (if feasible) are required.

FOOTNOTES

Author contributions: All authors have contributed to design of the study, surgical intervention, patients assessment and follow up, manuscript writing and editing.

Institutional review board statement: The study was approved by the ethical committee of faculty of medicine, Cairo university on 8/12/2018 with the number "N-147-2023".

Clinical trial registration statement: This is not an RCT it wasn't registered on clinical trial .gov.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: All authors confirm that there is no conflict of interest related to this study.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Randomized Clinical Trial

Instrumented assisted soft tissue mobilization *vs* extracorporeal shock wave therapy in treatment of myofascial pain syndrome

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Abstract

BACKGROUND

Active myofascial trigger points (TrPs) often occur in the upper region of the upper trapezius (UT) muscle. These TrPs can be a significant source of neck, shoulder, and upper back pain and headaches. These TrPs and their related pain and disability can adversely affect an individual's everyday routine functioning, work-related productivity, and general quality of life.

AIM

To investigate the effects of instrument assisted soft tissue mobilization (IASTM) *vs* extracorporeal shock wave therapy (ESWT) on the TrPs of the UT muscle.

METHODS

A randomized, single-blind, comparative clinical study was conducted at the Medical Center of the Egyptian Railway Station in Cairo. Forty patients (28 females and 12 males), aged between 20-years-old and 40-years-old, with active myofascial TrPs in the UT muscle were randomly assigned to two equal groups (A and B). Group A received IASTM, while group B received ESWT. Each group was treated twice weekly for 2 weeks. Both groups received muscle energy technique for the UT muscle. Patients were evaluated twice (pre- and post-treatment) for pain intensity using the visual analogue scale and for pain pressure threshold (PPT) using a pressure algometer.

RESULTS

Comparing the pre- and post-treatment mean values for all variables for group A, there were significant differences in pain intensity for TrP1 and TrP2 (P = 0.0001) and PPT for TrP1 (P = 0.0002) and TrP2 (P = 0.0001). Also, for group B, there were

significant differences between the pre- and post-treatment pain intensity for TrP1 and TrP2 and PPT for TrP1 and TrP2 (P = 0.0001). There were no significant differences between the two groups in the post-treatment mean values of pain intensity for TrP1 (P = 0.9) and TrP2 (P = 0.76) and PPT for TrP1 (P = 0.09) and for TrP2 (P = 0.91).

CONCLUSION
IASTM and ESWT are effective methods for improving pain and PPT in patients with UT muscle TrPs. There is no significant difference between either treatment method.

Key Words: Myofascial trigger points; Upper trapezius muscle; Instrument-assisted soft tissue mobilization; Extracorporeal shock wave therapy; Myofascial pain syndrome

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Core Tip: This is the first study to compare the effects of instrument-assisted soft tissue mobilization (IASTM) *vs* extracorporeal shock wave therapy (ESWT) on trigger points of the upper trapezius muscle in myofascial pain syndrome. The results of the current study revealed no statistically significant differences between the effect of IASTM and ESWT on pain intensity and pain pressure threshold of upper trapezius muscle trigger points. However, both IASTM and ESWT improved pain measures in both groups of patients suffering from myofascial pain syndrome. Based on these results, treatment methods can be selected based on availability, cost, therapist experience, and patient preference.

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INTRODUCTION

Myofascial pain syndrome (MPS) is a complex of sensory, motor, and autonomic symptoms that are caused by myofascial trigger points (MTrPs) "muscle knots"[1]. It is the most potent cause of persistent regional pain[2] that affects all ages[3]. MPS commonly affects the neck and shoulder muscles, with the upper trapezius (UT) being the most involved[4]. MTrPs are hypersensitive, palpable spots involving muscle fibers and fascia[5]. They are classified into two clinical types: active and latent. Active TrPs cause persistent pain at rest and referred pain patterns, while latent TrPs cause pain with direct pressure and movement limitation[1]. Patients with myofascial pain represent a large number of musculoskeletal patients. The estimated overall prevalence of active MTrPs is 46.1% ± 27.4%[6]. It has been estimated that around 85% of patients visiting chronic pain clinics and 30% of patients visiting internal medicine clinics have myofascial pain[7].

MPS can be presented clinically after repetitive muscle microtrauma, while other patients have no precipitating factors. Pain onset of pain may be acute or gradual[8]. A physical examination can detect the existence and type of MTrPs by manual palpation[3,8]. The physical therapy for MPS might include stretching exercises, ultrasound[9], massage[10], kinesio tape[11], dry needling (an invasive technique)[12], and muscle energy technique (MET)[13].

Instrument-assisted soft tissue mobilization (IASTM) is one of the techniques used to treat MPS. After an injury, inflammation and proliferation of inflammatory cells occur, during which fibrosis and scar tissue formation in the injured soft tissue may occur[14]. These changes reduce tissue elasticity and cause adhesions, diminishing soft tissue function and pain[15]. In particular, scar tissue limits perfusion to the injured soft tissue, restricting oxygen and nutrients supply and interfering with collagen synthesis and tissue regeneration, which may then cause incomplete functional recovery[16,17] and increase the risk of reinjury[15]. IASTM creates microtrauma to scar tissue or myofascial adhesions using a specially designed instrument to reduce pain and improve range of motion and function. Additionally, it minimizes the stress on the practitioner's hand and the effort he has to put forth[18].

Extracorporeal shock wave therapy (ESWT) produces mechanical energy through high-pressure air. The mechanical signal is converted into biochemical or molecular biological signals in the tissues by propagating as a longitudinal wave. This mechanism is called mechanotransduction. It has been proven that ESWT has a pain-relieving effect described in plantar fasciitis[19], calcifying tendinitis[20], and MPS[21,22]. ESWT has no serious side effects besides minimal pain, bruising, and swelling, which can be significant after treatment[23].

Currently, no study has compared the effects of IASTM and ESWT in treating myofascial TrPs of the UT muscle in patients with MPS. We hypothesized that there was no significant difference between the two methods on pain and pain pressure threshold (PPT).

MATERIALS AND METHODS

This study was conducted at the outpatient physical therapy clinic, Medical Center of the Egyptian Railway Station. It was registered at Cairo University and approved by the Faculty of Physical Therapy, Research Ethics Committee (P.T.REC/012/003180).

Study design

A single-blinded comparative clinical study.

Sample size calculation

The sample size was calculated using the MedCalc® version 12.3.0.0 program "Ostend, Belgium" and was 38 cases, according to a 95% confidence interval and the power of the study 80% with 5% error. Assuming a drop-out ratio of 5%, the sample size was 20 cases in each group.

Patients

Forty male and female patients were referred by orthopedic surgeons with a diagnosis of MPS in the neck with active TrPs of the UT muscle. Their ages ranged from 20 years to 40 years[24]. They were randomly assigned into two equal experimental groups, using a simple randomization method (patients enrolled consecutively in group A or B). Group A (n = 20) received ISTAM on TrPs of the UT muscle (TrP1 and TrP2), and group B (n = 20) received ESWT on TrPs of the UT muscle (TrP1 and TrP2). Each patient signed an informed consent before starting the study.

All patients received four treatment sessions, twice per week over 2 weeks[25]. Both groups received a post isometric relaxation technique for the UT muscle. Patients were evaluated before treatment and 2 days after treatment for neck pain intensity and PPT of the UT TrPs (TrP1 and TrP2).

Patients were included if they had MTrPs of unilateral UT muscle (TrP1 and TrP2) that exhibit the following characteristics[26,27]: (1) A taut band within a muscle; (2) Extreme tenderness at a point within the taut band; (3) Reproduction of the patient's pain; (4) Referred pain; (5) Eliciting a localized twitch response; (6) Muscle weakness; (7) Limited range of motion; and (8) Autonomic signs (erythema, lacrimation, pilo-erection). To make a diagnosis, the first three characteristics must be present[26,27].

Patients with malignancy, cervical spine fractures, cervical radiculopathy, myelopathy, or vascular syndromes (such as vertebrobasilar insufficiency) were excluded[28]. Also, patients were excluded if they received any other treatment, in the form of physical therapy or medication, that would interfere with the results of this study and if they exhibited any contraindication for IASTM and ESWT[29].

Assessment procedures

All patients were evaluated before and 2 days after treatment by a research assistant who was unaware of the treatment program given to each patient. The patients were positioned comfortably in a prone position on a plinth with sufficient exposure to the UT muscle. The head was slightly tilted ipsilateral to the side being palpated. Using a pincer grasp, the free margin of the UT fibers was held firmly. Once the palpable band was located, it would be firmly rolled between fingers and thumb. Local tenderness and referral pattern were noted. The process was carried out for two points (TrP1 and TrP2). TrP1 was palpated in the angle between the neck and shoulder[30], while TrP2 was palpated halfway between the spinous processes of the C5/C6 vertebrae and the acromion process of the scapula using a small pincer grip[31]. Manual palpation of the muscle is the most reliable method of diagnosing a MTrP[32].

Assessment of pain intensity using the visual analogue scale

The visual analog scale (VAS) is a self-reported pain measurement scale. It consists of a 10 cm long line, and the extremes of the line are labeled as no pain and most severe pain. It is valid, reliable, and suitable for clinical practice[33]. The patient was asked to mark a point on the VAS, and then this number was taken for statistical analysis[34].

Assessment of PPT using pressure algometer

The pressure algometer is a valid and reliable tool to determine PPT. An algometer is a force gauge with a spring-operated plunger. The gauge is attached to a short metal pole with a round 1 cm rubber tip. The device is calibrated in kilograms of pressure per centimeter squared (kg/cm^2). The gauge has a range of 0 to 10 kg/cm^2. Once a measurement was recorded, the device was reset to 0 to take another measurement[21,35].

The research assistant positioned the tip of the algometer (Greenwich, CT, United States) at the TrP and increased the pressure by 1 kg/s. When the patient indicated discomfort, the pressure value was recorded in kg/cm^2. The procedure was repeated three times at 60 s intervals, and the mean of these measurements was taken for statistical analysis.

Treatment procedures

Treatment procedures for group A: This group of patients received IASTM with an M2T blade. Upon a table in front of the patient, his or her forehead resting on his or her forearm. Before treatment, a lubricant (petroleum jelly) was applied to the skin around the neck area, and the M2T blade was cleaned with an alcohol pad.

Following the localization of TrP1 and TrP2, the M2T blade was positioned at a 45° angle. For about 3 min, slow strokes were applied along the muscle from its origin to its insertion without discomfort or pain. The strokes were longitudinally parallel to the muscle fibers. If patients experienced burning sensations after the session, they were instructed to apply an ice pack to the treated area[24].

Treatment procedures for group B: Patients in this group received ESWT (Unify Elekromedizin, Germany, SN:3012095,2012). All aspects of the procedure were explained to the patient before treatment. The patients were informed that the shockwave machine produces intense pressure when applied and creates considerable noise. The patient requested to speak with the researcher if the intensity was too uncomfortable.

The patient was positioned on a plinth. The treatment area was sufficiently exposed, and a coupling gel was applied. The shockwave unit was calibrated to the correct therapeutic settings. For MTrPs, the settings were 2.0 bars at 15 Hz for 2000 pulses[22,36]. The handheld transmitter head was applied to the area to be treated. Slight pressure was applied with circular movements to treat the TrP sufficiently. The shockwave unit automatically stopped the treatment once all 2000 pulses were delivered. Any residue from the coupling gel was wiped off with a paper towel[22,36].

Post-isometric relaxation technique for UT muscle

All patients in both groups received the post-isometric relaxation technique for the UT muscle. The patient was instructed to lie in a supine position with the cervical spine in opposite lateral flexion to the affected side to lengthen the UT muscle fibers. Sub-maximal resistance was applied to the UT muscle for about 5 s, followed by 3 s of relaxation, and then stretching the UT muscle for 15-30 s to reach a new barrier. This maneuver was repeated four times in each session[37].

Statistical analysis

This study's data analysis used the SPSS version 26 for Windows (IBM Corp, Armonk, NY, United State). The data distribution was tested *via* the Shapiro-Wilk test. Independent *t*-test and χ^2 test were used to compare demographic data between both groups. A paired *t*-test was used to compare pre- and post-treatment mean values of all variables within both groups. For comparing all the dependent variables pre- and post-treatment between both groups we used an independent *t*-test. The significance level of a *P* value of ≤ 0.05 was considered statistically significant using 95% confidence intervals.

RESULTS

Descriptive statistics of demographic data for all patients in both groups

The data showed that each dependent variable was normally distributed and did not violate the parametric assumption. Using an independent *t*-test, there were no significant differences between patients in both groups in age ($P = 0.16$), weight ($P = 0.83$), height ($P = 0.8$), and body mass index ($P = 0.34$). The distribution of males and females in group A was 20% and 80%, respectively. In group B, there was 40% males and 60% females. Comparing the sex distribution for all patients in both groups using the χ^2 test, there were no significant differences ($P = 0.17$) (Table 1).

Pre-treatment between group comparisons of all variables in both groups

Comparing the pre-treatment mean values between both groups using the independent *t*-test, there were no significant differences in pain intensity for TrP1 ($P = 0.55$), pain intensity for TrP2 ($P = 0.94$), PPT for TrP1 ($P = 0.18$), and PPT for TrP2 ($P = 0.58$) (Table 2).

Post-treatment between group comparisons of all variables in both groups

Comparing the post-treatment mean values between both groups using an independent *t*-test, there were no significant differences in pain intensity for TrP1 ($P = 0.9$), pain intensity for TrP2 ($P = 0.76$), PPT for TrP1 ($P = 0.09$), and PPT for TrP2 ($P = 0.91$) (Table 2).

Within group pre-treatment and post-treatment comparison of all variables in group A

Comparing the pre-treatment and post-treatment mean values using paired *t*-test for all variables in group A, there were significant differences in pain intensity for TrP1 ($P = 0.0001$), pain intensity for TrP2 ($P = 0.0001$), PPT for TrP1 ($P = 0.0002$), and PPT for TrP2 ($P = 0.0001$) (Table 3).

Within group pre-treatment and post-treatment comparison of all variables in group B

Comparing the pre-treatment and post-treatment mean values using a paired *t*-test for all variables in group B, there were significant differences in pain intensity for TrP1 ($P = 0.0001$), pain intensity for TrP2 ($P = 0.0001$), PPT for TrP1 ($P = 0.0001$), and PPT for TrP2 ($P = 0.0001$) (Table 3).

DISCUSSION

This is the first study to compare the effects of IASTM *vs* ESWT on TrPs of the UT muscle in MPS. The current study revealed no statistical differences between IASTM and ESWT on pain intensity and PPT of UT muscle TrPs. However, IASTM or ESWT improved pain measures in both groups of patients suffering from MPS.

Table 1 Descriptive statistics for the mean values of age, weight, height, body mass index, and sex distribution of all patients in both groups

	Group A	Group B	*t* value	*P* value	Significance
	n = 20	*n* = 20			
Age in yr	31.20 ± 4.15	29.10 ± 5.12	1.43	0.16	NS
Weight	72.55 ± 7.65	73.35 ± 14.23	-0.22	0.83	NS
Height	168.40 ± 5.90	169.05 ± 9.83	-0.25	0.80	NS
BMI in kg/m^2	25.50 ± 2.25	24.80 ± 2.29	0.98	0.34	NS
Sex distribution	20% male and 80% female	40% male and 60% female	χ^2 = 1.91	0.17	NS

NS: Non-significant; BMI: Body mass index. Group A: Patients treated with instrument assisted soft tissue mobilization; Group B: Patients treated with extracorporeal shock wave therapy.

Table 2 Independent *t*-test for comparison of pre- and post-treatment mean values between both groups

Treatment period	Group A	Group B	*t* value	*P* value	Significance
	n = 20	*n* = 20			
Pre-treatment					
Pain intensity for TrP1	6.05 ± 1.90	6.38 ± 1.50	-0.61	0.55	NS
Pain intensity for TrP2	7.15 ± 1.90	7.20 ± 1.56	-0.08	0.94	NS
PPT for TrP1	17.08 ± 4.99	14.83 ± 5.31	1.38	0.18	NS
PPT for TrP2	15.72 ± 5.75	14.68 ± 6.13	0.55	0.58	NS
Post-treatment					
Pain intensity for TrP1	3.75 ± 1.69	3.82 ± 1.53	-0.13	0.9	NS
Pain intensity for TrP2	4.06 ± 1.45	3.93 ± 1.22	0.31	0.76	NS
PPT for TrP1	30.75 ± 18.12	22.82 ± 9.55	1.7	0.09	NS
PPT for TrP2	27.93 ± 9.90	28.29 ± 10.08	-0.11	0.91	NS

Data are presented as mean ± SD unless otherwise indicated. NS: Non-significant; PPT: Pressure pain threshold; TrP: Trigger point. Group A: Patients treated with instrument assisted soft tissue mobilization; Group B: Patients treated with extracorporeal shock wave therapy.

Effects of IASTM on pain intensity and PPT

The results of the current study confirmed the results of previous studies. This proved the effectiveness of IASTM in decreasing pain intensity and increasing PPT in MTrP in the UT muscle. El-Hafez *et al*[25] showed a significant difference between pre-treatment and post-treatment within the group of patients treated with IASTM twice a week for 4 weeks, regarding pain intensity and PPT. In like manner, other studies showed that using IASTM twice a week for 2 weeks, significantly improved pain and PPT of active MTrPs of the UT muscle[38,39]. Also, IASTM induced thinning of the UT muscle when applied for six sessions at 1-day intervals[38].

Moreover, after one session, IASTM induced immediate significant results concerning decreasing the resting pain[40, 41] and increasing the pain threshold in the neck and lower back[40]. Erden *et al*[42] stated that adding IASTM to the conventional physical therapy program for 8 wk was superior to conventional physical therapy alone for patients with myofascial pain with upper and mid back TrPs in the improvement of pain intensity and PPT. The effect of IASTM on pain could be explained by increasing blood flow, which removes pain substrates[43-45]. Furthermore, IASTM stimulates the A-beta sensory fibers and blocks the A-delta and C-fibers. As for the "gate control theory", this blocks substance P from pain receptors *via* presynaptic inhibition at the dorsal horn[46]. Also, it improves collagen fiber bundle formation and orientation, which decreases cell matrix adhesions within the MTrP, which explains the increased PPT after using IASTM[47].

Effect of ESWT on pain intensity and PPT

In the same manner, the group that received ESWT showed a significant improvement in pain and PPT after four sessions of treatment. This was in agreement with previous evidence investigating the effect of ESWT on MTrPs of the UT muscle in MPS cases.

Table 3 Paired *t*-test comparison for pre- and post-treatment mean values of all variables for all group (A and B) patients

Group	Pre-treatment	Post-treatment	*t* value	*P* value	Significance
	n = 20	*n* = 20			
Group A					
Pain intensity for TrP1	6.05 ± 1.90	3.75 ± 1.69	6.55	0.0001[1]	HS
Pain intensity for TrP2	7.15 ± 1.90	4.06 ± 1.45	8.32	0.0001[1]	HS
PPT for TrP1	17.08 ± 4.99	30.75 ± 18.12	-3.51	0.002[1]	Sig
PPT for TrP2	15.72 ± 5.75	27.93 ± 9.90	-6.97	0.0001[1]	HS
Group B					
Pain intensity for TrP1	6.38 ± 1.5	3.82 ± 1.53	9.56	0.0001[1]	HS
Pain intensity for TrP2	7.20 ± 1.56	3.93 ± 1.22	12.82	0.0001[1]	HS
PPT for TrP1	14.83 ± 5.31	22.82 ± 9.55	-5.86	0.0001[1]	HS
PPT for TrP2	14.68 ± 6.13	28.29 ± 10.08	-7.03	0.0001[1]	HS

Data are presented as mean ± SD unless otherwise indicated.

[1]Statistically significant.

HS: Highly significant; PPT: Pressure pain threshold; Sig: Significance; TrP: Trigger point. Group A: Patients treated with instrument assisted soft tissue mobilization; Group B: Patients treated with extracorporeal shock wave therapy.

A recent systematic review and meta-analysis showed that ESWT significantly affects pain reduction compared with sham ESWT or ultrasound treatment. However, conventional treatments, such as dry needling, TrP injection, and laser therapy, have no significant differences in pain intensity and neck disability index[48]. Taheri *et al*[49] and Jeon *et al*[50] confirmed that three sessions of ESWT had a comparable effect with laser therapy[49], TENS, and TrP injection[50] for relieving pain in patients with MPS. Choi *et al*[51] reported that combining ESWT with the myofascial release technique improved in pain intensity and PPT more than myofascial release alone.

In addition, Lee and Han[52] compared the effects of ESWT, proprioceptive neuromuscular facilitation, and TrP injection on pain intensity and PPT in patients with UT muscle MPS. In line with the findings of the current study, VAS and PPT showed statistically significant differences among patients in the ESWT group. Ji *et al*[53] examined the VAS and PPT in the UT before and after 4 treatment sessions of ESWT. It showed a significant increase in PPT and a significant decrease in VAS. Moreover, in patients with non-specific neck pain, pain intensity and PPT were significantly improved after applying three ESWT sessions performed once a week for 3 weeks, on the UT muscle TrP[54]. On the other hand, Lee *et al*[55] revealed that two treatment sessions of ESWT in patients with MTrPs in the trapezius muscle significantly reduced the amount of pain, although there was no change in the PPT. Gür *et al*[56] reported that one session and three sessions once a week of low-energy ESWT revealed statistically significant improvements in pain, quality of life, and anxiety scores in patients with MPS. Additionally, the three sessions produced more substantial efficacy. Also, Király *et al* [23] proved the long-term effect of ESWT and reported improvement of resting pain and pain tolerance at the week 3 and week 15 follow-up in patients with MPS who received ESWT at the TrP of UT.

A analgesic effect of shock waves may be explained by increased blood and nutrients flow to the MTrPs, selective destruction of unmyelinated nerve fibers (C nerve fibers)[57], reduced substance P[58], and increased nitric oxide release [59]. The second possible mechanism is hyperstimulation, indicating that a shock wave triggers the release of endorphins and other analgesic molecules by activating the descending inhibitory system[60-62].

Recent studies on animal models focusing on the peripheral nervous system after ESWT application to the musculoskeletal system *in vivo* pointed specifically to reducing two substances involved in pain perception: calcitonin gene-related peptide and substance P[58,63,64]. The results of these mechanisms of action have resulted in ESWT being well used in treating myofascial pain.

There were some limitations to this study because of the study design and nature of tools. There is no "placebo" group, and the evidence is insufficient to disprove that either the patient's expectation or interaction with the physiotherapist is the cause of all the improvements after both treatments. In addition, this study did not include a follow-up assessment. IASTM and ESWT are performed with MET, which may influence the outcome. Future studies will be required to study the effect of applying IASTM and ESWT without other techniques that may influence the outcome.

CONCLUSION

Patients with MPS benefit from IASTM and ESWT combined with MET to reduce pain and improve PPT.

ARTICLE HIGHLIGHTS

Research background

Active myofascial trigger points (MTrPs), commonly occurring in the upper region of the upper trapezius (UT), can be a significant source of neck, shoulder, upper back, and headache pain. This can negatively impact daily routine functioning, work-related productivity, and overall quality of life. With the rising prevalence of musculoskeletal pain and disability, it is critical to identify the most effective interventions to improve patient outcomes. This will reduce the societal burden.

Research motivation

Instrument assisted soft tissue mobilization (IASTM) and extracorporeal shock wave therapy (ESWT) are two treatment methods for MTrPs. Each method was tested independently and compared to another modality. To the author's knowledge, this is the first study to compare IASTM *vs* ESWT on MTrPs of the UT.

Research objectives

This study compared the effects of IASTM *vs* ESWT in patients with UT MTrPs. These findings are critical in guiding the therapist in selecting treatment methods based on availability, cost, therapist experience, and patient preference.

Research methods

Forty patients (28 females and 12 males) with active TrP in the UT muscle were randomly assigned to one of two equal groups (A and B). Group A received IASTM, while group B received ESWT. Each group received treatment twice a week for 2 weeks. Both groups received muscle energy technique for the UT muscle. Patients were assessed twice (pre-treatment and post-treatment) for pain intensity using the visual analog scale and pain pressure threshold (PPT) using a pressure algometer. A paired *t*-test was used to compare the pre-treatment and post-treatment mean values of all variables within both groups. For comparing all the dependent variables pre-treatment and post-treatment between both groups, we used an independent *t*-test. The significance level of a *P* value of ≤ 0.05 was considered statistically significant with a 95% confidence interval.

Research results

In group A (treated with IASTM) as well as in group B (treated with ESWT), there were significant differences between pre-treatment and post-treatment for pain intensity of TrP1 and TrP2 ($P = 0.0001$) and PPT for TrP1 and TrP2 ($P = 0.0002$ and $P = 0.0001$, respectively). There were no significant differences for pain intensity for TrP1 ($P = 0.9$), pain intensity for TrP2 ($P = 0.76$), PPT for TrP1 ($P = 0.09$), and PPT for TrP2 ($P = 0.91$) when comparing the post-treatment mean values between both groups.

Research conclusions

IASTM and ESWT are effective methods for treating pain and PPT in patients with UT muscle TrPs. However, there is no statistically significant difference between the two methods.

Research perspectives

Future research will be required to investigate the effect of only using IASTM and ESWT without other techniques that may influence the outcome.

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FOOTNOTES

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CASE REPORT

Isolated lateral leg compartment syndrome: A case report

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Abstract

BACKGROUND

Acute leg compartment syndrome is a well-known orthopedic emergency associated with potentially devastating consequences if not treated immediately. Multiple compartments are usually involved with a clear history of trauma and classic symptoms and signs. However, isolated lateral leg compartment syndrome is relatively rare and is often misdiagnosed due to the atypical presentation of no trauma and the lack of pathognomonic signs.

CASE SUMMARY

A 31-year-old male patient presented to our emergency room with excruciating left calf pain and inability to mobilize one-day after participating in a football match despite no clear history of preceding trauma. The patient went to another hospital before presenting to us where he was diagnosed to have a soft tissue injury and was discharged home on simple analgesics. On clinical examination, the left leg showed a tense lateral compartment with severe tenderness. The pain was aggravated by dorsiflexion and ankle inversion. Neurovascular examination of the limb was normal. We suspected a compartment syndrome but as the presentation was atypical and an magnetic resonance imaging (MRI) was readily available in our institution, we immediately performed an MRI and this confirmed a large hematoma in the lateral compartment with a possible partial proximal peroneus longus muscle tear. The patient was taken immediately for an emergency open fasciotomy. The patient is now 18 mo postoperatively having recovered completely and engages fully in sports with no restrictions.

CONCLUSION

Atypical presentation due to the lack of pathognomonic signs makes the diagnosis of isolated lateral leg compartment syndrome difficult. Pain on passive inversion

and dorsiflexion and weak active eversion may be suggested as sensitive signs.

Key Words: Isolated; Lateral compartment; Peroneal compartment; Atraumatic compartment syndrome; Case report

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Core Tip: Atraumatic isolated lateral leg compartment syndrome is rare and constitutes a diagnostic challenge due to the atypical presentation and lack of pathognomonic signs. It should be considered even in the context of atraumatic events. Pain on passive inversion and dorsiflexion and weak active eversion may be suggested as sensitive signs. Drop foot is a delayed presentation as a result of deep peroneal nerve involvement. A high index of clinical suspicion is the key to early diagnosis and timely surgical intervention.

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INTRODUCTION

Compartment syndrome of the leg is a well-known orthopedic emergency. It usually involves the anterior compartment of the leg or multiple compartments. However, isolated lateral (also known as peroneal) leg compartment syndrome is rare and may be caused by a traumatic or atraumatic (exertional) event[1,2]. In these cases, the peroneus longus muscle is typically affected and the accompanying hematoma is presumed to be the reason for the intracompartmental pressure rise[3]. Early diagnosis can be challenging especially in atraumatic events due to the atypical presentation. Hereby, we present a case of an isolated lateral leg compartment syndrome in the context of an atraumatic event. Additionally, we performed a comprehensive review of all reported cases of acute atraumatic isolated lateral leg compartment syndrome.

CASE PRESENTATION

Chief complaints

A 31-year-old male patient with no past medical history presented to our emergency room (ER) with severe left calf pain and inability to walk after participating in a football game the preceding day despite no clear history of trauma.

History of present illness

The patient went to another hospital on the same day of the injury and was diagnosed to have a soft tissue injury and got reassured and discharged home on simple analgesics. The following day, the patient presented to our hospital as the pain was worsening and became intolerable.

Physical examination

On examination, the patient was in excruciating pain, his vitals were normal, and his left leg showed a tense lateral compartment with severe tenderness. The overlying skin was normal, and no bullae were seen. The pain was aggravated by dorsiflexion and ankle inversion. Distal pulses were intact, and the neurological status was normal.

Laboratory examinations

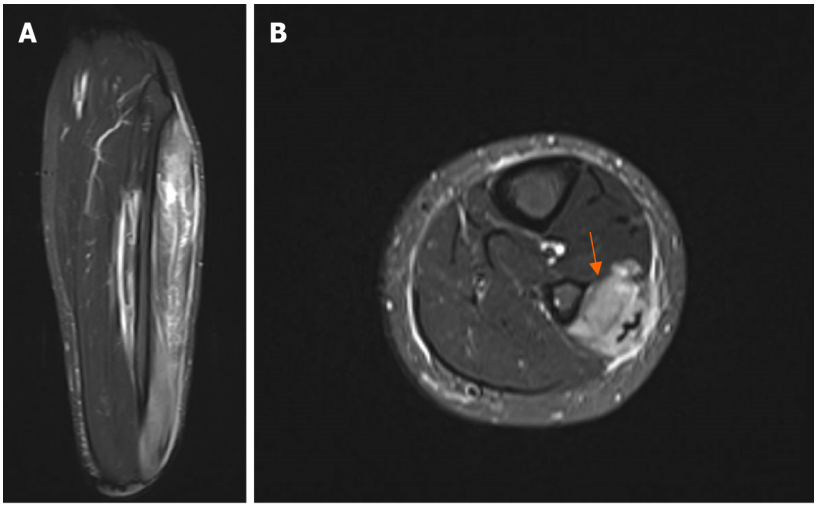
Laboratory tests were normal.

Imaging examinations

X-rays were normal. As magnetic resonance imaging (MRI) is readily available at our institution, it was performed immediately without any delay and showed diffuse abnormal signals over the lateral compartment indicating a large hematoma in the lateral compartment with a possible partial proximal peroneus longus muscle tear (Figure 1).

FINAL DIAGNOSIS

Acute isolated lateral leg compartment syndrome was diagnosed based on the clinical picture and the MRI findings which was further confirmed intraoperatively.



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Figure 1 Magnetic resonance imaging of the left leg. A: Coronal view demonstrating diffuse abnormal signals over the left lateral compartment; B: Axial view, showing possible proximal partial tear of the peroneal muscle as indicated by the orange arrow.

TREATMENT

The patient was taken directly to the operating room (OR) for an emergency open fasciotomy. In the OR, a longitudinal incision over the lateral compartment was made extending from the fibula down to the lateral malleolus. Immediate relief and bulging of the underlying muscles which were under significant pressure was noted. Most of the hematoma was seen at the proximal and distal thirds of the compartment and surrounding the peroneus longus muscle but there was no active bleeding seen. The entire compartment was successfully decompressed. The muscles appeared dusky in color and edematous and were slow to respond to stimulation with diathermy initially but towards the end of the operation, they recovered fully with no evidence of muscle damage or necrosis. A washout of the entire area was performed. As the skin was healthy and other compartments were not affected, the skin edges were approximated and the wound closed primarily but avoiding any tight closure. The patient recovered well and was discharged home the following day after the operation.

OUTCOME AND FOLLOW-UP

The patient is now 18 mo postoperatively having recovered completely and engages fully in sports with no restrictions.

DISCUSSION

Anterior or multiple compartments syndrome of the leg is common and well documented in the literature. However, acute isolated lateral leg compartment syndrome is rare with a variety of etiologies, presentations, symptoms, and signs reported in the literature. Hence, we performed a comprehensive literature review using PubMed to summarise all reported cases. The following keywords were searched: [(lateral compartment) OR (peroneal compartment)] AND (isolated compartment syndrome). The relevant literature was carefully studied and the results were summarized in Table 1. Forty-seven papers were identified but only 12 were relevant and thus included.

Acute compartment syndrome commonly occurs shortly after substantial trauma in long bone fractures[4,5]. However, it could also arise as a result of minimal trauma or atraumatic events[2]. Isolated lateral leg compartment syndrome has been linked to atraumatic events and atypical presentations in 12 papers reporting 14 cases. Two interesting cases have linked atypical events to the development of isolated lateral compartment syndrome of the leg; wearing high heels without any obvious history of trauma[6] and using excessively tight compression stockings for DVT prophylaxis during surgery[7]. Additionally, other preceding events reported include playing football[2,8-12], basketball[9], running[13], dancing[14], and forced marching[15]. Hypothetically, any reduction of the compartment volume or increase in the amount of fluid present inside the compartment will lead to an elevation of the osseofascial compartment pressure which may result in reduction of the perfusion gradient across tissue capillaries. This leads to cellular anoxia and muscle ischemia resulting in the development of compartment syndrome[4,16]. The incidence is believed to be greatest in young men who have a larger muscle mass at this age contained within the restricted fascia[5,17]. This goes along with what we found in our review in which the mean age of the cases at presentation was 27 years and most cases occurred in males, with a male to female ratio of 7:1.

Table 1 A summary of the 12 included papers reporting on 14 cases of atraumatic isolated lateral leg compartment syndrome

Ref.	Age	Gender	Site	Presentation	Preceding event	Comorbidities	Intercompartmental pressure	Management	Other
[6]	Mid 30s	F	R	Atraumatic, painless ankle swelling and footdrop 1 d prior to presentation	Wearing high heels, no history of trauma	Obese, bipolar on lithium	Lateral compartment pressure 92 mmHg	Anterior and lateral compartment fasciotomy; significant muscle necrosis lateral compartment	-
[7]	44	M	R	Severe pain lateral aspect of the lower extremity and loss of protective sensation over the dorsolateral aspect of the foot	Excessively tight compression stockings used for DVT prophylaxis post surgery	Obesity, atrial fibrillation, congestive heart failure, obstructive sleep apnea, and obesity	Lateral compartment pressure 122 mmHg	Lateral compartment fasciotomy and delayed closure with a split-thickness skin graft	-
[9]	21	M	R	Mild pain in the lower leg and drop foot	Basketball, no history of trauma	Medically free	Anterior compartment pressure 42; lateral compartment pressure 120 mmHg	Lateral compartment fasciotomy closed primarily then reopened next day due to recurrent pain and raised intercompartmental pressure underwent delayed closure after 14 d	Peroneus longus found completely detached from its proximal origin
	16	M	R	Swelling, pain and numbness in the leg	Football, no history of trauma	Medically free	Lateral compartment pressure 100 mmHg, anterior compartment pressure 42 mmHg	Lateral compartment fasciotomy, with delayed closure	Peroneus longus found completely detached from its proximal origin
[2]	34	M	R	Dorsal foot numbness and burning pain, excruciating lateral leg pain and persistent but not severe swelling of the leg	Football, no history of trauma	Medically free	Lateral compartment pressure 130 mmHg	Lateral compartment fasciotomy	Peroneus longus partially exhibited a burgundy discoloration
[13]	33	M	R	Excruciating lateral leg pain, numbness and tingling dorsum of the foot	Noncontact injury with forceful inversion of the ankle while running on uneven ground	Not reported	Lateral compartment pressure 120 mmHg	Lateral compartment fasciotomy with delayed closure	Hematoma at the musculotendinous junction of the peroneus longus
[1]	27	M	L	Pain and tightness along the lateral aspect of the leg and swelling; passive foot inversion produced significant pain in the ankle and lateral leg	Noncontact inversion ankle injury during practice	Not reported	Lateral compartment pressure 115 mmHg anterior compartment pressure 5 mmHg	Lateral compartment fasciotomy	Peroneus longus belly initially dusky in color and edematous but no evidence of muscle rupture or hematoma
[12]	25	M	L	Lateral ankle pain rapidly increasing in intensity and spreading to the leg, lateral malleolus edema and severe pain with foot inversion and weakness on foot eversion	Football, inversion ankle injury	Not reported	Lateral compartment pressure > 130 mmHg	Lateral compartment fasciotomy	Partial muscle necrosis with proximal rupture of the peroneus longus muscle
[15]	21	M	R	Severe lateral leg pain, decreased	Two- mile mark of a 12-	Not reported	Lateral compartment pressure > 130 mmHg	Lateral compartment fasciotomy with	-

				range of motion of the foot and paresthesias over the dorsum of the foot, peroneal pain on passive inversion of the subtalar joint	mile forced-march			delayed closure	
	24	M	L	Pain and tenderness over the lateral aspect of the leg, tense peroneal compartment and pain on passive stretch of the peroneal muscles with inversion of the foot. Reduced sensation to pin-prick in the first web space	18-km cross-country march	Not reported	Lateral compartment pressure 130-140 mmHg	Lateral compartment fasciotomy with delayed closure	-
[10]	17	M	R	Anterolateral leg pain, swelling and numbness in the lateral leg and dorsal foot	Football practice, no history of trauma	Medically free	Lateral compartment pressure 44 mmHg anterior compartment pressure 26 mmHg	Anterolateral fasciotomy; lateral compartment was under severe pressure, vac pump applied, returned to OR after 2 d	At 2 d, peroneus longus necrotic and noncontractile with tendon detachment proximally
[11]	29	M	R	Extreme pain, paresthesia and decreased sensation in the second web space with extreme tenderness over the proximal lateral compartment	Touch football, insignificant twisting of the knee while warming up	Not reported	Lateral compartment pressure 55 mmHg Anterior compartment pressure 20 mmHg	Lateral compartment fasciotomy with delayed closure	Ischemic muscles in the lateral compartment and small bleeding vessel in the mid portion of the muscle
[14]	25	F	R	Pain distal to the fibular head, difficulty to walk, calf swelling and spasms	Inversion ankle injury while dancing	Medically free	Lateral compartment pressure 70 mmHg	Lateral compartment fasciotomy with delayed closure	50% of the lateral compartment muscles necrotic
[8]	28	M	R	Pain and paresthesia, tense swelling in the lateral compartment with extreme pain to passive stretching of the compartment	Football, no history of injury	Medically free	Lateral compartment pressure 122 mmHg	Lateral compartment fasciotomy	-

DVP: Dose-volume parameter; OR: Operating room.

Acute compartment syndrome is usually diagnosed clinically with pain, pallor, paresthesia, paralysis, and pulselessness as classic symptoms and signs[4,18]. However, the diagnosis of acute isolated lateral leg compartment syndrome in specific is quite challenging due to the lack of characteristic clinical symptoms and signs. Thus, it is often missed or delayed[9]. Persistent or worsening pain following a minor injury or exertion is often described and the initial physical findings are usually nonspecific. A marked increase in pain with passive inversion, dorsiflexion, and weak active eversion of the ankle have been commonly reported among most cases and may be suggested as sensitive signs for the diagnosis of the lateral compartment syndrome of the leg. In cases that present late or where the diagnosis is initially missed, there is often common and/or deep peroneal nerve palsy which causes paresthesia or if severe enough leads to foot drop as reported by Hiramatsu *et al*[9].

The use of other diagnostic methods besides good history and physical examination such as intracompartmental pressure measurement may be beneficial when the physical exam is equivocal or in unconscious patients[4,18]. In our review, all authors have measured the compartmental pressures of the different compartments to confirm the diagnosis, and the lateral compartment pressure was particularly elevated with a mean pressure of 106 mmHg among the 14 cases. In our case, we did not measure the intracompartmental pressures as the clinical picture of the patient alongside the MRI report were sufficient to decide that surgery is warranted. However, we agree that measuring the pressures would have confirmed the diagnosis and this could be considered as a potential limitation in our workup despite no delays to surgery

or resultant adverse outcomes.

Prompt diagnosis and immediate surgical decompression of compartment syndrome are necessary to prevent permanent impairment[19]. As seen in the majority of cases reviewed in the literature, partial or complete injury to the peroneus longus muscle and the subsequent hematoma were the culprit for the isolated elevation of the lateral compartment pressure of the leg[3]. Interestingly, none of the cases included in the literature review reported any history of trauma or direct injury[1,2,14,15,6-13]. Hence, we presume that the pathophysiological process causing the detachment of the proximal origin of the peroneus longus muscle is an overuse or repetitive extensive eccentric muscular contraction against the floor during inversion of the subtalar joint. Interestingly, despite the late presentation of our patient at 24 h after playing football, he recovered well with no residual deficit. This may be attributed to him developing gradual increased pressures at the time when he presented to the other hospital and over the following hours prior to attending our hospital but reaching the threshold to having significant compartment syndrome only recently prior to his presentation to our ER.

Other principles of acute compartment syndrome management can be applied in isolated lateral compartment syndrome as well such as debridement of all nonviable tissues, delayed surgical site closure if needed, close postoperative monitoring, and pain control.

CONCLUSION

Acute isolated lateral leg compartment syndrome is rare and constitutes a diagnostic challenge. It can be missed easily due to the atypical presentation and the lack of diagnostic symptoms and signs. It should be considered even in the context of atraumatic events. Pain on passive inversion and dorsiflexion and weak active eversion may be suggested as sensitive signs. Drop foot is a delayed presentation as a result of deep peroneal nerve involvement. A high index of clinical suspicion is the key to early diagnosis and timely surgical intervention.

FOOTNOTES

Author contributions: Alrayes MM and Alqudah M contributed to manuscript writing, and literature search; Bani Hamad W contributed by providing and reviewing the radiological content; Sukeik M was the primary surgeon of the case and contributed to scientific content, paper revision, editing, and overall supervision.

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MINIREVIEWS

Use of topical vancomycin powder in total joint arthroplasty: Why the current literature is inconsistent?

Fabio Mancino, Piers J Yates, Benjamin Clark, Christopher W Jones

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Abstract

Periprosthetic joint infection (PJI) is a rare but terrible complication in hip and knee arthroplasty, and the use of topical vancomycin powder (VP) has been investigated as a tool to potentially reduce its incidence. However, there remains no consensus on its efficacy. Therefore, the aim of this review is to provide an overview on the application of topical vancomycin in orthopaedic surgery focusing on the recent evidence and results in total joint arthroplasty. Several systematic reviews and meta-analyses on topical VP in hip and knee arthroplasty have been recently published reporting sometimes conflicting results. Apart from all being limited by the quality of the included studies (mostly level III and IV), confounding variables are often included potentially leading to biased conclusions. If taken into consideration the exclusive use of VP in isolation, the available data, although very limited, suggest that it does not reduce the infection rate in routine primary hip and knee arthroplasty. Therefore, we still cannot advise for a routinary application. A properly powered randomized-controlled trial would be necessary to clarify the role of VP in hip and knee arthroplasty. Based on the analysis of the current evidence, the use of topical VP appears to be safe when used locally in terms of systemic adverse reactions, hence, if proven to be effective, it could bring great benefits due to its low cost and accessibility.

Key Words: Periprosthetic joint infection; Vancomycin powder; Total knee arthroplasty;

Total hip arthroplasty; Infection; antibiotic

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Core Tip: Vancomycin powder is widely used in orthopaedic surgery and it has been recently investigated in total joint arthroplasty (TJA), however, results are often conflicting. The aim of this study was to report on the use of vancomycin powder in orthopaedic surgery focusing on its application in TJA.

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INTRODUCTION

Periprosthetic joint infection (PJI) is one of the leading causes of revision in total joint arthroplasty (TJA) and its incidence has been reported between 1% to 4% after primary total knee arthroplasty (TKA) and 1% to 2% after primary total hip arthroplasty (THA) [1,2]. According to the available projections, the number of revisions is expected to grow proportionally to the number of primary implants performed every year[3] showing and increase of revision for PJI by 176% between 2014 and 2030 in THA, and by 170% in TKA[4]. Economic-based studies have reported that the yearly cost associated with PJI in the United States was approximately one billion United States dollars in 2017, and projected to reach almost two billion United States dollars by 2030[5].

Multiple strategies have been pursued to try to reduce the PJI rate in TJA, including preoperative screening, patient optimization, modified intraoperative techniques, and enhanced postoperative surveillance[6]. Vancomycin is a widely adopted and effective antibiotic in orthopaedic surgery, and its topical application has been investigated in different fields including spine surgery, trauma, and sport medicine to reduce the incidence of infection by providing a high concentration of antibiotic in a specific surgical site. Therefore, it has also been studied to reduce the PJI rate in TJA, reporting however conflicting conclusions.

The aim of this review is to provide an overview on the applications of topical vancomycin in orthopaedic surgery focusing on the use in TJA summarizing the results reported in the literature in order to clarify the current evidence for the use of topical VP.

The United States National Library of Medicine (PubMed/MEDLINE), EMBASE, and the Cochrane Database of Systematic Reviews were queried for publications utilizing various combinations of the search terms "VP", "vancomycin powder", "orthopaedic surgery", "orthopedic surgery" "arthroplasty", in combination with the Boolean operators (AND, OR, *) since January 2020 to December 2022. Two authors (Fabio Mancino and Christopher W Jones) independently conducted all the searches and screened the titles and abstracts to identify relevant studies. Differences were resolved by consulting a third senior reviewer (Piers J Yates). Only abstracts that evaluated the outcomes of VP in orthopaedic surgery were reviewed. If the title and abstract of each study contained insufficient information, the full manuscript was reviewed. An additional search was conducted by screening the references list of each selected article. Inclusion criteria were any systematic review and/or meta-analysis that pooled the results on the application of VP in orthopaedic surgery and TJA, analyzing the outcomes in terms of infection rate. Exclusion criteria were cohort studies, clinical trials, case reports, surgical technique reports, expert opinions, letters to editors, biomechanical reports, instructional course lectures, studies on animals, cadaver or *in vitro* investigations, book chapters, abstracts from scientific meetings, unpublished reports, and studies written in a non-English language. Two independent reviewers (Fabio Mancino and Christopher W Jones) separately examined all the identified studies and extracted data. During the initial review of the data, the following information was collected for each study: Title, first author, year of publication, study design, number of studies included, number of patients included, type of surgery, methods of application of VP, complications related to VP, superficial and deep infection rates.

BURDEN OF PERIPROSTHETIC JOINT INFECTION

PJI is a relatively rare complication. However, it is associated with a significantly greater morality when compared with patients undergoing aseptic revisions, up to five times higher at one year[7,8,9]. In addition, after the first case of PJI, the reinfection rate is up to 8.5% in THA and up to 16% in TKA[9], showing that the long-term consequences can be devastating. Kapadia *et al*[10], reported that patients with PJI had a significantly higher number of readmissions (3.6 *vs* 1.2; $P < 0.001$), length of hospitalization, clinic visits and sum-total episode cost than patients who had a non-infected primary implant (US$96,166 *vs* US$21,654; $P < 0.001$). When considering the economic burden, the cost of a revision for PJI is up to five times higher than a primary TJA ($116,382 *vs* $28,249)[11]. Moreover, managing this complication often

requires a two-stage revision strategy, costing approximately US$60,000 more than revisions for mechanical failure and/or aseptic loosening[12].

Currently, the only consensus recommendation for the use of antibiotics in TJA by international authorities is systemic perioperative administration[13].

VANCOMYCIN POWDER IN ORTHOPAEDIC SURGERY AND TJA

Gram-positive bacteria, particularly staphylococcal species, are the most common pathogenic organisms involved in post-operative orthopaedic infections[14]. Vancomycin is a tricyclic glycopeptide antibiotic with activity against gram-positive bacteria initially derived in 1953 from a compound produced by *Amycolatopsis orientalis*, a soil bacterium discovered within mud collected from a Borneo forest. The compound nicknamed "*Mississippi mud*" because of its appearance prior to purification became vancomycin (after the word "*vanquish*") and nearly 70 years later still retains antimicrobial activity against the majority of gram-positive organisms and remains the most commonly used antibiotic in the United States for the treatment of serious gram-positive infections, including those caused by methicillin-resistant Staphylococcus aureus (MRSA)[15].

The topical application of this antibiotic has been widely adopted in different fields of orthopaedic surgery with promising results. Sweet *et al*[16], demonstrated a significant reduction in postoperative deep wound infection rates (0.2% *vs* 2.6%; $P < 0.0001$) in posterior instrumented thoracolumbar spinal fusions with the adjunctive application of 2 g of VP before wound closure. Similar findings were reported by O'Neill *et al*[17], when analyzing 110 patients that underwent posterior spinal stabilization of traumatic injuries. The authors noted that the infection rate was significantly reduced (13% *vs* 0%; $P = 0.02$) when 1 g of vancomycin was applied before wound closure. Moreover, similarly reduced infection rates were reported both by Molinari *et al*[18] and by Bakhsheshian *et al*[19] when studying the effect of topical VP in instrumented and uninstrumented spine surgery.

The use of VP has been also investigated in tibial fractures, considered to be at high risk of infection, in an open-label multicentre randomized clinical trial reporting that the application of 1 g of VP was associated with a reduced risk of deep surgical site infection due to gram-positive organisms (risk difference, -3.7%; 95%CI, -6.7% to -0.8%; $P = 0.02$), in line with the activity of the antibiotic[20].

In addition, when VP was used in 422 shoulder arthroplasty, it has been associated with a significant reduction in PJI with no increased rate of aseptic wound complications, however, literature on shoulder surgery is limited and results are mostly based on retrospective analysis[21].

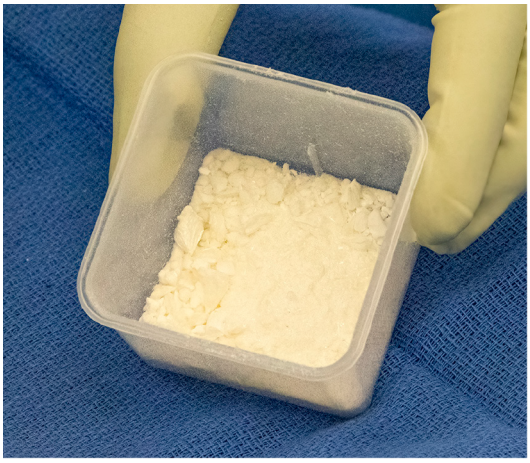
Similarly, studies on the application of topical VP in foot and ankle surgery and in total ankle arthroplasty (TAA) are limited, however, the economic viability has been investigated by Nam *et al*[22]. At their institutional cost of UD$3.06 per gram and a TAA PJI rate of 3%, VP would be cost-effective for TAA revision costs with an absolute risk reduction of 0.02% (number needed to treat = 5304). In addition, the authors showed that VP, when considered at their institutional price, would remain cost-effective even if the initial PJI rate was as low as 0.05%, and that if the PJI rate was held constant at 4%, VP would remain cost effective even within a range of price from US$2.50 to US$100.00 per gram. Nevertheless, the power analysis performed by the authors to confirm such results in a clinical trial shows the main limit of the investigations on VP.

Moreover, topical vancomycin is frequently used in anterior cruciate ligament reconstruction (ACLR) by wrapping the graft in a swab saturated with 5mg/mL vancomycin solution[23] and it has been associated with reduced incidence of postoperative septic arthritis[24]. In fact, Xiao *et al*[25], reported in a survey on the ACL Study Group members that 37.9% of the members pre-soak their ACL graft in vancomycin prior to implantation. In addition, Naendrup *et al*[24], pooled the results on 5075 ACLR showing a significant reduction in septic arthritis with no differences in clinical outcomes, biomechanical tendon properties, or cartilage integrity. Despite having many clinicians concerns regarding the potential toxicity on chondroblasts and osteoblasts, it has been proven *in-vitro* that when used at concentrations up to 5mg/mL, the vancomycin levels reached within the first 24-hours remain below the toxicity threshold for chondroblasts and osteoblasts [26].

Recently, vancomycin application has also been investigated in intraosseous (IO) infusion in THA at the concentration of 500mg/100cc of normal saline showing increased local tissue and decreased systemic concentrations when compared with standard prophylactic intravenous (IV) administration[27]. Similar findings have also been reported in a high body mass index (BMI) population that underwent TKA showing local concentrations up to 9-times higher than systemic administration[28].

Considering these promising results, VP is used in TJA with the hope of significantly reducing the risk of PJI (Figure 1). Weight-based (15 mg/Kg) IV vancomycin is already widely adopted as a second-line prophylaxis instead of first- or second-generation cephalosporin in case of allergies to penicillin, history of MRSA, or positive preoperative MRSA nasal-swab colture[29]. However, considering the better results associated with cephalosporins, the International Consensus on PJI recommended that these antibiotics can be safely used in case of non-anaphylactic penicillin allergy[30] since the cross-reactivity risk has been proven to be as low as 1%[31].

Topical application of VP allows higher concentrations in the surgical area while minimizing the systemic adverse effects[32]. In a rat model, the use of intra-articular VP combined with IV antibiotics resulted in the complete eradication of MRSA bacteria from contaminated implants[33]. Johnson *et al*[32] studied vancomycin concentration both locally and systemically after the administration of 1 g of intra-articular VP and 1 g after closure of the fascia in the superficial tissues in 34 THA reporting the different serum levels at 90 min, 3 h, 12 h, and 24 h, and the local levels at 3 h, 12 h, and 24 h. The authors reported that the mean serum concentration peaked at 12 h (4.7 mcg/mL; max observed 12.7 mcg/mL at 3 h)



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Figure 1 Vancomycin powder used in 1-st stage revision total knee arthroplasty.

while the systemic therapeutic levels of 15-20 mcg/mL were never reached in any of the time-points. In addition, the intra-wound half-life was estimated to be 7.2 h with mean wound levels > 900 mcg/mL at 3 h while maintaining the local concentration over 200 mcg/mL for 24 h. Finally, the authors estimated that it would take up to 64 h for intrawound levels to drop below the minimum inhibitory concentration for *S. aureus* of 2 mcg/mL (Table 1).

Despite the potential benefits, there are also theoretical drawbacks. Firstly, the low systemic concentration of vancomycin may induce the development of resistant species of gram-positive bacteria colonizing the body. The Infectious Disease Society of America recommended serum levels > 10 mcg/mL to avoid the potential development of resistance[34]. Given the short half-life of the antibiotic when administered parenterally (4-6 h), this is not problematic when administered as a single dose of prophylactic IV antibiotic providing coverage for the first 24 h, but maybe a factor during ongoing and prolonged systemic absorption of intra-articular antibiotics. Secondly, a potential third body wear mechanism has been hypothesized between crystalline vancomycin and implant components since the solubility of vancomycin may vary in an intra-articular environment compared to saline solution. Nevertheless, Qadir *et al*[35] reported no appreciable difference in wear rates after 10 million simulated cycles between ultra-high-molecular-weight-polyethylene and Cobalt-Chrome alloy with the addition of VP. Lastly, vancomycin may have negative effects on the proliferation of viable cells including osteoblasts. Braun *et al*[36], reported the *in-vitro* effect of vancomycin on osteoblasts, endothelial cells, fibroblasts and skeletal muscle cells showing that the toxic effects were time (from day-3) and concentration-dependent (> 0.01 mg/mL). However, such results are yet to be proven *in-vivo*, and as shown by Johnson, no such concentrations have been reported at the 3-d mark. Therefore, based on the aforementioned studies, topical administration of VP can reasonably be considered clinically safe when used in TJA. Finally, if proven to significantly impact the PJI rate, VP would be highly cost-effective as its price has been reported from $2.50 to the highest of $44.00 per gram[37].

CURRENT LITERATURE FOR VP IN TKA AND THA

Overall, seven systematic reviews and/or meta-analyses were identified and analyzed[38-44] (Table 2).

Movassaghi *et al*[38], reported that intrawound VP may reduce the risk of PJI in primary and revision TJA while not leading to systemic complications. The authors included in their analysis 16 studies and 17164 TJA that received intrawound VP reporting an overall decreased rate of PJI (OR 0.46, $P < 0.05$), a decreased rate when considering TKA and THA separately (OR 0.41, $P < 0.05$ and OR 0.45, $P < 0.05$, respectively), and a decreased rate when considering primary implants only (OR 0.44, $P < 0.05$). Most of their results came from the outcomes of 14262 primary TKA (of 17164 joints, 83%) and that among them, 9884 cases (69% of primary knees) came from a study[44] where the so-called "VIP protocol" was used by mixing VP and 0.35% povidone-iodine (PI) solution (17.5 mL in 500 mL saline).

Regarding PI lavage, Kim *et al*[46], reported in a systematic review on 7 studies and 8861 TJA no difference between PI and saline in reducing the PJI rate. However, more recent studies showed efficacy in revision TJA reducing the PJI rate from 3.4% to 0.4% ($P = 0.038$, 478 revisions)[47], and efficacy in reducing the rate of any infection over 3232 TJA (OR 0.45, $P < 0.05$) or superficial site infections (SSI, OR 0.3, $P < 0.05$)[47]. Finally, Shohat *et al*[49] recently reported on the outcomes of 31331 cases showing a 2.34 times lower rate of PJI when comparing PI lavage with saline in TJA (0.6% *vs* 1.3%) with an absolute risk reduction of 0.73% and a number needed to treat of 137 patients. Therefore, the positive outcomes reported by Movassaghi *et al*[38] may have been influenced by the inclusion of iodine lavage.

Similarly, Liao *et al*[43], published in strong favor of VP suggesting that VP has a clear effect on preventing PJI in primary TKA. The authors reported on 11292 TKA where VP was used with a Risk Ratio (RR) of 0.41 (95%CI 0.29 to 0.58, $P < 0.001$) when compared to cases where VP was not used. However, as previously mentioned, 46.7% of of the cases analyzed came from studies[45,50] where VP was used in combination with a PI solution, potentially having once again a significant effect on the final results.

Table 1 Serum and local levels of vancomycin at different post-wound closure collection times

Procedure	Serum levels after wound closure of VP intrawound administration (g/mL)				
	1.5 h (mean ± SD; max)	3 h (mean ± SD; max)	12 h (mean ± SD; max)	24 h (mean ± SD; max)	Highest level observed across the 24-h period
THA (n = 15)	3.8 ± 3.9; 9.5	4.9 ± 4.5; 12.7	5.1 ± 3.3; 8.4	3.5 ± 3.5; 8.0	6.6 ± 3.8; 12.7
TKA (n = 19)	1.0 ± 2.5; 8.7	1.8 ± 3.2; 9.8	4.4 ± 3.1; 7.3	3.5 ± 3.6; 10.4	5.2 ± 3.4; 10.4
THA + TKA (n = 34)	2.2 ± 3.4; 9.5	3.2 ± 4.1; 12.7	4.7 ± 3.2; 8.4	3.5 ± 3.5; 10.4	5.8 ± 3.6; 12.7
	Local levels after wound closure of VP intrawound administration, n (g/mL)				
	-	**3 h (mean ± SD)**	**12 h (mean ± SD)**	**24 h (mean ± SD)**	-
THA	-	988 ± 628 (12)	769 ± 1059 (11)	280 ± 436 (11)	-
TKA	-	877 ± 455 (18)	288 ± 203 (16)	163 ± 220 (18)	-
THA + TKA	-	922 ± 523 (30)	484 ± 716 (27)	207 ± 317 (29)	-

VP: Vancomycin powder; THA: Total hip arthroplasty; TKA: Total knee arthroplasty. Adapted from: Johnson JD, Nessler JM, Horazdovsky RD, Vang S, Thomas AJ, Marston SB. Serum and Wound Vancomycin Levels After Intrawound Administration in Primary Total Joint Arthroplasty. *J Arthroplasty* 2017 Mar; 32(3): 924-928. Copyright © 2015 Elsevier Inc. All rights reserved.

Table 2 Main characteristics and results of the recent literature on the topic vancomycin powder

Ref.	Type of study	No. of studies	No. of cases (control/intervention)	PJI Rate/RR (control *vs* intervention)	SSI/Aseptic wound complications (control *vs* intervention)	Authors' conclusions
Martin *et al* [36], 2022	Systematic review and meta-analysis	7/7	144724/8029	RR 0.39 (95%CI 0.27-0.56, P < 0.001)	6.48% *vs* 3.79%	VP ± PI lavage reduced PJI rate in primary and revision THA/TKA. Associated with reduced aseptic wound complications
Liao *et al*[35], 2022	Systematic review and meta-analysis	14	7720/1292	RR 0.41 (95%CI 0.29-0.58, P < 0.001)	-	VP recommended in primary TKA
Movassaghi *et al*[30], 2022	Systematic review and meta-analysis	16	3731/17164	1.65% *vs* 0.87% (P < 0.05)	-	Local VP may reduce the risk of PJI in primary and revision TJA
Wong *et al* [31], 2021	Systematic review	9	6255/3371	-	No difference	Recommend the surgeons not to use VP in routine THA and TKA
Peng *et al*[32], 2021	Systematic review and meta-analysis	9	4512/2354	RR 0.37 (95%CI 0.23-0.60, P < 0.001)	RR = 0.40, 95%CI 0.27-0.61 (P < 0.001)	Local VP could significantly decrease the rate of SSI and PJI in primary TJA
Saidahmed *et al*[33], 2021	Systematic review and meta-analysis	9	3714/1985	3.5% *vs* 1.6%, RR 0.53 (95%CI 0.35-0.79, P = 0.002, I^2 = 0.0%)	No difference 1.6% *vs* 0.7%, RR = 0.61, 95%CI 0.17-2.12, (P = 0.43, I^2 = 0.0%)	Local antibiotic application results in a moderate reduction in deep infection rates in primary TJA, with no significant impact on SSI rate
Xu *et al*[34], 2020	Systematic review and meta-analysis	9	4607/2497	2.75% *vs* 1.20% (OR 0.44, 95%CI 0.28-0.69, I^2 = 0.0%)	No difference 1.60% *vs* 0.67% (OR 0.60, 95%CI 0.17-2.12, I^2 = 0.0%)	VP used in primary hip and knee arthroplasty may reduce the incidence of PJI but it may increase the risk of aseptic wound complications

RR: Relative risk; SSI: Superficial site infection; VP: Vancomycin powder; PI: Povidone iodine; PJI: Periprosthetic joint infection; THA: Total hip arthroplasty; TKA: Total knee arthroplasty; TJA: Total joint arthroplasty; OR: Odds ratio.

Moreover, Peng *et al*[40], stated that "the local application of VP could significantly decrease the rate of SSI and PJI in primary TJA" recommending its topical administration before wound closure. The meta-analysis included nine studies and three of those[49,51,52], representing a weight on the result of 44%, did not involve only the application of topical VP, therefore, their inclusion could be misleading. One of these[50], reported on the combined application of PI lavage and

VP showing that administration of local antibiotics was preventative for PJI only in the primary TKA (OR 0.28, 95%CI 0.09–0.89). The other two[51,53], reported on the application of VP on the surface of cementless implants in THA and TKA and not in the soft tissue deep or superficial to the fascia/capsule, therefore, a completely different way of using VP.

Xu *et al*[42], reported that "the current literature suggests that intrawound vancomycin used in primary hip and knee arthroplasty may reduce the incidence of PJI, but it may also increase risk of aseptic wound complications". Nine studies were included in their final analysis with 4605 TJA, 2497 of which were treated with VP. The authors reported a reduced PJI rate in the VP group (1.20% *vs* 2.75%) with an OR of 0.44 (95%CI 0.28 to 0.69, $I^2 = 0.0\%$), a comparable risk of SSI (OR 0.60, 95%CI 0.17 to 2.12), and a higher incidence of aseptic wound complications (2.15% *vs* 0.96%, OR 2.39, 95%CI 1.09 to 5.23). However, when considering the aseptic wound complications, only four of the nine studies reported on such events (1069 treated cases), and all of them had different methodology protocols in terms of the amount of VP used, placement of the VP (deep to the fascia, superficial, or both), and the application of a drain for up to 48 h post-operative. Therefore, the conclusion that VP is associated with an increased risk of aseptic wound complications, based on such results, may require stronger evidence.

Saidahmed *et al*[41], stated that topical antibiotics led to a moderate reduction in PJI in primary TJA, with no significant impact on SSI rates but that it may be associated with a moderate increase in aseptic wound complication. However, once again, four of the nine studies reported mixed results considering the combined activity of PI lavage and VP[50], the application on cementless implants[52,53], or did not consider only the application of VP in TJA but more generally the use of topical antibiotics[54].

On the other hand, Wong *et al*[39] discouraged the application of VP in primary TJA after systematically analysing the outcomes of 9 studies and 3371 TJA in which VP was used compared with 2884 in which it was not. Only studies with similar procedures and those limited to the application of VP were included. The authors reported that only one of the studies included[51] was associated with significant improvement while the remaining eight had OR that broadly bracketed the line of no difference (range, 0.09 to 1.97). In addition, the authors noted insufficient evidence on the question of safety, therefore, their final statement was against the use of topical VP in routine THA and TKA unless adequately powered, multicentre, prospective trials demonstrate clear evidence. However, despite the methodology and the inclusion criteria being well defined to include only studies using topical VP in isolation, no statistical analysis was performed to verify the results.

Lastly, Martin *et al*[44] recently pooled together the studies using VP alone (7 studies) and in combination with PI lavage (7 studies) reporting a significant reduction of PJI rate (RR 0.39, 95%CI 0.27 to 0.56, $P < 0.001$) in primary and revision THA and TKA when compared with a control group. However, there remain doubts on the contribution of the PI lavage as we are still missing clear results on the VP alone used with standardized methods and compared with a control group. Interestingly, the authors reported a reduced aseptic wound complication rate in the treatment pool (110/2903, 3.79% *vs* 98/1512, 6.48%), though, still considering the combined effect of VP and PI lavage.

CONCLUSION

PJI in TJA is certainly one of the biggest challenges that the orthopaedic community is now facing with tremendous impact on the patient, the treating multi-disciplinary team, and the health care system. Despite the topical application of VP appears to be safe in terms of systemic complications, there are potential risks regarding the development of antimicrobial resistance following the administration of VP and most importantly, from the available data, we cannot conclude that when used in isolation it is effective in reducing the PJI rate. Evidence remains lacking with varying methodologies and important technical differences (amount of VP, placement deep or superficial to the fascia, use of drain). In fact, positive outcomes appear only to have been reported when the additional application of PI is considered together with VP. It must also be noted that the use of intraoperative antimicrobial irrigation (*e.g.* deep or subcutaneous tissues), or the application of antimicrobial agents (*e.g.* ointments, solutions, or powders) to the surgical incision for the prevention of SSI are not currently recommended by The Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection[55]. Moreover, evidence supports the perceived increased risk of aseptic wound complications, which should be further investigated.

Therefore, despite the multiple studies recently published, the efficacy of VP in TJA for reducing PJI is still essentially unknown. To overcome this issue, a randomized controlled trial with homogeneous methodology and exclusion of additional confounding variables (such as PI lavage) would be necessary.

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MINIREVIEWS

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Abstract

The musculoskeletal system involves multiple tissues which are constantly exposed to being exposed to various biological and mechanical stimuli. As such, isolating and studying a particular system from a complex human clinical environment is not always a realistic expectation. On top of that, recruitment limitations, in addition to the nature of orthopaedic interventions and their associated cost, sometimes preclude consideration of human trials to answer a clinical question. Therefore, in this mini review, we sought to rationalize the rapid evolution of biomedical research at a basic scientific level and explain why the perception of orthopaedic conditions has fundamentally changed over the last decades. In more detail, we highlight that the number of orthopaedic *in vitro* publications has soared since 1990. Last but not least, we elaborated on the minimum requirements for conducting a scientifically sound infection-related laboratory experiment to offer valuable information to clinical practitioners. We also explained the rationale behind implementing molecular biology techniques,

ex vivo experiments, and artificial intelligence in this type of laboratory research.

Key Words: Biofilm; *In vitro*; Laboratory research; Methodology

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Core Tip: This paper highlights some major orthopaedic research advances at a basic science level. On top of that, it is highlighted that the perception of orthopaedic conditions has fundamentally changed recently, reflecting on clinical practice. We also described the basic aspects of a successful *in vitro* infection laboratory experiment and expanded on recent evidence relating to molecular biology, *ex vivo* investigations, and artificial intelligence in orthopaedics.

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INTRODUCTION

Why and when to proceed with basic science orthopaedic research?

Barriers to orthopaedic research: It is widely recognized that high-quality randomized evidence is lacking in orthopaedics. The main reasons behind that include the increased cost of conducting a trial, the lack of funding and resources, the limited availability of time from the clinicians[1], and the overall recruitment limitations. Although significant musculoskeletal concerns are fraught with ambiguity in the scientific community, it has been demonstrated that many surgeons are insufficiently motivated to discuss trial participation with their patients[2]. On top of that, orthopaedic trainees may show limited interest in conducting research, feel unsupported, and lack mentorship and/or opportunities to get involved in experimental projects[3]. According to the above, when assessing the feasibility of orthopaedic projects, researchers should have realistic expectations and carefully select the appropriate study design.

Is *in vitro* research the appropriate remedy? It should be noted that *in vitro* models are laboratory-based experiments that imitate biological processes outside a real organism. *In vitro* models are frequently utilized in orthopaedic research to investigate many aspects of musculoskeletal diseases, tissue engineering, and medication development[4]. Conducting *in vitro* laboratory research enables researchers to overcome the complexity of multiple organ interactions in human beings [4]. Furthermore, funding for clinical and translational animal research is usually insufficient to address the unanswered orthopaedic research questions. Therefore, opting for basic science projects appears beneficial, particularly when investigating topics that have not been dealt with before. Nevertheless, we should underline that although basic science orthopaedic research intends to bridge the gap between the absence of knowledge on a given topic and clinical practice, we advocate that the results of *in vitro* trials must be interpreted cautiously and should not be exclusively extrapolated in human setting.

How to properly conduct infection orthopeadic research at a basic science level?

Infection outcomes and administration/training requirements: First, it must be pointed out that the standard strain of a given microorganism is investigated for reproducibility and transparency reasons. Initial testing should include planktonic growth evaluation not only in the presence of antimicrobial agents as well as untreated control, in order for the researcher to reliably evaluate the antimicrobial capacity of a potential antimicrobial agent. Subsequently, biofilm studies should include intervention(s) group(s) and an untreated biofilm control.

When assessing the results of the exposure of microorganisms to potential anti-bacterial agents, there are plenty of options to investigate their effectiveness in the lab. The most common method features a colorimetric evaluation of cell viability with the 2-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide reduction assay, which is a highly reliable method and particularly useful for investigating multiple technical replications in the lab[5,6].

Regarding the infection prevention experiments, attention should be paid to the difference in cell viability between the intervention and control groups. The minimum inhibition threshold of 80% must be surpassed for this difference to be clinically meaningful[7].

From an administrative perspective, attaining Institutional Review Board Approval before performing a formal microbiological experiment is advisable to ensure Good Laboratory Practice. According to our experience and literature, substantial up-front investment in infrastructure and lab consumables is suggested to ensure an uninterrupted flow of experiments. From a scientific point of view, collaboration with well-established infection labs as well as ongoing lab training of the personnel are essential steps for the successful execution of experiments.

Guidelines, statistical considerations, pictorial presentations and extrapolation of results: Similar to other types of research, reporting guidelines should be provided along with the experimental studies[8]. More specifically, the primary

and secondary outcomes of a given *in vitro* experiment should be clearly reported in the methods sections.

From a statistical point of view, researchers should bear in mind that achieving sufficient study power applies to clinical papers and basic science research. In other words, implementing a sufficient sample size based on the primary outcomes of an *in vitro* study enables the authors to reach consistent and clinically meaningful conclusions. Moreover, authors are encouraged to comment on any potential biases which may compromise the reliability of their findings[8].

Pictorial and graphical presentation of the results is essential: Regarding infection-related *in vitro* pre-clinical research, it is proposed that the authors produce a graphical representation of microbial development that will serve as the basis for their future tests[9] (Figure 1).

In doing so, the credibility of the work and the establishment of future, more advanced and sophisticated investigations can be improved. Furthermore, in case of comparisons with control groups, implementation of a dedicated piece of software such as Prism (GraphPad Software, Inc, La Jolla, CA, United States) is advocated to generate scientifically sound figures[9] (Figure 2).

Furthermore, considering that *in vitro* research is the first step of the evidence-based procedure, researchers and clinicians alike should adopt a stepwise approach when validating the results of an *in vitro* laboratory experiment. More specifically, a proper animal model study should be generated following a successful *in vitro* experiment[10], so that the authors can assess their primary findings against *in vivo* conditions. As a last step, human testing should be performed for confirmation purposes[4].

Recently introduced techniques: Do they merit consideration?

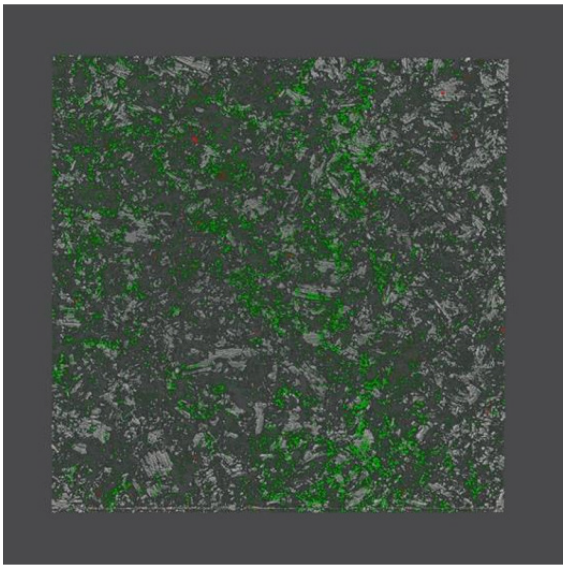
Molecular biology techniques: Molecular-biology-based techniques have rapidly evolved in the last years in orthopedic infections and other fields, such as in diagnosing severe acute respiratory syndrome coronavirus 2[11] and water surveillance industry. In particular, more sophisticated molecular methods, including but not limited to clustered regularly interspaced short palindromic repeats, next-generation sequencing and droplet-digital polymerase chain reaction (PCR) are currently being investigated to contribute to the detection of the above mentioned virus. Moreover, rapid detection of harmful bacteria in wastewater is achievable when utilising DNA microarray and sequencing-based methods[12].

Similar progression has been recorded over the past years in orthopedic infections, not only in experimental laboratory settings but also in clinical practice. To illustrate, utilisation of PCR-based techniques, including but not limited to DNA microarrays and multiplex PCR, has been one of the most important advances in periprosthetic joint infections (PJI) diagnosis during the last decades[13]. The readily available multiplex polymerase chain reaction techniques (*i.e.*, commercial and bespoke ones) feature satisfactory diagnostic accuracy, with a specificity approaching 100% and sensitivity varying between 70% to 80%[13]. In addition, newer diagnostic modalities such as metagenomic next-generation sequencing enable DNA sequencing directly from synovial fluid[14]. It has been claimed that metagenomic next-generation sequencing may revolutionise PJI diagnosis as it demonstrates increased sensitivity relative to PCR, while maintaining specificity at the same ultimate levels[13].

Is artificial intelligence applicable to *in vitro* models? Artificial intelligence (AI) may be implemented into orthopaedic *in vitro* models. For example, AI may aid in evaluating massive volumes of information from *in vitro* studies, such as gene expression data, protein profiles, and biomechanical data, to detect trends and make predictions. Another example would be application of AI to tumor models to monitor tumorigenesis progression in addition to real-time modelling[15]. Furthermore, AI could also aid in controlling the quality of organoids in the field of organogenesis and bioprinting technology[16]. In general, *in vitro* models frequently generate enormous volumes of data, including pictures and signals from several imaging modalities such as microscopy, radiography, and biomechanical sensors. AI enables assessing those data, extracting relevant information, and spotting small changes that human eyes may miss. This can facilitate measuring cellular activity, tissue shape, and mechanical characteristics, thus resulting in a more complete knowledge of the underlying biology[17,18]. Therefore, researchers may better understand the underlying process of orthopaedic illness, predict disease development, and consider prospective therapy efficacy[19]. In addition, AI can optimize experimental research designs by finetuning experimental settings, addressing sample size issues, and recommending the most important experiment variables that should be prioritised during analysis. Therefore, researchers may become more effective and productive, eliminate trial-and-error and save time and money at the same time[17]. Another example of AI application is referred to personalized/individualised medicine. AI may utilise patient-specific data, such as genetic information and medical history and construct tailored *in vitro* models that simulate the patient's clinical condition. Researchers can monitor illness development and explore individualized treatment strategies, leading to more effective and targeted therapeutic approaches.

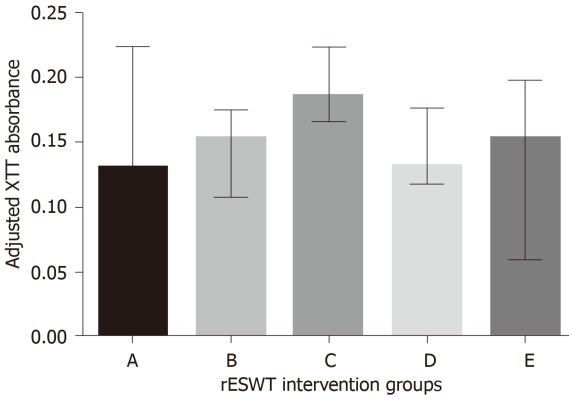
Additionally, AI can enhance the potential of medication research by evaluating enormous databases of chemical substances and predicting their possible effects on orthopaedic diseases. This can further identify interesting drug candidates and optimize their chemical structures, improving effectiveness and safety. Moreover, AI can generate virtual simulations of *in vitro* models, thus allowing researchers to test various scenarios and treatments in a controlled and cost-effective setting[20]. As a result, it could potentially refine experimental methods, minimise the requirement for physical experiments, and reduce the need to implement animal models.

Overall, AI has the potential to significantly improve orthopaedic *in vitro* models by enhancing predictive modeling, optimizing experimental design, assisting in image and signal analysis. Therefore, it improves customized therapy, expedites drug development, and facilitates virtual simulations. According to the above, orthopaedic researchers may obtain deeper insights into disease causes, devise more effective therapies, and ultimately enhance patient outcomes by utilizing the potential of AI.



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Figure 1 Image of a two-dimensional representation of *Cutibacterium acnes* growth on titanium alloy (Ti6Al4V) disk using Confocal laser microscopy (Leica model TCS SP5; Leica Microsystems CMS GmbH, Mannheim, Germany) following 72 h of anaerobic incubation. Live bacteria are represented in green and dead cells are in red.



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Figure 2 Graphical illustration enables visual comparison between the intervention groups. Variant absorption among the included radial extracorporeal shock wave treatment study groups following spectrophotometric evaluation is depicted. rESWT: Radial extracorporeal shock wave treatment; XTT: 2-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide.

Are *in vitro* "*ex-vivo*" infection models viable options? *Ex vivo* orthopaedic models allow using bone or muscle tissue as a substrate to form biofilm infections such as osteomyelitis[21]. These models appear particularly advantageous relative to their *in vitro* counterparts as they maintain important biological factors from the hosts[22]. *Ex vivo* experiments are cheaper than animal models and can spare animal lives[23]. However, careful consideration prior to selecting this type of laboratory research is advisable since no immune system interactions occur, and therefore the results may be suboptimal compared to *in vivo* settings[24].

CONCLUSION

Over the last years, the perception of orthopaedic conditions has shifted towards a more basic science-oriented approach. Therefore, the value of conducting high-quality basic science research tends to be increasingly appreciated by the orthopaedic community. In addition, when appropriate, favouring basic science over clinical investigations could mitigate the clinical research obstacles to some extent. However, it is important to highlight that unwarranted extrapolations of basic science research to human biology should be avoided.

FOOTNOTES

Author contributions: Tsikopoulos K conceptualized and drafted the paper; Meroni G contributed to the organization and writing of this article; Kitridis D, Chalidis B, and Papageorgiou F contributed to the orthopaedic part of this manuscript; Drago L and Papaioannidou P supervised this project.

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MINIREVIEWS

Fractures around the shoulder in the skeletally immature: A scoping review

Tim Kraal, Peter AA Struijs, Lisette C Langenberg, Christiaan JA van Bergen

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Peer-review report's scientific quality classification

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Abstract

Fractures around the shoulder girdle in children are mainly caused by sports accidents. The clavicle and the proximal humerus are most commonly involved. Both the clavicle and the proximal humerus have a remarkable potential for remodeling, which is why most of these fractures in children can be treated conservatively. However, the key is to understand when a child benefits from surgical management. Clear indications for surgery of these fractures are lacking. This review focuses on the available evidence on the management of clavicle and proximal humerus fractures in children. The only strict indications for surgery for diaphyseal clavicle fractures in children are open fractures, tenting of the skin with necrosis, associated neurovascular injury, or a floating shoulder. There is no evidence to argue for surgery of displaced clavicle fractures to prevent malunion since most malunions are asymptomatic. In the rare case of a symptomatic malunion of the clavicle in children, corrective osteosynthesis is a viable treatment option. For proximal humerus fractures in children, treatment is dictated by the patient's age (and thus remodeling potential) and the amount of fracture displacement. Under ten years of age, even severely displaced fractures can be treated conservatively. From the age of 13 and onwards, surgery has better outcomes for severely displaced (Neer types III and IV) fractures. Between 10 and 13 years of age, the indications for surgical treatment are less clear, with varying cut-off values of angulation (30-60 degrees) or displacement (1/3 – 2/3 shaft width) in the current literature.

Key Words: Clavicle fracture; Proximal humerus fracture; Pediatric; Skeletally immature; Children; Shoulder

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Core Tip: Fractures of the clavicle and proximal humerus in children can be treated conservatively in most patients because of their large remodeling potential. The difficulty is to understand when a child is better off with surgical treatment of his/her clavicle or proximal humerus fracture. This review aims to provide a better understanding of the indications for surgical management of these fractures in the skeletally immature based on the latest literature.

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INTRODUCTION

Fractures of the shoulder girdle in the skeletally immature are relatively rare, and most fractures can be treated conservatively. However, precisely this situation makes deciding which pediatric shoulder fracture needs surgical treatment difficult. Of the pediatric shoulder girdle injuries, fractures of the clavicle and proximal humerus are the most common. This review article updates treatment recommendations for these fractures in the skeletally immature.

DIAPHYSEAL CLAVICLE FRACTURES

Epidemiology

The clavicle is the most commonly fractured shoulder girdle bone in children. It accounts for 10%-15% of all pediatric fractures, more common in boys compared to girls[1]. Most clavicle fractures occur during sports activities like bike accidents or horse riding. About 90% of clavicle fractures are diaphyseal, and most are Allman type 1 fractures, in the middle third of the shaft[2]. More than 50% of clavicle shaft fractures in children and adolescents are completely displaced with substantial shortening[3]. Clavicle fractures due to obstetrical injury are beyond the scope of this review.

Anatomy

The clavicle has a medial and lateral ossification center which usually fuse around the seventh week of gestation. A congenital pseudoarthrosis can develop if this fusion does not occur, leading to a painless protuberance[4]. Eighty percent of clavicular longitudinal growth occurs from the medial physis. The lateral physis closes around 18-19 years of age, and the medial physis is the last of the human body to close around 23 to 25 years of age. The clavicle is surrounded by a thick periosteum around both ends. Sternoclavicular (SC) injuries and, to a lesser extent, acromioclavicular (AC) injuries, are often trans-physeal fractures rather than true AC or SC joint dislocations[5,6].

Treatment

There are few clear indications for surgical treatment of clavicle fractures in children; open fractures, irreducible fractures with significant tenting of the skin with impending skin necrosis, acute neurovascular injury, or concomitant fractures of the scapula (floating shoulder). In adults, substantial dislocation of a clavicular shaft fracture often indicates osteosynthesis to avoid non-union or symptomatic malunion. In children, however, these fractures can usually be treated non-operatively with a sling or figure-of-eight bandage. Your mentor might have told you the adage: "If the two ends of the child's clavicle are in the same room, they will heal and remodel adequately". There are several articles with typical radiographs showing consolidation and remodeling after displaced clavicle fractures[7,8]. Even an initial displacement of more than 2cm will most likely lead to union without clinically meaningful loss of shoulder motion or strength[9,10]. The degree of dislocation will most likely improve during the initial healing phase, and substantial remodeling can occur since clavicle growth continues up to 25 years of age[11,12]. However, there seems to be a tendency towards more surgical procedures for clavicle fractures in teenagers[13]. This is most likely the result of a similar trend toward surgical treatment of clavicle fractures in adults. In contrast to the situation in adults, however, little evidence supports this trend in the skeletally immature.

The potential advantages of surgical management are a quicker return to sports and avoiding non- and malunion. A recent review showed a quicker return to sports of 4-6 wk in the surgically treated group[14,15]. However, other studies do not show a significantly shorter return to sports[16]. The gain in weeks for return to sports is relatively minimal, but might be a consideration for young athletes who wish to return to high-level sports as soon as possible. Surgery is associated with higher healthcare costs and a higher complication rate. The most common complications are sensory loss

at the chest region and implant prominence. Secondary surgery because of implant prominence is reported in 10%-20% of cases[8,17]. The pros and cons for young athletes should be used in shared decision-making if surgical treatment is considered, which is also highlighted in a current concepts review on this topic[18].

Nonunion, malunion, and re-fracture risk

Whether surgery should be performed to prevent non- and symptomatic malunion in children is highly questionable. Clavicular non-unions in children do exist, but are exceedingly rare. Figure 1 shows a rare case of a 15 year old boy with scapular dyskinesia caused by shortening of his clavicle due to a nonunion. A large randomized trial comparing surgical treatment with conservative treatment for displaced clavicular fractures found a non-union rate of 0.4%[19]. With such low numbers of non-union, the incidence of non-union is difficult to establish, but is estimated to be less than 1%[20]. Although most non-unions occur in completely displaced fractures, they can even happen in minimally displaced fractures[20]. The primary risk factor for non-union is a re-fracture[20,21]. Non-unions are usually treated successfully with plate fixation. Bone grafting from the locally available non-union fracture site is usually enough, and iliac crest bone graft is not necessary in most cases[20,22].

Historically, symptomatic malunion has been a concern, potentially leading to decreased function or strength of the affected shoulder. This hypothesis was mainly based on anatomical and biomechanical studies[23]. In clinical reports, it is assumed that malunion can cause a wide variety of symptoms, such as functional limitations of the arm with or without pain, weakness of the arm, scapular dyskinesia, thoracic outlet syndrome or compression on the brachial plexus, and cosmetic dissatisfaction[24].

There is good quality evidence on this topic available at the moment, with a recent large multicenter cohort study comparing operative *vs* non-operative treatment for displaced clavicle fractures in adolescents[19]. Multiple upper limb functional outcome scores showed no significant differences between both groups. Only two out of 291 patients in this cohort developed a symptomatic malunion after non-operative treatment. For the rare patient who develops a symptomatic malunion, delayed (corrective) osteosynthesis is a good option. Adequate pre-operative 3D planning and patient-specific cutting guides can aid in correcting the three-dimensional deformity of the clavicle. However, no reports could be found explicitly aimed at children concerning malunion corrections[25].

The re-fracture risk of the clavicle in pediatric patients is around 2% to 6%. Interestingly, the re-fracture risk is higher after angulation only for completely displaced fractures[7]. It is hypothesized that this can be caused by more callus formation in completely displaced fractures compared to angulation-only fractures. Re-fractures occur in both surgically and non-operatively treated patients, perhaps even more frequently in surgically treated patients[14,19]. Just like initial diaphyseal clavicle fractures, most re-fractures can be treated non-operatively.

To conclude, the standard of care for all diaphyseal clavicle fractures in the skeletally immature is non-operative treatment. A quicker return to sport is a relative argument to opt for surgery in the adolescent (professional) athlete. Non-union is very rare in the skeletally immature and can be treated with osteosynthesis. Most cases of initial shortening will remodel, and even most malunions will recover without functional limitations in the long term. Osteosynthesis of the clavicle should not be chosen to prevent non-union, shortening, or malunion in the skeletally immature. Corrective osteosynthesis should be reserved for rare cases with symptomatic malunion.

PROXIMAL HUMERUS FRACTURES

Epidemiology

Proximal humerus fractures in the pediatric population are quite rare and relatively uncommon compared to other upper limb fractures in children. This fracture accounts for approximately 0.5 to 3% of all pediatric fractures[26,27]. Pediatric proximal humerus fractures are more common in boys compared to girls in most geographical areas[28].

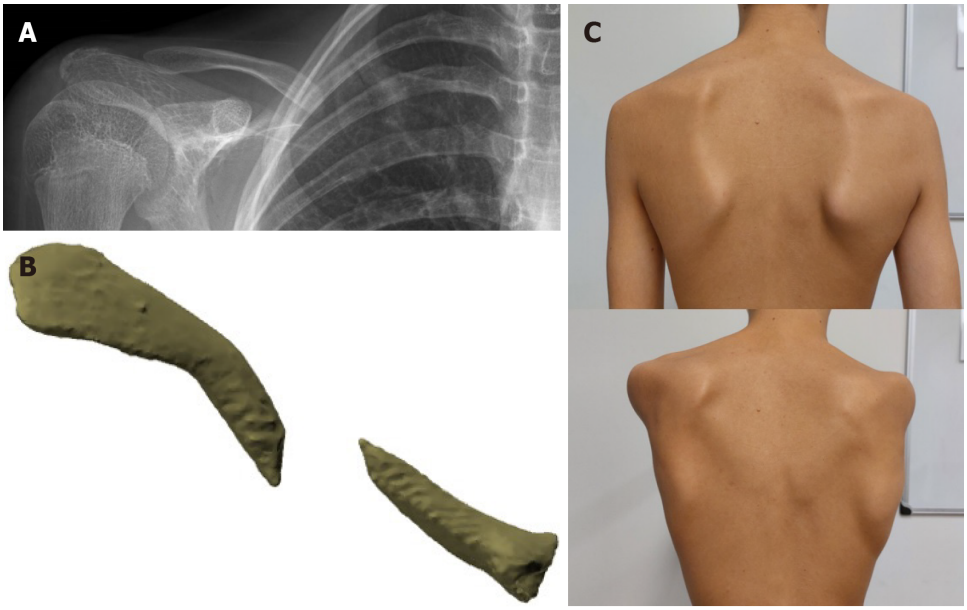
The trauma mechanism can be a backward fall on an extended and externally rotated arm. These injuries can result from sports, horse- or bike riding, and motor vehicle accidents. In the very young, especially under 18 mo of age, one must be aware of the possibility of child abuse[29].

Radiographs should be carefully screened for intra-osseous pathologic lesions or cysts if a proximal humerus fracture is diagnosed after minimal trauma. Of all pathologic fractures, the proximal humerus and the proximal femur are the most common locations for a pathologic fracture to occur[30]. Unicameral or solitary bone cysts are the leading cause of these pathologic fractures. Also, the presence of pain preceding the fracture should raise the suspicion of a pathologic fracture.

Little League Shoulder is an entity on its own. This is a stress- or insufficiency fracture of the proximal humeral physis due to overuse, most commonly repetitive throwing, such as in young baseball players. Patients typically report pain while throwing. In addition, radiographs can show widening of the physis and lateral physeal fragmentation, calcification, and/or sclerosis.

Anatomy

The proximal humerus develops from three ossification centers (head, greater and lesser tuberosity). The ossification center of the head appears between birth and six months, followed by the ossification center of the greater tuberosity around the age of 6-18 mo. Lastly, the ossification center of the minor tuberosity appears around the age of five. These ossification centers merge into one single proximal humerus physis between the 4th and 7th year of age[31].



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Figure 1 A rare case of a 15-year-old boy with scapular dyskinesia caused by shortening of his clavicle due to a nonunion. A: Anteroposterior radiograph showing the clavicle nonunion; B: Three dimensional computed tomography reconstruction of the same clavicle nonunion; C: Scapular dyskinesia (right sided) caused by shortening of the clavicle due to nonunion.

During growth, the shape of the physis changes from a rounded shape to a more V-shape or pyramidal shape, which is responsible for the double contour on an AP radiograph (Figure 2).

The physis of the proximal humerus is responsible for 80% of the longitudinal growth of the humerus and therefore has tremendous potential for remodeling. The blood supply of the humeral head is abundant and arises from the anterior and posterior humeral circumflex arteries with their anastomoses; both are branches of the axillary artery. Hence, in contrast to proximal humerus fractures in the elderly population, the risk of posttraumatic avascular necrosis is very low in the pediatric population.

Diagnosis and classification

Conventional radiographs are usually sufficient to diagnose this injury. AP, scapula Y (trans scapular), and axillary views are recommended. The axillary view is essential to rule out a glenohumeral dislocation or concomitant glenoid fracture. If it is impossible in the acute setting to obtain an axillary view with the arm in abduction, the Velpeau view with the arm in a sling is a valuable substitute[32]. Radiographs of the opposite shoulder can be taken for comparison if necessary. The indication for a CT scan in proximal humerus fractures is limited and should be used only in select cases, considering the ionizing radiation on the developing body.

Around 85% of all proximal humerus fractures in the pediatric population are non- or minimally displaced[28]. The amount of displacement can be graded with the Neer-Horwitz classification (Table 1). Type I and II are nondisplaced or minimally displaced fractures, less than 5 mm and less than one-third of the diameter of the shaft. Type III and IV are more severely displaced fractures with displacement of more than one-third of the shaft[33].

The fracture type is influenced by the development of the physis, thus, the patient's age. Pre-puberty children tend to sustain more metaphyseal fractures (around 70%), and epiphyseal fractures occur more frequently in adolescents (around 30%) and are almost always Salter-Harris (SH) type I physeal separations, or SH type II with a wedge extending medially [34].

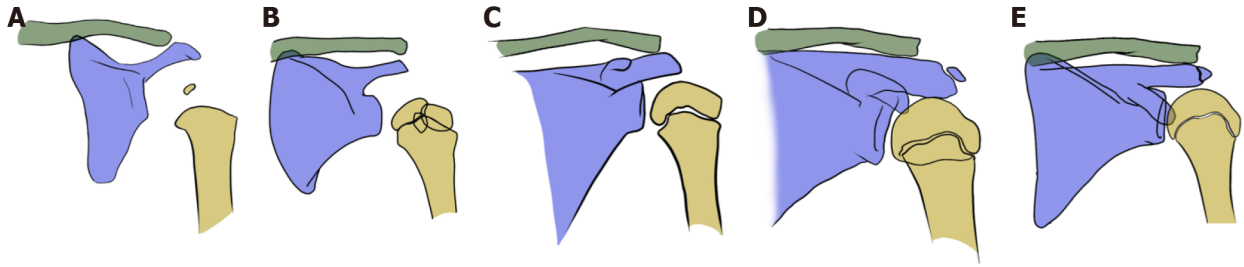
The direction of displacement is caused by the deforming forces of the muscles around the shoulder. The main direction of dislocation is varus. The supraspinatus, infraspinatus, and teres minor all pull the major tubercle, usually attached to the humeral head, posteriorly and medially, which causes the head to become dislocated in varus and external rotation. The pectoralis major pulls the shaft anteriorly and medially, a so-called "apex anterior fracture", potentially leading to a pro-curvatum deformity (Figure 3).

Treatment

All non- or minimally displaced proximal humerus fractures (Neer types I and II) can be successfully treated conservatively without long-term shoulder complaints[35]. Treatment of displaced proximal humerus fractures remains controversial. The remaining potential for remodeling is an important factor to take into consideration. It is still difficult to judge what amount of deformity will lead to a less-than-desirable clinical outcome, and age does not correspond accurately with skeletal maturity. There are no generally accepted guidelines with clear cut-off values, and there are no randomized trials comparing conservative *vs* operative treatment for displaced proximal humerus fractures. However, modestly increasing trends of surgical treatment for these fractures were found in large database studies in the United States and Finland[28,36]. Most articles on this topic state that until age ten, conservative treatment is a safe option, even

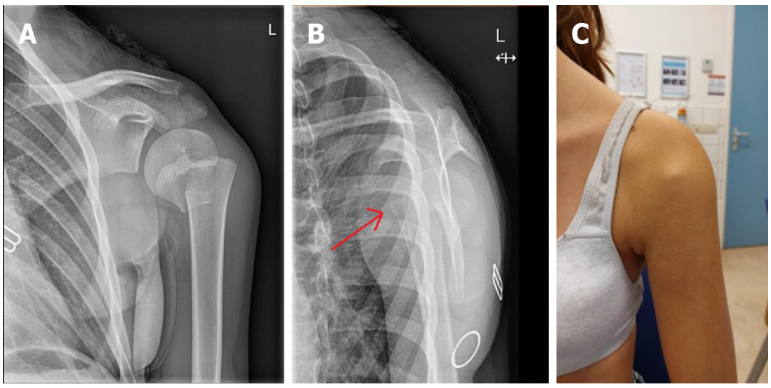
Table 1 Neer and Horwitz classification of pediatric proximal humerus fractures[33]

Grade	Displacement
I	< 5 mm
II	< 1/3 shaft width
III	1/3 – 2/3 shaft width
IV	> 2/3 shaft width



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Figure 2 Schematic drawing of the physis of the proximal humerus during growth. A: 1 mo; B: 5 years; C: 9 years; D: 11 years; E: 15 years of age.



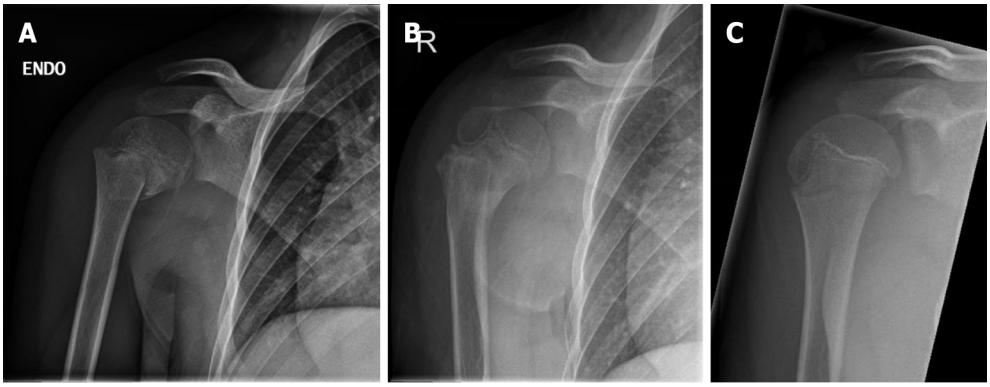
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Figure 3 Case example of a 14-year-old girl. A: Anteroposterior; B: Transscapular radiograph showing an 'apex anterior' displacement of a proximal humerus fracture (arrow); C: Clinical photograph showing the apex anterior displacement visibly beneath the skin.

for severely displaced fractures[37,38]. In a comparative matched case-cohort study from Chaus *et al*[39], surgical treatment was compared to non-operative treatment for Neer type III and IV fractures. There were no patients younger than thirteen with a less-than-desirable outcome in the non-operative group. The risk of a poor (or less than desirable) outcome after conservative treatment of severely displaced fracture did increase substantially from the age of 13. Some authors advocate surgical treatment under the age of ten in case of 100% displacement or over 70 degrees of angulation [28,34]. But this is still debatable because of the remarkable potential of remodeling of the proximal humerus under age 10 (Figure 4).

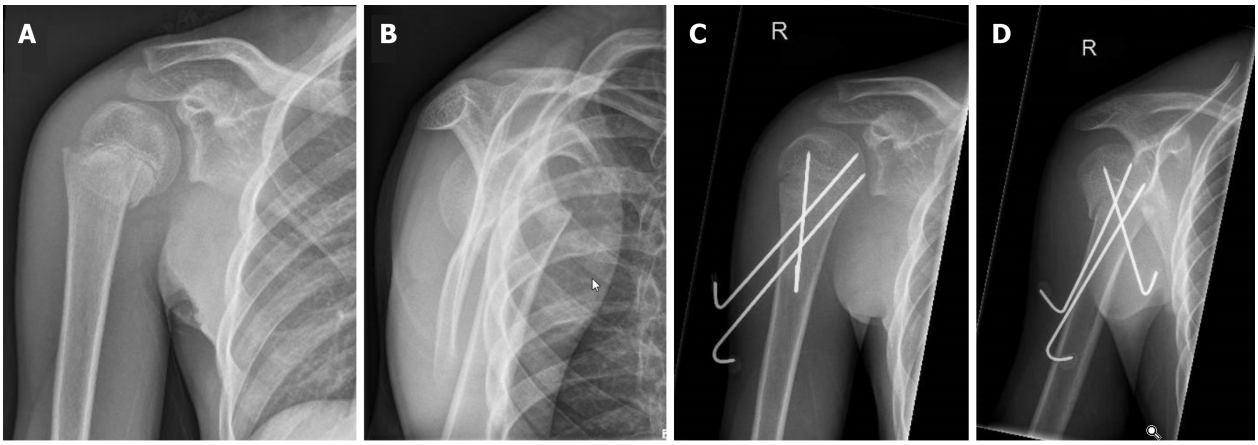
Surgical treatment should be considered for displaced (Neer type III or IV) fractures in patients older than ten years. Kim *et al*[32] have shown varying cut-off values in the current relevant literature on this topic. In children aged 13 and older, cut-off values from 20 – 40 degrees angulation and over one-third of shaft displacement are found. The least consensus exists in the age group of 10 to 13 years, with 40 to 60 degrees of angulation as cut-off values as an indication for surgical treatment[32]. From the age of 13, surgery seems to have a higher success rate compared to conservative treatment in severely displaced fractures (Neer III/IV or more than 20 degrees of angulation)[37].

If surgical treatment is opted for, one should strive to avoid open reduction because deltopectoral incisions at a young age can lead to unsightly hypertrophic scar formation. Closed reduction should be attempted first. The arm should be brought into abduction (to correct the varus), and the proximal shaft should be pushed posteriorly (to counteract the anterior pull of the pectoralis major)[34]. In a minority of cases, closed reduction cannot be achieved because of interposition of soft tissue, such as the long head of the biceps, periosteum, or deltoid muscle. In these cases, open reduction through the deltopectoral approach should be considered, which is most commonly used[40]. If the reduction is adequate, fixation can be achieved by either percutaneous K-wires or retrograde elastic stable intramedullary nailing



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Figure 4 Remodeling of a proximal humerus fracture in an 8-year-old boy. A: Anteroposterior radiographs taken at the initial trauma; B: After 3 mo; C: After 8 mo.



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Figure 5 An example of a Neer type II displaced proximal humerus fracture in a 12-year-old boy. A: Anteroposterior; B: Transscapular radiographs taken after the trauma; C and D: After closed reduction and percutaneous K-wire fixation.

(ESIN). The advantage of percutaneous K-wires is that the surgery is quick, inexpensive, and relatively easy to perform without the need for secondary surgery. Figure 5 Immobilization in a sling or a shoulder immobilizer is required until removal of the K-wires, usually after 3-4 wk. The technique of retrograde ESIN can be somewhat more challenging but is an elegant option to treat these fractures. Two nails, diverging in the proximal fragment, should be used. Both nails should be inserted just proximal to the lateral epicondyle, taking care not to injure the radial nerve. Sharp-tipped nails should be used to perforate into the humeral head, as blunt-tipped nails may push the proximal fragment away. Immobilization can be quite minimal after ESIN, with a sling worn for two weeks. A disadvantage of ESIN is the need for a second surgical procedure to remove the nails. Removing the nails relatively early, starting from the fifth postoperative week, is recommended, given the risk of complete distal penetration into the humeral shaft caused by growth[34,37]. The functional outcome did not differ significantly between surgical treatment options in the most extensive meta-analysis [37].

According to a large meta-analysis, the overall complication rate of ESIN and K-wires was not significantly different, with 7% and 9%, respectively[37]. No cases of radial nerve injury (ESIN group) or axillary nerve injury (K-wires group) were found in this systematic review. However, premature closure of the physis with arm length discrepancy did occur more frequently in the K-wires group, up to 19% in severely displaced fractures. Although it is uncertain to what extent this was clinically relevant. Specific complications for ESIN are penetration of the humeral head, loss of reduction, and temporary elbow stiffness. However, most complications are preventable with an adequate 'two nail' surgical technique.

In summary, proximal humerus fractures can often be treated conservatively because of the large potential for remodeling of the proximal humerus physis, especially under age 10. However, surgery is recommended for displaced fractures (Neer types III and IV) in patients older than 13 years. Closed reduction should be attempted, and fixation with either two retrograde elastic intramedullary nails or K-wires is acceptable. For children between 10 and 13 years of age, the indication for surgical treatment is less clear, with varying cut-off values of angulation (30-60 degrees) or displacement (1/3 – 2/3 shaft width) in the current literature.

CONCLUSION

In conclusion, both clavicle and proximal humerus fractures have a large potential for remodeling in the pediatric population. Expected residual growth, and thus remodeling, is an important factor in decision-making for these fractures. Although rarely mentioned in the relevant literature, especially in young teenagers around 10 to 15 years, there is a considerable difference in residual growth for boys compared to girls at the same age. Future research, such as pediatric trauma registry data with long-term follow-up, should ideally give better insight into cut-off values of the indication for surgery in these fractures, thereby enabling evidence-based, more detailed flowcharts. Because pediatric fractures around the shoulder that need surgical intervention are uncommon, guidelines with clear indications for surgery could take pediatric trauma care to a higher level. Without clear guidelines, there is a potential risk of overtreatment (too much surgery) and the rare case that will benefit from surgery going unrecognized.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Failure rate, return-to-sports and magnetic resonance imaging after meniscal repair: 119 patients with 7 years mean follow up

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Abstract

BACKGROUND

One of the most important factors to consider in relation to meniscal repair is the high failure rate reported in the existing literature.

AIM

To evaluate failure rates, return to sports (RTS) rate, clinical outcomes and magnetic resonance image (MRI) evaluation after meniscus suture repair for longitudinal tears at a minimum 2-year-follow-up.

METHODS

We conducted a retrospective review of meniscal repairs between January 2004 and December 2018. All patients treated for longitudinal tears associated or not with an anterior cruciate ligament reconstruction (ACL-R) were included. Meniscal ramp lesions, radial and root tears, associated with multiligament injuries, tibial fracture and meniscal allograft transplants were excluded. Surgical details and failure rate, defined as symptomatic patients who underwent a revision surgery, were analyzed. As isolated bucket handle tears (BHTs) were usually associated with higher failure rates, we compared BHTs and not BHTs associated or not with an ACL-R. Since 2014, the inside-out technique using cannulas and suture needles with 2-0 Tycron began to predominate. In addition, the number of stitches per repair was increased. In view of differences in surgical technique, we compared two different cohorts: before and after 2014. We recorded the RTS according to the level achieved and the time to RTS. Lysholm and IKDC scores were recorded. Patients were studied with x-rays and MRI as standard postoperative control.

RESULTS

One hundred and nineteen patients were included with a mean follow up of 7 years (SD: 4.08). Overall failure rate was 20.3% at a mean 20.1 mo. No statistically significant differences were found when comparing failure for medial and lateral

meniscal repair (22.7% and 15.3%, $P = 0.36$), BHTs and not BHTs (26% and 17.6%, $P = 0.27$), isolated or associated with an ACL-R (22.9% and 18%, $P = 0.47$), or when comparing only BHTs associated with an ACL-R (23% and 27.7%, $P = 0.9$) or not. When comparing cohorts before and after 2014, we found a significant decrease in the overall failure rate from 26% to 11% ($P < 0.03$). Isolated lesions presented a decrease from 28% to 6.6% ($P = 0.02$), BHTs from 34% to 8% ($P = 0.09$) and those associated with an ACL-R from 25% to 10% ($P = 0.09$). Mean RTS time was 6.5 mo in isolated lesions and 8.64 mo when associated with an ACL-R. Overall, 56% of patients returned to the same sport activity level. Mean pre and postoperative Lysholm scores were 64 and 85 ($P = 0.02$), and IKDC 58 and 70 ($P = 0.03$). Out of 84 asymptomatic patients evaluated with MRI, 39% were classified as "not healed" and 61% as "healed".

CONCLUSION

Even though the overall failure rate of our series was 20.3%, we found a statistically significant decrease from 26% to 11%, not only for isolated lesions, but also for BHT's and those associated with an ACL-R when comparing our series in two different cohorts, most probably due to improvements in surgical technique.

Key Words: Meniscus repair; Bucket handle tears; Meniscal suture; Failure rate; Longitudinal meniscus tears

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Core Tip: One of the most important factors to consider in relation to meniscal repair is the high failure rate reported in the literature. In this retrospective cohort we observed that new and improved suturing techniques have shown significantly lower failure rates, encouraging the need for meniscal repair whenever possible.

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INTRODUCTION

Due to the high rate of osteoarthritis observed after partial or total meniscectomy[1], meniscal repair techniques have been gaining significance over the last decades[2], total meniscectomy being particularly important in young patients and athletes[3]. Moreover in the case of Anterior cruciate ligament reconstruction (ACL-R), meniscal deficiency is frequently associated with residual rotational laxity affecting long term clinical outcomes[4-6]. Consequently, it is mandatory to preserve the meniscus when performing an ACL-R whenever possible.

The rate of meniscus repair has increased over the past few decades, along with the number of revision surgeries due to failed repair[6-8]. All-inside sutures required mainly for posterior horn lesions had historically been associated with higher failure rates and revision surgery[9]. Recent studies have shown that improvement in surgical strategies coupled with the development of more sophisticated suture devices, has led to an improvement in the success rate of meniscal preservation[10,11].

In our institution, the number of meniscal repairs has been growing exponentially since 2010. In addition, techniques have been changing over time. Therefore, the main purpose of our study was to evaluate failure rates after meniscus suture repair. As secondary objectives we analyzed return to sports (RTS) rate, clinical outcomes and magnetic resonance image (MRI) evaluation.

MATERIALS AND METHODS

After institutional review board approval, we performed a retrospective review of prospectively collected registry data including all patients treated with meniscal repair at our institution between January 2004 and December 2018. We included patients operated on vertical meniscal tears. Ramp lesions, radial lesions and root tears were excluded, as well as patients with meniscal allograft transplant, associated with multiligament knee injuries and patients with less than a two-year follow-up.

All surgical procedures were performed by the same surgical team, followed by a standard rehabilitation protocol. Variables analyzed included the patient's gender and age, tear type and surgical technique. Repair was registered as follows: all-inside, inside-out, outside-in. Failure was defined as symptomatic patients who underwent a revision surgery due to re-rupture at the previously treated portion of the meniscus. Historically, higher healing rates have been associated with meniscal repair in the setting of an ACL-R[12], as well as small vertical lesions have been compared to Bucket Handle Tears (BHTs)[9,13]. Hence, we analyze our cohort in different subgroups: Meniscal repairs associated with

ACL-R compared to isolated meniscal repairs, and BHTs compared to non BHTs.

In addition, rate and time to RTS, subsequent surgeries, preoperative and postoperative subjective assessment (Lysholm and IKDC scores) were reported, and postoperative complications were recorded and analyzed.

X-rays and MRI were routinely obtained during follow-up in order to evaluate meniscal healing. Results were classified and categorized as: "Not healed", when a gap greater than 2 mm was present in the repaired meniscus with a hyperintense continuous homogeneous line (Figure 1) and "healed", when continuity was observed (Figure 2). MRI categorization did not define failure, only a description of the images even in asymptomatic patients.

Indication and Surgical technique

All inside sutures were indicated for posterior horn lesions. Inside-out technique was usually indicated for lesions of the middle third of the meniscus. In selected cases, anterior horn and posterior horn lesions (using a postero-medial or postero-lateral approach to retrieve the sutures) were also treated with this technique. In the case of inside-out technique, specific cannulas were introduced through the contralateral portal, and long needles with 2-0 Tycron sutures were passed through. Outside-in technique was indicated for the anterior third of the meniscus, using 2-0 Tycron sutures or 0 PDS sutures.

In the case of BHTs, usually, two or three of these techniques were combined. In most cases, all-inside devices were used for the posterior horn in combination with inside-out or outside-in techniques for the rest of the meniscus. When all-inside devices were not available, the inside-out technique was used, retrieving the stitches through a postero-medial or postero-lateral approach.

One of the greatest changes in our surgical approach was to begin to perform multiple vertical stitches spaced every 4 mm using cannulas for the inside-out technique with 2-0 Tycron sutures as compared to most sutures performed prior to 2014 using few horizontal inside-out 0 PDS stitches (Figure 3).

Regarding ACL-R, either using hamstrings graft or bone-patellar tendon-bone, we performed transportal anatomic technique, maintaining the anatomic insertion footprint in both the femur and the tibia.

Postoperative Rehabilitation Protocol

Two different protocols were used after surgery for three different scenarios: isolated lesions, lesions associated with ACL-R and BHTs.

Isolated lesions, as well as those associated with an ACL-R were allowed for immediate partial weight bearing using a knee brace for three weeks. Flexion was limited to 90° for the first three weeks with progressive mobilization until complete flexion. Non-impact activities were allowed after three weeks. RTS was allowed by the fourth month. When associated with an ACL-R, RTS was determined according to the ACL-R protocol.

BHTs were indicated for non-weight bearing and flexion 0-70° for three weeks, followed by partial weight bearing for three more weeks and progressive flexion to 90°. After that period, progressive flexion and non-impact activities were indicated until complete range of motion. Impact sports activities were allowed from the fifth month onwards or according to the ACL-R protocol.

Statistical analysis

Descriptive statistics including means, standard deviations, median and quartile ranges were deemed appropriate to assess the available demographic, surgical, physical examination and patient-reported outcome data. Statistical hypothesis testing was performed using the Fisher exact test and Wilcoxon rank-sum test. Chi-square test was performed for categorical data. Analysis was performed with 95%CIs, and P values < 0.05 were considered statistically significant. All statistical analyses were performed using STATA version 15.

RESULTS

A total of 140 patients underwent a meniscal repair during the study period. Ten patients did not meet the inclusion criteria and eleven were lost in follow-up. There were no patients whose meniscus was re-ruptured and declined receiving revision surgery. Therefore, 119 patients were included in the study, 83% (n = 99) males, with a mean age of 27.1 years (SD: 8.02). Mean follow-up was 7 years (SD: 4.08). Table 1 shows the number of meniscal sutures, the distribution for isolated or BHT's, associated or not with an ACL-R, failure rates and time to failure.

Total

Overall failure rate was 20.3% (24/119) at a mean of 20.1 mo (range 11-60 mo). We found no statistically significant differences when comparing BHT's with not BHT's (26% and 17.6%, P = 0.27), associated with an ACL-R with isolated repairs (18% and 22.9%, P = 0.47), or BHT's associated or not with an ACL-R (23% and 27.7%, P = 0.9) (Table 1).

No significant difference was found when comparing overall failure rate for medial *vs* lateral meniscal repair (22.7% and 15.3%, P = 0.36), though medial meniscus lesions were more frequently associated with an ACL-R than lateral meniscus lesions (70% and 41%) (Table 2).

There was an increase in the number of stitches, from a mean of 1.4 (SD: 1.01) to 3.5 (SD: 2.31) for BHTs and 1.2 (SD: 0.5) to 2.1 (SD: 1.1) for isolated repairs. We found a statistically significant decrease (Table 3) in overall failure rate after meniscal repair from 26% for 67 meniscal repairs in the period between 2004 and 2014 to 11% for 52 repairs after that period (P = 0.03) as for isolated lesions (not associated with an ACL-R) with a decrease from 28% (9/32) to 6.6% (1/15) after 2014 (P = 0.02). Although there was no statistically significant difference, overall BHT's failure rate decreased from

Table 1 Demographic data and overall failure rate, *n* (%)

Overall meniscal sutures			
	Total	**Failure**	**Time to failure, months**
Total sutures	119 (100)	24 (20.3)	20.1
BHT	34 (28)	9 (26.4)	20.8
Not BHT	85 (72)	15 (17.6)	19.7
Posterior horn	37 (43)	7 (18.9)	19.1
Body	43 (50)	8 (18.6)	20.2
Anterior horn	5 (7)	0 (0)	0
Associated w/ACL-R	71 (60)	13 (18.5)	17
ACL-R + BHT	17 (23)	4 (23)	12.5
ACL-R + Not BHT	54 (77)	9 (16.6)	19.1
Isolated	48 (40)	11 (22.9)	23.8
BHT	18 (37)	5 (27.7)	27.6
Other	30 (63)	6 (20)	20.6

BHT: Bucket handle tear; ACL-R: Anterior cruciate ligament reconstruction.

Table 2 Descriptive data for medial and lateral meniscus, *n* (%)

Location	Total	Failure	Time (months)
Medial meniscus	80	18 (22.7)	18
ACL-R[1]	56 (70)	11 (19.6)	16.6
Isolated	24 (30)	7 (29)	18.5
Lateral meniscus	39	6 (15.3)	28.5
ACL-R[1]	16 (41)	2 (12.5)	19.5
Isolated	24 (59)	4 (16)	33

[1]Results represent patients treated with sutures associated with ACL-R.
ACL-R: Anterior cruciate ligament reconstruction.

34% (8/23) to 8% (1/12) (P = 0.09), and meniscal sutures associated with an ACL-R decreased from 25% (9/35) to 10% (4/37) (P = 0.09).

RTS and Subjective Scores (Patient-Reported Outcome Measures)

Overall mean time to RTS was 7.8 mo (SD: 2.77), 6.55 mo (SD: 2.36) for isolated lesions and 8.64 mo (SD: 2.72) when associated with an ACL-R. At the final follow-up, 67 patients (56%) returned to the same activity level, 28 (24%) reported a lower activity level and 3 patients (2%) decided not to return to sport activities. Twenty-one patients (18%) did not practice any sports at all.

The mean pre and postoperative Lysholm score was 64 (SD: 10.2) and 85 (SD: 14.08) respectively (P = 0.02) and the mean pre and postoperative IKDC score was 58 (SD: 7.51) and 70 (SD: 10.22), respectively (P = 0.03).

Radiological assessment

Eighty-four asymptomatic patients (71%) were evaluated with X-rays and MRI at a mean 3 years postoperative. X-rays did not reveal arthritic changes during that period. A total of 33 MRI's (39%) were classified as "not healed" and 51 (61%) as "healed". It is important to emphasize that these were asymptomatic, active patients.

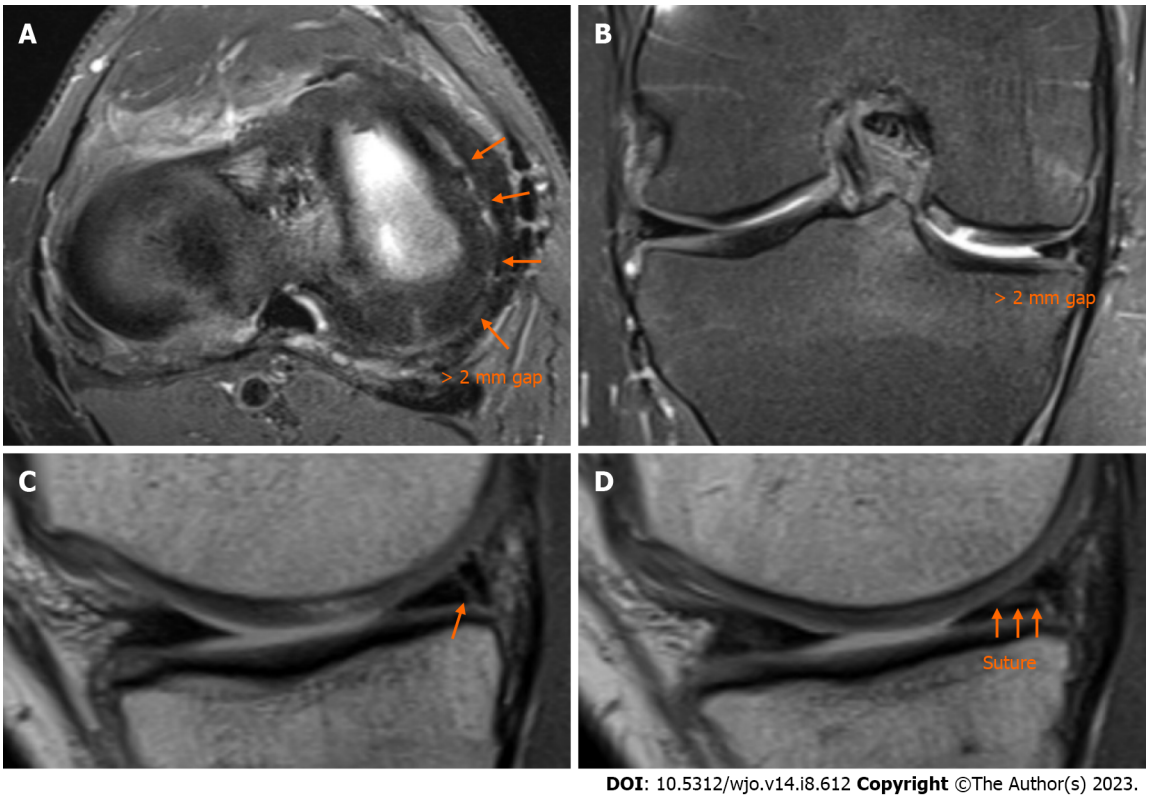
Complications

No intraoperative complications were reported. As to postoperative complications, two cases (1.6%) presented septic arthritis in the setting of an ACL-R and were treated with arthroscopic irrigation and debridement followed by intravenous antibiotics for four weeks, and one (0.8%) patient was operated on for isolated meniscal repair presented a

Table 3 Demographic data and failure rates for patients operated before and after 2014, *n* (%)

Period	2004-2013		2014-2018		*P* value
Age yr (range)	25.94 (16-48)		28.21 (18-59)		0.72
Gender, female	13 (19)		7 (13)		0.12
Total	*n*	Failure	*n*	Failure	0.03
	67	18 (26)	52	6 (11)	
Associated w/ACL-R	35 (52)	9 (25)	37 (71)	4 (10)	0.09
BHT	11 (31)	3 (27)	5 (14)	1 (20)	0.63
Not BHT	24 (69)	6 (25)	32 (86)	3 (9)	0.11
Isolated	32 (48)	9 (28)	15(29)	1 (6.6)	0.02
BHT	11 (34)	5 (45)	7 (47)	0 (0)	0.05
Not BHT	21 (66)	4 (19)	8 (53)	1 (12)	0.57
BHT[1]	23 (34)	8 (34)	12 (23)	1 (8)	0.09

[1]The results represent the overall bucket handle tear before and after 2014.
BHT: Bucket handle tear; ACL-R: Anterior cruciate ligament reconstruction.



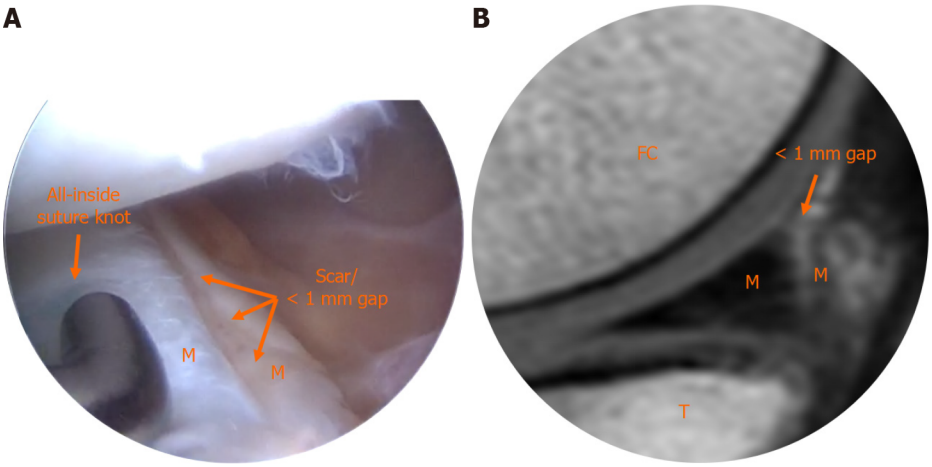
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Figure 1 Two-years postoperative magnetic resonance imaging classified as "not healed". This asymptomatic patient was treated with a bucket handle tears suture associated with Anterior cruciate ligament reconstruction. A: Axial plane showing a more than 2 mm gap; B: Same gap in the coronal plane; C: The posterior horn in the sagittal plane shows a gap less than 1mm wide in the meniscus; D: The transversal line in the posterior horn of the meniscus pointed by the arrows is the suture crossing from anterior to posterior.

superficial wound infection which was treated with oral antibiotics for 10 d.

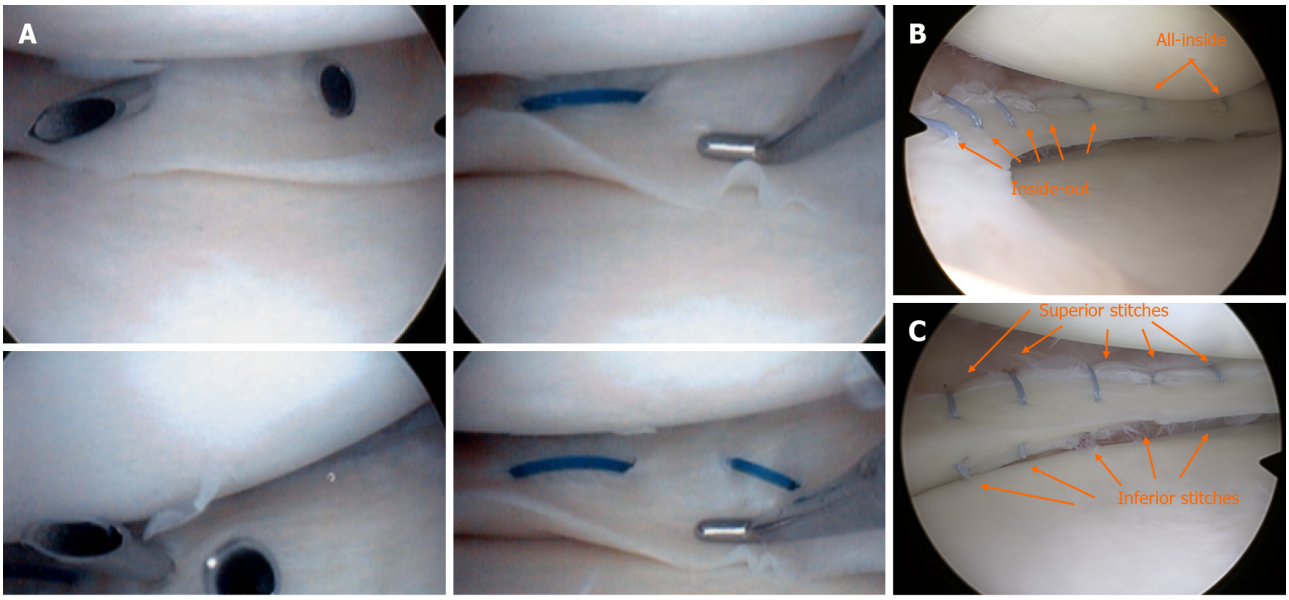
DISCUSSION

The most important finding of our study was that even though the overall failure rate was 20.3% (26% for BHTs, 18%



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Figure 2 Second look arthroscopy and postoperative magnetic resonance imaging. A: Shows a second look arthroscopy 1 year after posterior horn meniscus repair; B: The < 1 mm gap classified as "healed" in the magnetic resonance is confirmed in the arthroscopy with a fibrous stable scar. FC: femoral condyle, M: Meniscus, T: Tibia.



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Figure 3 Arthroscopic view of repaired bucket handle tear. A: Shows a bucket handle tear repaired in 2012 using 3 PDS stitches with an outside-in technique; B and C: Show a bucket handle tear repaired in 2016 using 10 inside-out and 2 all-inside 2-0 nonabsorbable high resistant sutures.

when associated with an ACL-R and 22% for isolated lesions), we found a significant decrease of failure rate when comparing two different cohorts in view of differences in surgical technique from 26% to 11% (P = 0.03). Not only for isolated lesions (from 28% to 6.6% for isolated lesions, P = 0.02), but also BHTs (from 34% to 8%, P = 0.09) and those associated with an ACL-R (from 25% to 10%, P = 0.09). These findings add to a growing body of literature on the importance of surgical technique when analyzing failure rate after meniscal repair[7,9,14,15]

For the last two decades meniscal preservation has become the main goal for treatment of meniscal lesions. In 2013, Abrams *et al*[16] reported that between 2005 and 2011 the incidence of meniscal repair has doubled in the United States. This tendency has continued to increase up to date, thus becoming the gold standard procedure when deciding the fate of a meniscus repairable lesion nowadays[1-17].

Systematic reviews prior to 2012, reported failure rates of 18% to 23%[7,15,16] after meniscal repair. Fillingham *et al*[9] in 2017 compared inside-out *vs* modern all-inside devices techniques and reported similar functional outcomes, with equivalent anatomical and clinical failure rates: 11% and 10% respectively. These results were interestingly lower when compared to 17% and 19% previously reported by Grant *et al*[14] in 2012. Fillingham *et al*[9] also found that all-inside repairs had an average of 2 stitches, while inside-out had an average of 3. Therefore, they associated the inside-out technique with more complex lesions.

When we analyzed the overall failure rate for meniscal sutures in our series, we found 20.3% with a mean time to failure of 20.1 mo, which is very similar to prior reports in the literature[7,16,18]. Moreover, an overall failure rate for isolated lesions of 22.9%, (27.7% for BHTs) and 18.5% when associated with an ACL-R (23% for BHTs) was found.

The analysis of the evolution of failure rate during our research yields a significant decrease when comparing our series in two different periods. Even though patients treated after 2014 have a shorter follow up, we consider that it is enough to establish a comparison considering that the overall mean time to failure was 20 mo. There might be multiple factors to explain this decrease in failure rates. Most horizontal mattress sutures (usually no more than 2 stitches) were replaced for vertical sutures (one stitch every 5 to 10 mm), which provides more stability and prevents meniscal cutout [19]. This resulted in an increase in the number of stitches, from a mean of 1.4 (SD: 1.01) to 3.5 (SD: 2.31) for BHTs (Figure 3) and 1.2 (SD: 0.5) to 2.1 (SD: 1.1) for isolated repairs, and it continues to increase up to date. Another important factor might be an improvement in the all-inside devices for meniscal sutures as reported in clinical[9] and biomechanical [20] studies.

Blanchard *et al*[21] reported an overall RTS rate of 83% after 8.7 mo in 21 studies evaluated after isolated meniscal repair. Other authors reported variable time to RTS from 4.2[22,23], 5.6[24] and 5.5[25] mo. When associated with an ACL-R time to RTS is reported from 8.2 (64 Vanderhave) to 11.8 mo (48 Logan). We found a mean RTS of 6.55 mo (SD: 2.36) for isolated lesions and 8.64 mo (SD: 2.72) when associated with an ACL-R. After a mean of 7 years follow-up, only 56% returned to the same activity level and 24% reported a lower activity level. Though this seems to be a low RTS rate, many authors have reported better outcomes after meniscal repair compared with meniscectomy (2018 KSSTA Phillips, 2014 AJSM Westermann, 2021 OJSM Blanchard).

Regarding the role of MRI as a postoperative control measure, we found that it was not useful in evaluating meniscal repairs. We found that 39% out of the 85 asymptomatic patients that performed a routine MRI presented an image compatible with a "not healed" repair. The report even suggested a "failure" or "rupture" of the repair. All of these patients were asymptomatic and performing regular sport activities. Faunø *et al*[26] in 2020 reported 72% sensitivity for finding meniscal re-ruptures in 80 symptomatic patients who underwent a revision surgery. Yamasaki *et al*[27] suggested a T2 mapping to improve the sensitivity for unhealed meniscus after comparing standard and T2 mapping MRI for 26 asymptomatic patients who underwent a second look arthroscopy.

The role of biologics in the setting of meniscal repair in order to increase the chance of healing and reduce failure rate is still controversial and very few clinical studies have been reported. In a recent systematic review, Haunschild *et al*[28] reported that there was considerable heterogeneity in the reporting and preparation of platelet rich plasma (PRP) used for augmentation, and concluded that there was insufficient evidence to support the use of PRP to improve meniscal healing and reduce failure rate. Controversially, Zaffagnini *et al*[29] and Sochacki *et al*[30] reported an improvement in survival rate after isolated meniscal repair augmented with PRP.

Strengths and limitations

The limitations of our study need to be acknowledged. First, the main limitation was the retrospective design, yielding an analysis limited to the data available in the medical record database, with potential for selection bias. Second, the fact that we considered asymptomatic patients and analyzed the results as "healed" or "not healed" for MRI subsequent analysis without a second-look arthroscopy confirmation. And finally, the lack of radiographic evaluations which did not allow us to evaluate any degenerative progression.

Despite these limitations, the large sample size and subgroup analysis, as well as the long term follow-up of 7 years constitute a major strength of our study.

CONCLUSION

The overall meniscal repair failure rate after a mean follow-up of 7 years was 20.3%, with 26% for BHTs, 18% when associated with an ACL-R and 22% for isolated lesions. Interestingly, when comparing our series in two different cohorts in view of differences in surgical technique, we found a decrease from 26% to 11% ($P = 0.03$), 28% to 6.6% ($P = 0.02$) for isolated lesions, 34% to 8% ($P = 0.09$) for BHT's, and 25% to 10% ($P = 0.09$) for meniscal sutures associated with an ACL-R. The mean time for return-to-sports was 6.5 mo for isolated meniscal repairs and 8.6 when associated with an ACL-R. Finally, MRI was not efficient for evaluating the condition of the meniscal repair in asymptomatic patients. It is recommended that care should be taken when considering MRI as a routine control practice after meniscal repair.

ARTICLE HIGHLIGHTS

Research background

We perform a large number of meniscal repairs every year. Our surgical techniques have been improving along the years, and with it, the outcomes achieved.

Research motivation

We observed a great improvement over the years in our patient outcomes. That is why we decided to analyze and report the long-term results of our series.

Research objectives
To analyze the failure rate and compare outcomes in our series of patients operated on for longitudinal meniscal lesions. It is important to understand that improvement in the number of stitches and surgical technique is associated with better outcomes than what is reported in the literature.

Research methods
We retrospectively analyzed and compared demographic data, surgical details, return to sport and failure rate using specific statistical tools.

Research results
In our series we found an important decrease in failure rates by improving our surgical technique and increasing the number of stitches. Even so, there is still a high percentage of patients in whom this type of repair fails. It is very important to continue investigating complementary methods that can help to further reduce this failure rate.

Research conclusions
The new theory provided by the paper is that the failure rate may continue to fall even further.

Research perspectives
Future work could compare the same type of sutures with biological augmentation such as platelet-rich plasma or stem cells.

FOOTNOTES

Author contributions: Zicaro JP and Garrido N analyzed the data and wrote the manuscript; Garcia-Mansilla I contributed with research and data analysis; Yacuzzi C and Costa-Paz M contributed to the number of patients operated on; Costa-Paz M is the head of the sector; All authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the "Ethics Committee of the Hospital Italiano" (CEPI) Institutional Review Board, No. 5458.

Informed consent statement: Due to the retrospective nature of our study no informed consent was required.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data were required (retrospective study).

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ORIGINAL ARTICLE

Retrospective Study

Survival analysis in nonagenarian patients with non-hip lower limb fractures

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Abstract

BACKGROUND

The United Kingdom has an aging population with nearly 1 in 5 being over the age of 65, and over 0.5 million over the age of 90. The treatment of acute fractures of the lower limb in the nonagenarian cohort of patients poses a technical challenge to orthopaedic surgeons.

AIM

To report the fracture incidence, survival outcomes of treating acute non-hip lower limb fractures in nonagenarians in Major Trauma Centre.

METHODS

Thirty Lower limb long bone fractures in patients of age from 90 to 99 years were identified during 12-mo at a Level 1 trauma centre from a computerized database. A retrospective evaluation performed for fracture incidence, treatment, length of hospital duration and mortality at 30-d, 1-year and 2-year.

RESULTS

Thirty fractures (28 patients) were identified, twenty-four fractures were treated with surgery (mean age 93 years SD ± 2.59) and 6 managed conservatively (mean age 94 years SD ± 2.07). The mean length of the hospital stay was 18.2 d for both groups. The 30-d, 1-year and 2-year mortality risks were 1/23, 6/23 and 9/23 (4%, 26% and 39%) in the surgery group and 0/5, 1/5 and 2/5 (0%, 20% and 40%) in the conservative group, with no evidence for a difference between the two groups at any time point.

CONCLUSION
Nonagenarians in the surgical group had similar length of hospital stay and mortality risks as those treated conservatively. Patients with fewer comorbidities and admitted from their own home were offered surgery.

Key Words: Nonagenarian; Survival; Conservative; Non-hip; Fragility; Orthogeriatrics

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Core Tip: The treatment of acute lower limb fractures in nonagenarian population poses a technical challenge to orthopaedic surgeons, given the multiple co-morbidities, complex fracture pattern and poor bone quality. Nonagenarians account for 8% of all patients requiring acute fracture surgery. The main findings of this study are that surgery is more likely to be offered to those patients with fewer co-morbidities and those admitted from their own home, which indicates a higher functional status.

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INTRODUCTION

The treatment of fractures within the nonagenarian population (> 90 years)[1-2] poses a technical challenge to orthopaedic surgeons. This is because patients within this demographic often have multiple co-morbidities, poor bone quality and exhibit complex fracture patterns. 'Super-elderly' patients account for 8% of all patients requiring acute fracture surgery[2]. The World Health Organization has estimated that by 2050 the global population who are 65 years or more will be 1.5 billion and represent 16% of the world's population[2]. This will place an immense burden on the medical resources of the National Health Service for both the acute and rehabilitative care[3].

Much of the work pertaining to fractures in the elderly has centered on hip fractures[3]. There is sparse evidence in literature looking beyond the scope of hip fractures to other lower limb trauma within this patient population. It is unknown whether this group of patients share similar outcomes to those affected by hip fractures.

The purpose of this study is to share our experience at a level 1 major trauma centre in treating long bone fractures of the lower limb in nonagenarians. We aim to report the fracture incidence, short-term outcome and the 30-d, 1-year and 2-year mortality.

MATERIALS AND METHODS

This study was conducted at a level 1 major trauma centre. Interrogation of a prospectively maintained electronic admissions database was performed retrospectively. We included all patients between the ages of 90 and 99 years who were admitted with a long bone fracture of the lower limb during 2015 and 2016, including periprosthetic fractures. We excluded all soft-tissue trauma, foot and ankle fractures and all primary hip fractures.

Within our institution all patients who are fit to undergo anaesthesia are considered for surgery, depending on the fracture configuration, the aim of which is to restore the patient to their pre-injury function. Conservative (non-operative) management is reserved for patients who have undisplaced fractures and those that are unfit for surgery.

Information including patient demographics, place of residence, discharge destination, number of co-morbidities, gender, high or low mechanism of injury, fracture type and treatment, length of hospital stay and time to theatre from admission was collected from electronic patient records and picture archiving communication systems. The 30-d, 1-year and 2-year mortality was calculated for long bone fractures of the lower limb treated with or without surgery and compared using a Fisher's exact test. Statistical analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria) and a 2-sided *P* value below 0.05 was assumed to denote statistical significance.

RESULTS

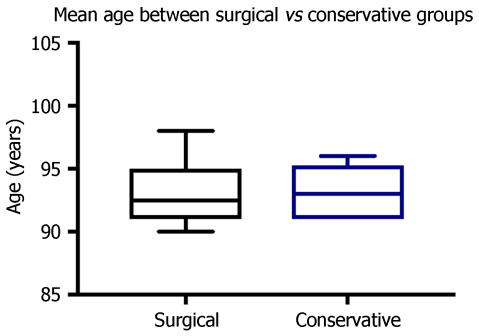
A total of 537 adult lower limb fractures were admitted over a 12-mo period within our institution, with 30 Long bone fractures of the lower limb in 28 patients between 90 and 99 years of age. Twenty-seven patients (96%) were female and 1 (4%) was male (Table 1). The mean age in the surgical group was 93 years (range 90-98 years) (SD ± 2.59) and 94 years (range 91-96 years) (SD ± 2.07) in the conservative group (Figure 1).

Table 1 Patient demographics, fracture type, treatment type, number of comorbidities, length of hospital stay, admission residence, discharge destination and time from admission to death in both surgical and conservative groups

Patient No.	Sex	Age, yr	Fracture type	Treatment	Number of co-morbidities	Length of hospital stay, d	Admission residence	Discharge destination	Time from admission to death, d
1	F	98	Periprosthetic – THR	Surgery	3	22	Home	Institution	Alive
2	F	98	Distal femur	Surgery	3	25	Home	Home	Alive
3	F	96	Periprosthetic - Thompsons	Surgery	4	29	Institutional	Dead	29
4	F	96	Distal femur	Surgery	0	21	Home	Institution	Alive
5	F	96	Distal femur	Surgery	0	30	Home	Home	Alive
6	F	95	Periprosthetic – Thompsons	Conservative	5	20	Home	Institution	Alive
7	F	95	Distal femur	Surgery	3	8	Home	Institution	Alive
8	F	95	Periprosthetic – Thompsons	Surgery	3	12	Home	Institution	Alive
9	F	95	Distal tibia/fibula	Conservative	4	17	Institutional	Institution	237
10	F	95	Distal femur	Surgery	0	11	Home	Institution	300
11	F	94	Distal tibia/fibula	Surgery	0	18	Home	Institution	Alive
12	F	94	Periprosthetic – THR	Conservative	7	17	Home	Institution	376
13	F	94	Distal femur	Surgery	0	12	Home	Institution	429
14	F	94	Distal femur	Surgery	3	14	Home	Institution	264
15	F	93	Distal tibia/fibula	Surgery	3	24	Home	Institution	Alive
16	F	92	Periprosthetic – Thompsons	Conservative	2	24	Institutional	Institution	Alive
17	F	92	Periprosthetic – THR	Surgery	2	11	Home	Institution	Alive
18	F	92	Distal femur	Surgery	0	11	Home	Institution	Alive
19	F	92	Distal femur	Surgery	1	15	Home	Institution	39
20	F	92	Distal tibia/ fibula	Surgery	2	39	Home	Institution	50
21	F	91	Distal femur-bilateral	Conservative	2	13	Home	Institution	Alive
22	F	91	Femoral shaft	Surgery	3	16	Home	Institution	50
23	F	91	Distal femur – Bilateral	Surgery	3	28	Home	Institution	Alive
24	F	90	Periprosthetic – THR	Surgery	1	28	Home	Institution	Alive
25	F	90	Periprosthetic – Thompsons	Surgery	8	28	Home	Institution	505
26	M	90	Distal femur	Surgery	4	11	Home	Institution	451
27	F	90	Femoral shaft	Surgery	2	17	Home	Institution	Alive
28	F	90	Proximal tibia/fibula	Surgery	1	5	Home	Institution	Alive

F: Female; M: Male; THR: Total hip replacement.

Twenty-seven patients (96%) sustained a fracture after low energy trauma with a fall from standing height. One patient sustained bilateral distal femoral insufficiency fractures without any history of trauma. Fracture type consisted of 12 (40%) distal femoral (two patients had bilateral distal femoral fractures), 11 (37%) periprosthetic, 4 (13%) distal tibia/



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Figure 1 Mean of the patients age between surgical cohort (nonagenarians undergoing surgery) and conservative cohort (nonagenarians not undergoing surgery).

fibula, 2 (7%) femoral shaft and 1 (3%) proximal tibia (Figure 2).

Twenty-four fractures (80%) in 23 patients were operated on. Surgical intervention consisted of 8 (27%) undergoing open reduction and internal fixation, 5 (17%) a revision arthroplasty, 10 (33%) an intramedullary nail and 1 patient (3%) underwent a distal femoral replacement (Figures 3-5)

The mean time from admission to first surgery was 2.5 d (range 0-9 d). Definitive fracture treatment for all closed injuries was performed within 2.9 d (range 0-9 d). Four patients had open fractures, which were managed in accordance with the British Orthopedic Association Standards for Trauma and Orthopaedics[4] and treated with an initial debridement and external fixation before definitive treatment performed on a designated orthoplastic list. The mean time from admission to definitive fracture treatment in these patients was 2.5 d (range 2-3 d).

In 13 patients' operative records the type of anesthetic used was documented; 5 patients received a general anesthetic, 5 combined with regional blocks and 3 patients had a spinal anesthetic with sedation. In all patients, a tourniquet was not used primarily due to fracture location.

Within the surgical group (n = 23): 22 patients (96%) were admitted from their own home and 1 (4%) from an institution. Physiotherapy and continuous passive motion were started on the postoperative day. On discharge only 2 patients were discharged back home; the rest were transferred to further rehabilitation institutions. It is unknown how many of these patients were subsequently able to return to their prehospital admission residence.

The mean number of co-morbidities was 2.1, time to definitive surgery 2.6 d (SD ± 2.09) and mean length of hospital stay was 18.2 d. The 30-d, 1-year and 2-year mortality in this group was 4.3%, 26% and 39% respectively.

Six fractures in 5 patients (20%) were treated conservatively. Within the conservative group (n = 5): 3 patients (60%) were admitted from their own home and 2 (40%) from an institution (Table 2). On discharge all patients were transferred to an institution. Mean number of co-morbidities was 4; mean length of hospital stay was 18.2 d. There were no deaths within 30 d; the 1-year and 2-year mortality was 20% and 40% respectively.

A comparison of mortality risk between the surgical and conservative groups found no evidence for a difference at any time point (P = 1 for each time point).

DISCUSSION

Long bone fractures of the lower limb in nonagenarians represents 5% of the total adult lower limb trauma admission during 1 year within our major trauma centre. Fractures within this age group nearly all result from low energy trauma and were found to be more prevalent in females. This study has found the most common lower limb fracture to occur is that of distal femoral fractures.

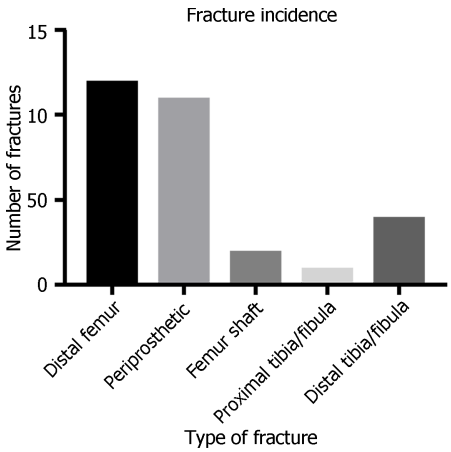
The most interesting finding of this study is surgically treated fractures of the lower limb is associated with an initial higher 30-d and 1-year mortality than those managed conservatively (P = 0.97, Wilcoxon-Rank), despite an increased number of comorbidities (see Figures 6 and 7). Reasons for this are likely to be multifactorial and we are unable to draw any direct conclusions due to a small cohort sample.

We are not aware of any literature which has specifically reported the mortality of fractures of the lower limb in nonagenarians. Streubel *et al*[5] reported a 25% 1-year mortality of patients with distal femoral fractures undergoing surgery with a mean age of 77.9 years[6]. The mortality of hip fractures has been well documented within literature. For similar age-matched groups the literature has reported 30-d and 1-year mortality between 10%-24%[5,7-9], rising to 15%-56%[10-13] in centenarians. Recently, Bolton *et al*[14] reported the 30-d and 1-year mortality rate in the non-agenarian hip fractures to be 12.4% and 38.1%[14].

We found surgery is more likely to be offered to patients with less comorbidity and those admitted from their own home. Postoperatively, however, all patients from both groups required admission into an institution for further rehabilitation. It is unclear how many patients were subsequently able to return to their preadmission residence. Interestingly we found there was no difference in the mean length of hospital stay between the two groups. This is similar to findings by Holton *et al*[15] where the mean hospital admission was longer in patients were their ankle fracture was treated with surgery (P = 0.006), compared to those offered conservative management.

Table 2 Summary showing discharge outcomes of both surgical (group 1) and conservative (group 2)

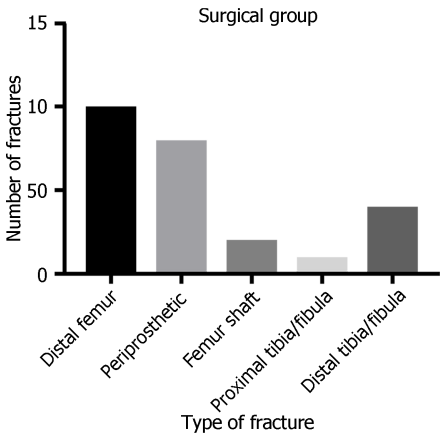
	No. of patients (%)
Gender	
Male	1 (3.6)
Female	27 (96.4)
Fracture type	
Distal femur	12 (40)
Periprosthetic	11 (37)
Distal tibia/fibular	4 (13)
Femoral shaft	2 (7)
Proximal tibia/fibula	1 (3)
Type of operation	
Open reduction internal fixation	8 (27)
Revision arthroplasty	5 (17)
Intramedullary nail	10 (33)
Distal femoral replacement	1 (3)
No operation	6 (20)
Surgical (Group 1)	
Admitted from home	22 (96)
Admitted from an institution	1 (4)
Discharged home	2 (9)
Discharged to an institution	21 (91)
Conservative (Group 2)	
Admitted from home	3 (60)
Admitted from an institution	2 (40)
Discharged home	0 (0)
Discharged to an institution	5 (100)



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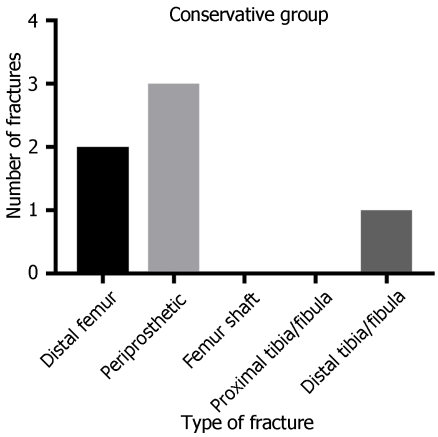
Figure 2 Anatomical fracture locations in both the surgical and conservative groups.

Surgery in nonagenarian patients is associated with greater anaesthetic risks and technically challenging surgery because of poor bone quality and higher rates of primary fixation failure[16-17]. Despite these factors surgery is often recommended especially for those with femoral neck fractures. Surgery aims to reduce pain, assist with nursing care, and



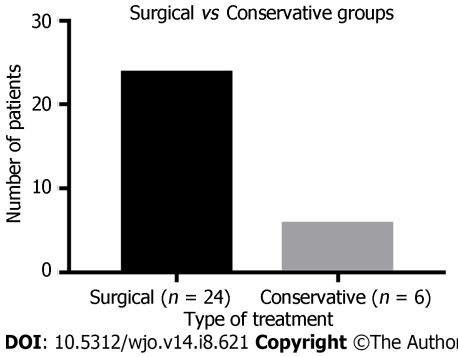
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Figure 3 Anatomical location of fractures with their incidence in surgical group.



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Figure 4 Anatomical location of fractures with their incidence in conservative group.

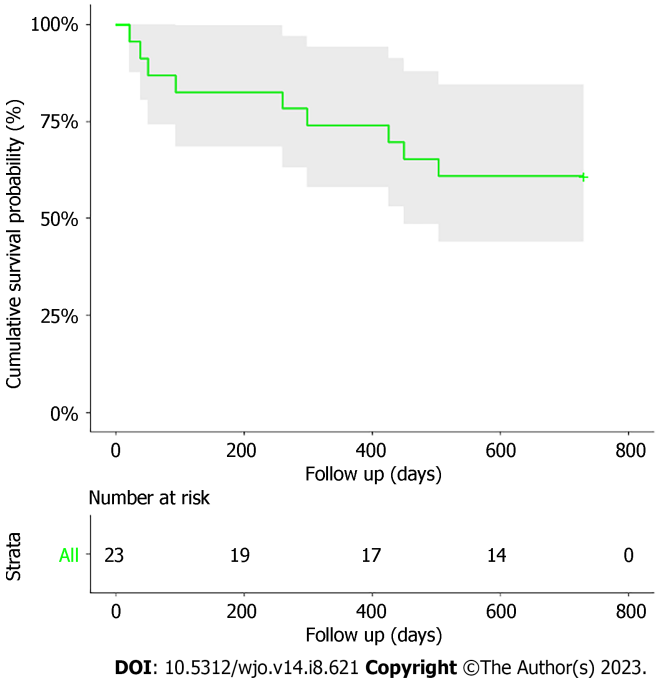


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Figure 5 Number of patients respective to the management offered–surgical and conservative.

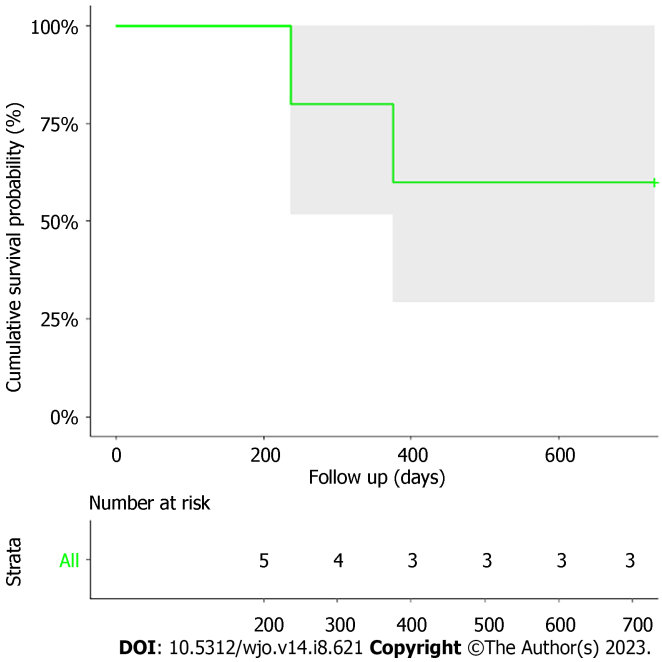
reduce the risks and sequela of complications, which can manifest from prolonged bed rest[18]. Contrary to what we have found, recent studies suggest good results may be achieved with surgery. Ng and Kwek[10] reported the operative outcomes of centenarians with hip fractures. They found centenarians had a low Charlson Comorbidity Index, postulating these patients tended to be healthier and found no deaths at 30-d with 1-year mortality of 33.3%.

The timing of surgery is also a crucial factor that must be considered in these patients. Lin *et al*[8] analyzed 101 patients over the age of 90 years undergoing hip fracture surgery. They found the mortality nearly doubled if surgery was not performed within 24 h of admission. Moja *et al*[19] performed a meta-analysis involving 191873 patients, and again demonstrated an increase in the mortality of patients if there was a delay to surgery. Within our institution we recognize this, and the authors advocate early surgery for elderly patients; however, this is not always possible due to the volume of admissions requiring treatment, the surgeon skill set and the requirement for specialized implants.



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Figure 6 Cumulative survival probability (Y-axis) and follow-up in days (X-axis) showing survival analysis curve in Surgical group.



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Figure 7 Cumulative survival probability (Y-axis) and follow-up in days (X-axis) showing survival analysis curve for conservative group.

We recognize the limitations of this study, the most important of which is a small sample size for both groups. This makes it difficult to make a direct comparison between the two groups and as a result we are unable to draw any direct conclusions. Secondly, we are unable to comment on how many patients were able to return to their preadmission residence and functional status. Nevertheless, this study highlights super-elderly patients require further rehabilitation than their younger counterparts[9] and reflects an additional socioeconomic burden on limited health resources which must be addressed.

Nonagenarians have multiple co-existing medical pathologies including frailty, poor visual acuity, and polypharmacy, all of which contribute to increase the risk of falls[16]. We found 23 patients (82%) suffered a fall from standing height at home. This suggests certain patients may benefit from primary prevention strategies by identifying at risk individuals with the focus of creating a safe environment and falls prevention advice through a multidisciplinary team approach and to improve their living environment with assisted living devices.

CONCLUSION

We report the incidence and the short-term outcome of fractures of the lower limb in nonagenarians at our level 1 trauma centre. The main findings of this study are that surgery is more likely to be offered to those patients with fewer co-morbidities and those admitted from their own home, which indicates a higher functional status. Nonagenarians in the surgical group had similar length of hospital stay and mortality risks as those treated conservatively.

Nonagenarians require further rehabilitative support to gain independence and pre-injury functional level, in an institutive setting irrespective of the treatment that is instituted and arrangements for this should be sought as soon as possible. More investment, awareness and socioeconomic support will be required to keep up with current demands.

ARTICLE HIGHLIGHTS

Research background

There is paucity of literature pertaining to the management and survival of non-hip fractures in the nonagenarian population. This is significant, given the rising nonagenarian population in the United Kingdom.

Research motivation

This study aims to analyze the prognosis/survival in a level 1 major trauma centre, in managing non-hip fractures in nonagenarian population in the United Kingdom.

Research objectives

To summarize the survival prognosis on nonagenarian population with non-hip fractures in a level 1 major trauma centre.

Research methods

We referred to the hospital electronic database between 2015 and 2016 to include all patients with age ranging from 90 to 99 years, who had lower limb long bone fractures, including periprosthetic fractures. We excluded all hip fractures, soft tissue trauma, foot and ankle fractures. Both conservative and operative management were considered depending on the anaesthetic fitness and medical background. 30-d, 1-year and 2-year mortality were calculated for both surgical and conservative groups and compared using Fisher's exact test.

Research results

Out of 28 patients, 23 patients (24 fractures) had surgical intervention and 5 patients (6 fractures) were for conservative treatment. The mean time from admission to definitive fracture treatment was 2.5 d (range 2-3 d). In surgical cohort, only 2 patients went home post-discharge, the rest all were transferred to rehabilitation institutions. In the conservative cohort, all patients were transferred to an institution. The 30-d, 1-year and 2- year mortality risks were 1/23, 6/23 and 9/23 (4%, 26% and 39%) in the surgery group and 0/5, 1/5 and 2/5 (0%, 20% and 40%) in the conservative group, with no evidence for a difference between the two groups at any time point.

Research conclusions

Surgery was more likely to be offered to patients with fewer comorbidities and both conservative and surgical groups had similar length of hospital stay and mortality risks. Early planning for institutional rehabilitation and socio-economic support is utmost needed in the management of these patients.

Research perspectives

Standard national guidelines for lower limb fractures in the nonagenarian population would streamline the diagnosis, management, and rehabilitation.

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FOOTNOTES

Author contributions: Narayana Murthy S, Siddiqui RS and Cheruvu MS conceptualized, designed, reviewed the existing literature, did the statistical analysis, wrote the manuscript and prepared the first draft; Dass D and Sharma N critically reviewed the first draft and gave their expert suggestions; Ali A reviewed the final draft before submission and suggested further changes.

Institutional review board statement: This is an observational study which does not include any of the patient identifiable data. Additionally, as there are no interventions, there was no need to obtain an institutional board review statement.

Informed consent statement: Consent for an original study involving humans is not necessary as we have not included any patient identifiable details in our manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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META-ANALYSIS

Cemented *versus* uncemented stems for revision total hip replacement: A systematic review and meta-analysis

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Abstract

BACKGROUND

The popularity of uncemented stems in revision total hip arthroplasty (THA) has increased in the last decade.

AIM

To assess the outcomes of both cemented and uncemented stems after mid-term follow up.

METHODS

This study was performed following both the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement and the Cochrane Handbook for systematic reviews and meta-analysis guidelines. Articles were chosen irrespective of country of origin or language utilized for the article full texts. This paper included studies that reviewed revision THA for both cemented or uncemented long stems.

RESULTS

Three eligible studies were included in the meta-analysis. Analysis was conducted by using Review Manager version 5.3. We computed the risk ratio as a measure of the treatment effect, taking into account heterogeneity. We used random-effect models. There were no significant differences found for intraoperative periprosthetic fractures [risk ratio (RR) = 1.25; 95% confidence interval (CI): 0.29-5.32; *P* =

0.76], aseptic loosening (RR = 2.15, 95%CI: 0.81-5.70; *P* = 0.13), dislocation rate (RR = 0.50; 95%CI: 0.10-2.47; *P* = 0.39), or infection rate (RR = 0.99, 95%CI: 0.82-1.19; *P* = 0.89), between the uncemented and the cemented long stems for revision THA after mid-term follow-up.

CONCLUSION
This study has evaluated the mid-term outcomes of both cemented and uncemented stems at first-time revision THA. In summary, there were no significant differences in the dislocation rate, aseptic loosening, intraoperative periprosthetic fracture and infection rate between the two cohorts.

Key Words: Long stem; Cemented; Uncemented; Revision total hip arthroplasty; Meta-analysis

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Core Tip: This paper included a meta-analysis of three studies involving 7600 revision total hip replacements, of which 3050 were performed using cemented stems, while 2539 were performed utilising uncemented stems. Based on the evidence from this study, there are no statistically significant differences in the rates for intraoperative periprosthetic fractures, aseptic loosening, dislocation and periprosthetic joint infection, for the cemented and uncemented long stems in revision total hip arthroplasty. Nevertheless, there was significant heterogeneity in the included studies for periprosthetic fractures, aseptic loosening and dislocation.

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INTRODUCTION

The numbers of revision total hip replacement (rTHR) have been increasing due to increasing numbers of primary hip replacements worldwide[1]. The uncemented femoral stem has shown increasing popularity among revision hip surgeons[2,3]. However, some authors claim that the cemented long stem prothesis has a longer life span than the uncemented stem, especially in the elderly patient cohort[4,5]. Older studies did not find any difference in the survival rate between the two stem types[6]. 71% of Danish orthopaedic surgeons prefer the uncemented stem. However, only 24% in Sweden use this type of femoral stem[7]. For the first decade of this century, there has been a dramatic increase in the number of uncemented primary hip replacements[8]. Evolutions in the design of the uncemented long femoral stem has added more stability to the distal femur, with a marginal effect on the bone loosening process, which is less predictable, especially in revision surgeries[9]. Consequently, the uncemented stem is a good choice in scenarios where there is bone loss[10]. This study aims to use meta-analysis and systematic review techniques to assess the outcomes of both the uncemented and cemented femoral stems in rTHR. The primary outcome measures were periprosthetic fractures and aseptic loosening. The secondary outcome measures were the dislocation and infection rates.

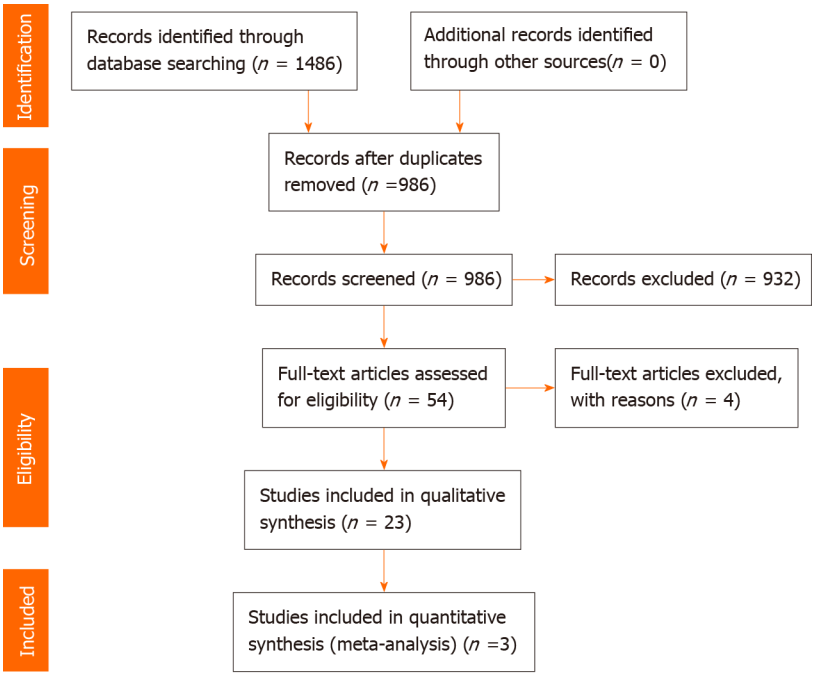
MATERIALS AND METHODS

Literature search

This study was conducted following both the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement as shown in Figure 1, and the Cochrane Handbook for systematic reviews and meta-analysis[11]. An initial search was conducted using PubMed, Google scholar and the Cochrane Library. Grey and unpublished literature were also explored by searching: Grey Matters BIOSIS Previews, International Clinical Trial Registry, ClinicalTrials.gov, UK Clinical Trials Gateway, Networked Digital Library of Theses and Dissertations, UK Clinical Research Network Study Portfolio, Open Grey and Grey Literature Report. The following keywords were used alone or in combinations: Cemented, uncemented, long stem, revision, and total hip arthroplasty (THA). Articles published up to December 2022 were included in the literature search, and were limited to studies in human subjects published in any language. Additionally, we cross-referenced the bibliographies of retrieved articles and review papers to ensure that we captured all relevant studies.

Eligibility criteria

All full-text observational studies that evaluated the outcomes of both cemented and uncemented stems in rTHR were included. All biomechanical, radiological, and cadaveric studies were excluded. Furthermore, any study that did not meet one or more of the eligibility criteria were excluded.



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Figure 1 Preferred reporting items for systematic reviews and meta-analyses flow chart.

Study selection and data extraction

Three authors (Elbardesy H, Anazor F, and Maatough A) independently screened all titles and abstracts identified from the initial search to assess their eligibility for inclusion. Identified titles and abstracts from the initial search were then screened and the full text articles of the eligible manuscripts were obtained. After all eligible full text manuscripts had been evaluated for inclusion criteria eligibility, data extraction was conducted by the same reviewers. Any discrepancies with collected data were resolved by consensus between the reviewers. Outcome measures (periprosthetic fracture, aseptic loosening, dislocation rate, and infection) were recorded. Additionally, the study titles, year of publication, the publishing journal, type of study, level of evidence, number and the brand of the stems, period of follow up, gender and age of the patients included in each study were analysed.

Risk of bias

The risk of bias for retrospective non-randomized studies was assessed using the Newcastle-Ottawa Scale[12], as shown in Table 1. Four reviewers (Elbardesy H, Anazor F, Mirza M, and Maatough A) independently crossed-checked the quality of the included studies. Disagreements were resolved through consensus discussions.

Statistical analysis

Statistical analysis was performed using Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2009, Copenhagen, Denmark)[13]. Heterogeneity between studies was evaluated using the I^2 statistic and a χ^2 of < 0.05 was used to determine the significance of the heterogeneity between studies[11]. Risk ratios (RRs) were reported for dichotomous variables such as wound complications, whereas mean differences and standard deviations (SDs) were used for continuous variables. All analyses were conducted using the Mantel-Haenszel random-effects model. The results of our meta-analysis were then illustrated using forest plots, which used a 95% confidence interval (CI) for each study. A *P* value of < 0.05 was taken to be of statistical significance. Variables that were inconsistently reported were investigated in the systematic review portion of this study[11].

RESULTS

Study characteristics

Our literature search revealed 1486 unique references. After reviewing the titles and abstracts of all studies, three studies were eligible for both quantitative and qualitative analysis. The three selected studies included 7600 revision THRs, of which 3050 were performed using cemented stems, while 2539 were performed utilising uncemented stems. 23 studies were included in the qualitive analysis: Six of them investigated the cemented stems, while 17 focused on uncemented stems (Figure 1). A summary of study characteristics and patients' demographics is presented in Tables 2-6.

Table 1 Newcastle-Ottawa Scale for assessing the quality of observational studies

	Selection				Comparability	Exposure			Total
Ref.	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total number of stars
Tyson *et al* [39], 2021	*	*	*	*	**	*	*	*	9
Weiss *et al* [38], 2011	*	*	*	*	*	*	*	*	8
Iorio *et al* [6], 2008	*	*	-	*	*	*	*	*	7

Table 2 Study characteristics

Ref.	Country	Journal	Study type	Centres	Level of evidence	Number of stems	Stem brand for cemented	Stem brand for uncemented
Tyson *et al* [39], 2021	Sweden	*Acta Orthopaedica*	Observational study	Multi	III	266 cemented, 601 uncemented	Lubinus SPII 123 (46%), exeter 94 (35%), spectron 49 (18%)	MP 291 (48%), restoration 162 (27%), wagner 78 (13%), revitan 70 (12%)
Weiss *et al*[38], 2011	Sweden	*Acta Orthopaedica*	Observational study	Multi	III	1073 cemented, 812 uncemented	Lubinus SPII 610 (57%), exeter long stem 248 (23%), spectron revision hip system 215 (20%)	MP stem 812 (100%)
Iorio *et al*[6], 2008	United States	*Journal of arthroplasty*	Prospective cohort study	Single	II	43 cemented, 43 uncemented	13 premise, 6 precision, 5 reliance (stryker), 3 re cemented, 2 charnley elite plus, 2 ultima, 1 PFC (depuy), 4 calcar replacing, 7 extra long	S-ROM modular metaphyseal femoral stem 31 (72%), calcar replacing 9 (23%), extra long 3 (7.7%)

Study characteristic for the studies included in the MA.

Table 3 Patient's demographics

Ref.	Gender M	Age (SD)	Follow up in years (SD)
Tyson *et al*[39], 2021	Uncemented 318 (53%), cemented 138 (52%)	Uncemented 72 (10), cemented 74 (9)	Uncemented 4 (3), cemented 5 (3)
Weiss *et al*[38], 2011	Uncemented 443 (55%), cemented 544 (51%)	Uncemented 72 (11), cemented 76 (9)	Uncemented 3.4 (2.9), cemented 4.2 (2.5)
Iorio *et al*[6], 2008	22 cemented (51%), 22 uncemented (51%)	Uncemented 71.2 (9), cemented 67.5 (10)	Uncemented 7 (1), cemented 9 (1.5)

SD: Standard deviation.

Patient baseline characteristics

For the meta-analysis, the subjects in the uncemented group had an average age of 71 years and 1159 (45.6%) males, with an average follow-up period of 4.8 (± 2.3) years. The cemented cohort had a similar distribution, with an average age of 71.6 years and 1391 (45.6%) males, with an average follow-up period of 6 (± 2.33) years.

Table 4 Study characteristics for the studies about the uncemented stem

Ref.	Total number	Country	Journal	Study type	Centres	Level of evidence
Mahoney *et al*[20], 2010	40	United States	*JOA*	ORS	Single	3
Hasegawa *et al*[22], 2021	45	Japan	*International Orthopaedics*	ORS	Single	3
Zheng *et al*[23], 2021	34	China	*OSJ*	ORS	Single	3
Wallace *et al*[24], 2020	55	United Kingdom	*J Arthroplasty*	ORS	Single	3
Zang *et al*[25], 2019	40	China/Japan	*JOS (Hong Kong)*	ORS	Single	3
Herry *et al*[26], 2019	116	Multi	*International Orthopaedics*	ORS	Multi	3
Shen *et al*[27], 2014	34	China	*COAJ*	ORS	Single	3
Wang *et al*[28], 2020	73	China	*Hip International*	ORS	Single	3
Singh *et al*[34], 2013	53	India	*IJO*	ORS	Single	3
Tsukeoka *et al*[41], 2011	14	Japan	*Modern Rheumatology*	ORS	Single	3
Oetgen *et al*[29], 2008	28	United States	*JOT*	ORS	Single	3
Sotereanos *et al*[36], 2006	16	United States	*JBJS*	ORS	Single	3
Philippot *et al*[35], 2009	43	France	*OTSR*	ORS	Single	3
Thorey *et al*[30], 2008	79	Germany	*AOTS*	ORS	Single	3
Malkani *et al*[31], 1996	74	United States	*JOA*	ORS	Single	3
Mulliken *et al*[32], 1996	66	Canada	*CORR*	ORS	Single	3
Meding *et al*[33], 1994	24	United States	*JOA*	ORS	Single	3

ORS: Observational retrospective study; *JOA*: The Journal of Arthroplasty; *OSJ*: *Orthopaedic Surgery Journal*; *CORR*: *Clinical Orthopaedics and Related Research*; *AOTS*: *Archives of Orthopaedic and Trauma Surgery*; *OTSR*: *Orthopaedics & Traumatology, Surgery & Research*; *JBJS*: *Journal of Bone & Joint Surgery*; *JOT*: *Journal of Orthopaedics & Traumatology*; *IJO*: *Indian Journal of Orthopaedics*; *OSJ*: *Orthopaedic Surgery Journal*; *CJRRS*: *Chinese Journal of Reparative & Reconstructive Surgery*; *JOS*: *Journal of Orthopaedic Surgery (Hong Kong)*; *COAJ*: *Chinese Orthopaedic Association Journal*.

Systematic review

Intraoperative periprosthetic fracture: Six studies reported periprosthetic fractures with the use of cemented stems. Intraoperative periprosthetic fractures were reported in 59 cases (10.64 %) out of a total of 554 hips[14-19]. In the uncemented stem group, 16 studies reported intraoperative periprosthetic fractures in 112 cases out of 824 (13.59 %)[20-35]. The percentage of the periprosthetic fractures was lower in the cemented stem cohort (Tables 7 and 8).

Aseptic loosening: Five studies (with a total number of 375 revision THRs) reported 22 cases of aseptic loosening with cemented stems (5.87%)[14-18]. However, 13 studies with a total of 706 revision THRs, reported 34 cases of aseptic loosening (4.82%)[20,22,26-33].

Dislocation rate: 15 studies which included 689 uncemented stems[20,21-29,31,33-36] reported 29 (4.21 %) cases of dislocation. Conversely, for cemented stems, five studies (with a total of 375 hips) reported a dislocation rate of 4.53 %.

Infection: 14 studies with 626 hips using uncemented long stems reported a total of 28 cases (4.47 %) of post operative infection[20,22-27,30,31,33,35-37]. On the other hand, five studies with a total of 484 cemented hip stems, reported a postoperative infection rate of 4.33%[14,15,17-19].

Meta-analysis

The meta-analysis comparatively assessed the outcomes of both cemented and uncemented stems in rTHR, and the outcomes of both stem types as it correlates to four postoperative outcomes: Intraoperative periprosthetic fracture, aseptic loosening, dislocation rate and infection (after a mid-term follow up period 4.8-6 years). As mentioned earlier, only three studies were eligible for inclusion in the meta-analysis.

Periprosthetic fractures: The three included eligible studies reported on periprosthetic fractures, encompassing a total of

Table 5 Patients demographic for the study involved uncemented stem

Ref.	Gender male/female	Age in years (SD)	Follow up in years (SD)
Mahoney *et al*[20], 2010	18/22	64 (30.5)	10.2 (2.8)
Zhao *et al*[21], 2009	12/8	65 (9.5)	3 (1.1)
Hasegawa *et al*[22], 2021	12/33	62.6 (26)	13.8 (2.2)
Zheng *et al*[23], 2021	16/18	63.9 (11.7)	9.1 (2.5)
Wallace *et al*[24], 2020	19/36	66.4 (9.3)	13.2 (2.17)
Zang *et al*[25], 2019	15/25	62 (19.5)	15.7 (7.1)
Herry *et al*[26], 2019	55/61	68 (12)	10 (3)
Shen *et al*[27], 2014	21/13	65 (13.5)	6 (1.5)
Wang *et al*[28], 2020	33/42	62.6 (16.5)	12.6 (2)
Singh *et al*[34], 2013	42/6	54.7 (15.3)	14 (4.5)
Oetgen *et al*[29], 2008	18/10	59 (12)	5.5 (1.5)
Sotereanos *et al*[36], 2006	9/7	66 (17.5)	7.4 (6.5)
Philippot *et al*[35], 2009	10/33	54 (17.5)	5.3 (1.5)
Thorey *et al*[30], 2008	33/46	72.4 (28.5)	4 (2)
Malkani *et al*[31], 1996	40/ 34	67.1 (10.1)	6.8 (3.9)
Mulliken *et al*[32], 1996	31/32	62 (12)	3 (1)
Meding *et al*[33], 1994	17/7	63.8 (29)	3.6 (2)

SD: Standard deviation.

Table 6 Study characteristics of the cemented stem

Ref.	Country	Journal	Study type	Canters	Level of evidence	Total number	Gender male/female	Age	Follow up in years (SD)
Te Stroet *et al*[14], 2014	Netherlands	*BJJ*	ROS	Single centre	3	37	17/20	76 (39-93)	9 (4)
Randhawa *et al* [15], 2009	United Kingdom	*JOT*	ROS	Single centre	3	57	27/30	73 (37-94)	3.25 (3)
Stigbrand and Ullmark, 2017	Sweden	*JOA*	ROS	Single centre	3	69	40/29	69	7 (3.2)
Pallaver *et al*[19], 2018	Switzerland	*AOTS*	ROS	Single	3	178	126/52	68.4 (36-90)	9.3 (5.2)
Davis *et al*[17], 2003	United States	*JBJS*	ROS	Single	3	48	27/21	67 (47-82)	6.5 (2)
Turner *et al*[18], 1987	United States	*JOA*	ROS	Single	3	165	81/84	62.1 (22-92)	6.7 (1.5)

ROS: Retrospective observational study; *BJJ*: *The Bone & Joint Journal*; *MSM*: *Medical Science Monitor*; *JOT*: *Journal of Orthopaedics & Traumatology*; *JOA*: *Journal of Arthroplasty*; *AOTS*: *Archives of Orthopaedic and Trauma Surgery*; *JBJS*: *The Journal of Bone and Joint Surgery*.

2838 hips. 252 periprosthetic fractures were reported out of the 1382 hips in the cemented long stem cohort, and 84 events were reported in the 1456 hips receiving uncemented stems. Heterogeneity analysis demonstrated high statistical evidence for variation within the studies (I^2 = 94%). Data pooled by random-effects model suggested insignificant difference in periprosthetic fractures among the two cohorts (RR = 1.25, 95%CI: 0.29-5.32; P = 0.76; Figure 2A).

Aseptic loosening: All three studies reported on aseptic loosening after rTHR from a total of 2838 revision hips. Heterogeneity analysis demonstrated high statistical evidence for variation within the studies (I^2 = 96%). Although aseptic loosening rates were less among patients with uncemented stems (RR = 2.15, 95%CI: 0.81-5.70), statistical analysis showed no significant differences (P = 0.13; Figure 2B).

Table 7 Outcomes of the uncemented stem

Ref.	Intraoperative periprosthetic fracture (%)	Aseptic loosening (%)	Dislocation (%)	Infection (%)
Mahoney *et al*[20], 2010	1 (2.5)	1 (2.5)	13 (32.5)	1 (2.5)
Hasegawa *et al*[22], 2021	1 (2.2)	1 (2.2)	1 (2.2)	0 (0)
Zheng *et al*[23], 2021	7 (20.5)	3 (8.8)	1 (2.9)	3 (8.8)
Wallace *et al*[24], 2020	2 (3.6)	0 (0)	3 (5.4)	2 (3.6)
Zang *et al*[25], 2019	11 (27.5)	1 (2.5)	2 (5.0)	2 (5.0)
Herry *et al*[26], 2019	12 (10.3)	4 (3.4)	2 (1.7)	3 (2.5)
Shen *et al*[27], 2014	0 (0)	0 (0)	0 (0)	0 (0)
Tsukeoka *et al*[41], 2011	9 (64.2)	NA	1 (7.1)	NA
Wang *et al*[28], 2020	0 (0)	5 (6.8)	0 (0)	2 (2.7)
Singh *et al*[34], 2013	0 (0)	NA	3 (5.6)	7 (13.2)
Oetgen *et al*[29], 2008	3 (10.7)	0 (0)	0 (0)	NA
Sotereanos *et al*[36], 2006	NA	NA	0 (0)	0 (0)
Philippot *et al*[35], 2009	2 (4.6)	NA	1 (2.3)	3 (6.9)
Thorey *et al*[30], 2008	16 (20.2)	2 (2.5)	NA	2 (2.5)
Malkani *et al*[31], 1996	34 (45.9)	5 (6.75)	2 (2.7)	1 (1.3)
Mulliken *et al*[32], 1996	20 (30.3)	12(18.1)	NA	NA
Meding *et al*[33], 1994	4 (16.6)	0 (0)	3 (12.5)	1 (4.1)

NA: Not applicable.

Table 8 Outcomes of the cemented stem

Ref.	Periprosthetic fracture	Aseptic loosening	Dislocation	Infection
Te Stroet *et al*[14], 2014	9 (24.3)	0 (0)	3 (8.1)	4 (10.8)
Randhawa *et al*[15], 2009	4 (7.0)	1 (1.7)	1 (1.7)	7 (12.2)
Stigbrand and Ullmark, 2017	3 (4.3)	4 (5.7)	2 (2.8)	NA
Pallaver *et al*[19], 2018	2 (1.1)	3 (1.7)	NA	6 (3.3)
Davis *et al*[17], 2003	7 (14.5)	10 (20.8)	7 (14.5)	1 (2.0)
Turner *et al*[18], 1987	34 (20.6)	7 (4.2)	4 (2.4)	3 (1.8)

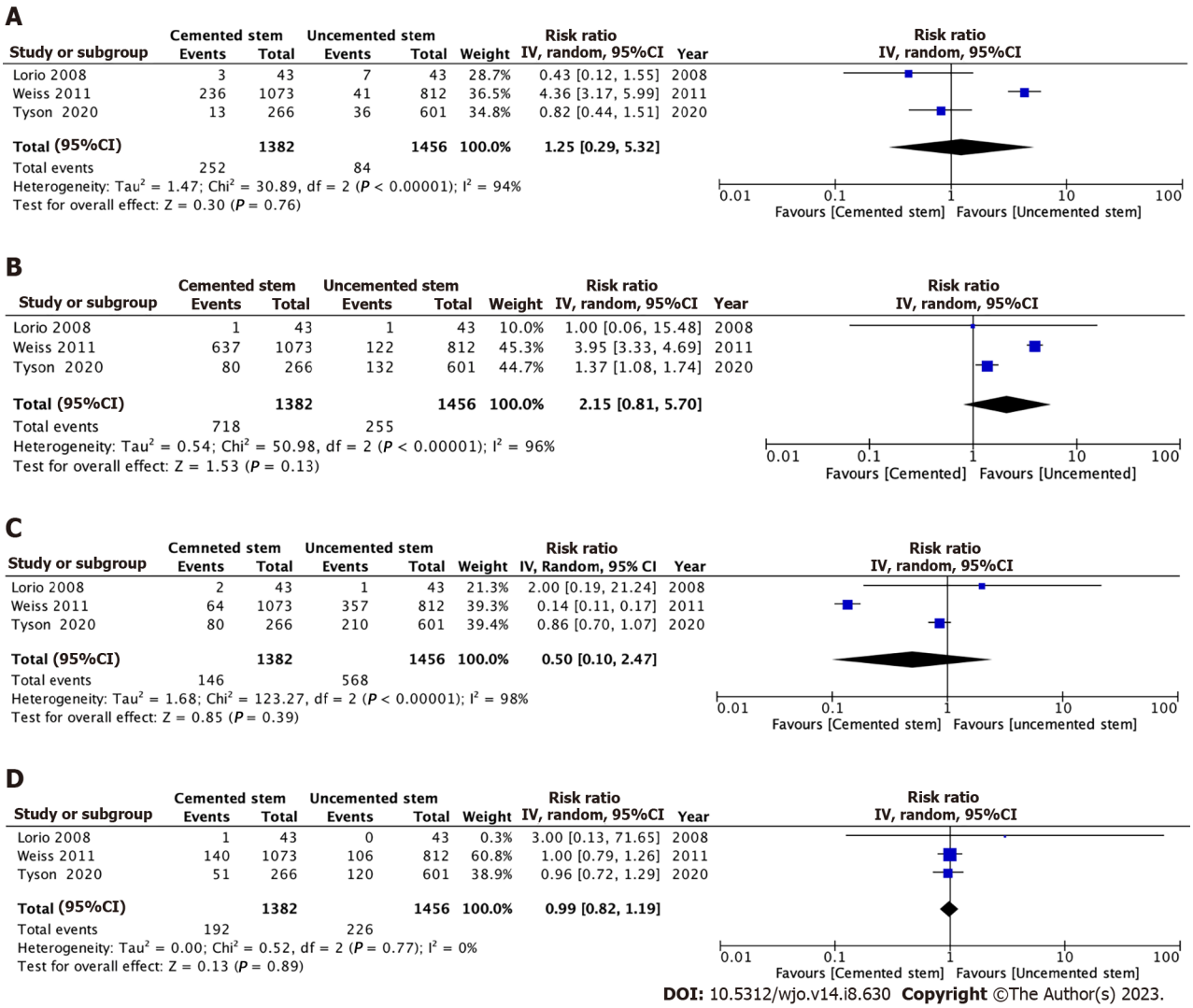
NA: Not applicable.

Dislocation rate: Of the 1382 cemented stems within the three studies, 146 (10.56 %) dislocations were reported, whereas 568 (39.01%) events were noted in the 1456 rTHAs performed with uncemented stems. Heterogeneity analysis demonstrated high statistical evidence for heterogeneity (I^2 = 98%). Although dislocation rates among patients with cemented stems was more than that seen in the uncemented group, the results were statistically insignificant (RR = 0.50; 95%CI: 0.10-2.47; P = 0.39; Figure 2C).

Infection rate: The three studies reported on infection rate with all of them reporting almost similar infection rates. Heterogeneity analysis demonstrated low statistical evidence for variation within the study (I^2 = 0%). There was no statistically significant difference between the groups (RR = 0.99, 95%CI: 0.82-1.19; P = 0.89; Figure 2D).

DISCUSSION

The most important finding in this review was the lack of statistically significant differences in the assessed outcomes after mid-term follow-up periods (4.8-6 years), between cemented and uncemented stems after first time revision THA.



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Figure 2 Forest plot of comparison. A: 1ry outcome, outcome: Periprosthetic fracture; B: 1ry outcome, outcome: Aseptic loosening; C: 2ry outcome, outcome: Dislocation rate; D: 2ry outcome, outcome: 1.4 infection rate. CI: Confidence interval.

To our knowledge, no other meta-analysis or systematic review has compared outcomes between cemented and uncemented stems for first-time revision THRs.

The preference of the femoral stem in revision THA is mainly dependent on the surgeon's choice. However, the uncemented stem is becoming more popular due to the anchoring effect of the distal part of the femoral stem within intact bone. Moreover, the uncemented stem offers different options in the proximal body of the prosthesis to achieve proper soft tissue tension, femoral anteversion, and femoral offset[9]. Some authors claim that the use of the uncemented stem may increase the risk of early postoperative failure but confers less risk of aseptic loosening in the long-term[4,38]. Another study reported better short-term (three years) outcomes for the cemented stem than the uncemented stem[39]. Tyson *et al*[39] reported the findings from a study of 867 uncemented and cemented revision THAs. Their study provided a hazard ratio (HR) of 5 for uncemented *versus* cemented stems for dislocations needing re-revision within the first three years. The HR gradually decreases to 3 between years 4-8. They postulated that the increased risk of subsidence in the uncemented revisions might lead to an increased risk of dislocation[39]. Similarly, Weiss *et al*[9] reported data collected from the Swedish THA register from 1999 to 2007. With a retrospective case-control study design, they showed an increased risk of re-revision in the uncemented hip prostheses in the first three years postoperatively. They included only one design (MP-Waldmar Link) of uncemented, titanium alloy, extensively-coated femoral stem owing to its popularity in Sweden. The control group had a variety of cemented stems implanted. There were 812 and 1073 cases of uncemented and cemented stems, respectively. Over a period of three years, the modular uncemented (MP) stem showed greater risk of re-revision than the cemented group. Crude risk of reoperation in the MP stem group was 5%. The commonest reason for re-revision was dislocation. The difference in re-revision rate was only found in the first 3 years postoperatively. Subsequently, after the three-year period, there was no significant difference in revision rates[38].

Davis *et al*[17] reported 14 (29%) cases of aseptic loosening in a series of 48 hips over a mean follow up period of 6.8 years. 10 (20.8%) of these were revised. The authors suggest that reduced stock of cancellous bone (arising from bone loss which occurs during loosening of the primary stem and during femoral preparation for prosthesis insertion) allows for less interdigitation of cement, which leads to an earlier onset of aseptic loosening. Whilst plausible, when comparing

outcomes of primary against revision cemented stems, this does not explain why their figures are lower compared to other series reporting on cemented stems. Earlier generation cementing techniques may explain this[17]. Other authors report aseptic loosening rates as high as 18.1%[32]. There appears to be no inferable pattern that may explain this from data provided. Systematic data aggregating levels of bone defects with rates of aseptic loosening may help shed light on the relationship between bone loss and aseptic loosening.

Te Stroet *et al*[14] reported nine (24%) intraoperative periprosthetic fractures but reported that none occurred during graft impaction[14]. They suggested that consistently worse preoperative bony defects than that seen in comparative studies was the causative factor. Most fractures occurred during stem extraction. They proposed that the use of a Wagner osteotomy may help reduce the risk of such complications[14]. Sierra *et al*[40] do not report on intraoperative fractures but discuss one case of femoral perforation which subsequently led to the development of a post-operative fracture. Impaction bone grafting allows for initial stability[16], but risks inducing fractures[40]. Sierra *et al*[40] suggested that the generous release of a circumferential rim of proximal soft tissues led to reduced bending and torsional forces during stem preparation, thereby reducing the risk of fractures. Relatively higher numbers of periprosthetic fractures were reported with uncemented stems. Tsukeoka *et al*[41] in their series of 20 hips, reported nine fractures (45%) and one perforation. Malkani *et al*[31] reported a similar 45.1% intraoperative fracture rate. Both studies reported on the findings from the use of proximally coated stems that are reliant on the "fit-and-fill" philosophy. Malkani *et al*[31] suggested that the impaired quality of bony, along with the size and stiffness of the implant, might explain the observed numbers of periprosthetic fractures. In conclusion, both types of femoral stems are safe options for revision THA.

Study limitations

One of the limitations of this study, was the fact that there were only three studies included in the meta-analysis. Significant heterogeneity occurred between the studies for the four assessed outcomes except for infection rate. Furthermore, all included studies were retrospective. These types of observational studies are more prone to bias in data collection, and are affected by the inability to control for all the variables assessed between the different cohorts included in each study. Another limitation was the fact that the postoperative follow up period was not long enough. Randomized control studies with long-term follow up periods comparing outcomes between these types of femoral stem are required, in order to provide data of a higher quality in this area.

CONCLUSION

In summary, this study has evaluated the mid-term outcomes of both cemented and uncemented stems for first time revision THA. No statistically significant differences in dislocation rate, aseptic loosening, intraoperative periprosthetic fracture and infection rate between the two cohorts were found. Nevertheless, the evidence from this study should be interpreted with caution, due to the unavailability of any randomized controlled studies for the meta-analysis. Finally, significant heterogeneity occurred between the studies for the four assessed outcomes, except for infection rate.

ARTICLE HIGHLIGHTS

Research background

There is no published systematic review and meta-analysis looking at the research question in this study, despite the large number of revision total hip arthroplasties (THA) performed worldwide.

Research motivation

We have had this nagging question: "Is there any scientific evidence from published studies that shows a difference in outcomes between the cemented and uncemented stems, for revision total hip arthroplasty?"

Research objectives

To assess the outcomes (intraoperative periprosthetic fractures, aseptic loosening, dislocation and infection rates) of both cemented and uncemented stems after mid-term follow up.

Research methods

A meta-analysis of non-randomized interventional studies.

Research results

This paper included a meta-analysis of three studies involving 7600 revision total hip replacements, of which 3050 were performed using cemented stems, while 2539 were performed utilising uncemented stems. There were no statistically significant differences found for intraoperative periprosthetic fractures [risk ratios (RRs) = 1.25; 95% confidence interval (CI): 0.29-5.32; P = 0.76], aseptic loosening (RR = 2.15, 95%CI: 0.81-5.70; P = 0.13), dislocation rate (RR = 0.50; 95%CI: 0.10-2.47; P = 0.39), or infection rate (RR = 0.99, 95%CI: 0.82-1.19; P = 0.89), between the uncemented and the cemented long stems for revision THA after mid-term follow-up.

Research conclusions

Low-moderate quality evidence showing no statistically significant differences between the cemented and uncemented stems for revision THA.

Research perspectives

We believe the evidence from this study should be interpreted with caution, due to the lack of any randomized controlled study being eligible for inclusion in the meta-analysis. Furthermore, significant heterogeneity was found between the included studies.

FOOTNOTES

Author contributions: Elbardesy H and Anazor F involved in the conceptualization of the study and data interpretation; Elbardesy H, Anazor F, and Mirza M contributed to the data analysis; Elbardesy H, Anazor F, and Aly M contributed to the study design; Elbardesy H, Anazor F, and Maatough A involved in the selection and screening of studies; Elbardesy H, Anazor F, Mirza M, Aly M, and Maatough A contributed to the manuscript preparation-writing and editing; and all authors read and approved the final draft of the manuscript.

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Abstract

BACKGROUND

East Asia is the most dynamic region in the world and includes three major countries: Japan, South Korea and China. Due to rapid economic growth, orthopedics research in East Asia has achieved great advances during the past 10 years. However, the current status of orthopedic research in Japan, South Korea and China is still unclear.

AIM

To understand the current status of orthopedic research in Japan, South Korea, and China.

METHODS

Journals listed in the ''Orthopedics'' category of Science Citation Index Expanded subject categories were included. The PubMed and Web of Knowledge electronic databases were searched to identify scientific publications from the selected journals written by researchers from Japan, South Korea and China. A systematic analysis was conducted to analyze orthopedic research articles published in the three countries based on the number of articles, study design, impact factors (IFs) and citations. Furthermore, we also ranked the top 10 countries worldwide with the highest publications in the past 10 years. Additionally, we ranked the top 10 countries with the highest number of publications in the world in the past 10 years. Statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, United States), and statistical results are given in Tables and Figures. The Kruskal-Wallis test and the Mann-Whitney test were used to detect differences between countries. The tendency regarding the number of articles was analyzed by curvilinear regression. A two-tailed $P < 0.05$ was considered significant.

RESULTS

From 2012-2021, a total of 144518 articles were published in the 86 selected orthopedic journals. During this period, the number of worldwide published orthopedic articles has shown an annual increasing trend. A total of 27164 orthopedic research articles were published by Japan, South Korea and China during the past 10 years; 44.32% were from China, 32.98% were from Japan, and 22.70% were from South Korea. From 2012 to 2021, the annual number of articles markedly increased in each of the three countries. Over time, the worldwide share of articles increased substantially in South Korea (3.37% to 6.53%, $P < 0.001$) and China (5.29% to 9.61%, $P < 0.001$). However, the worldwide share of articles significantly decreased in Japan (5.22% to 3.80%, $P < 0.001$). The annual total IFs of articles from China were well above those of articles from Japan and South Korea (36597.69 *vs* 27244.48 *vs* 20657.83, $P < 0.05$). There was no significant difference among the articles in the top 10 high-IF orthopedics journals published from those three countries [South Korea (800) > China (787) > Japan (646), $P > 0.05$].

CONCLUSION

Over the past 10 years, China's scientific publications in orthopedic journals have shown an increasing trend. Considering the relative scale of the populations, Japan and South Korea have outpaced China with respect to quality.

Key Words: Japan; South Korea; China; Medical publication; Orthopedics; Research

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Core Tip: Our study was the first to systematically analyze and compare the scientific publication trends of orthopedic surgery studies over the past 10 years in three major East Asian countries–*i.e.*, Japan, South Korea, and China–and to summarize the current status of orthopedic science research in these three countries, thus providing useful information for orthopedic science research.

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INTRODUCTION

Orthopedic disorders are a general health problem that affects people of all ages and demographic backgrounds. These disorders are a major burden for individuals, health systems, and social care systems, with indirect costs being the most dominant burden. In particular, the majority of the global burden of orthopedic disease occurs in low- and middle-income countries and is susceptible to neglect. China is the largest developing country in the world; it has more than 1.37 billion people, and it is facing the big challenge of reducing the burden of disease. For instance, more than 50000 hip or knee joint replacements are annually performed in China[1-3]. Researchers have progressively focused more attention on this situation and are now trying to advance the understanding, treatment and prevention of musculoskeletal disorders[4,5].

East Asia is an important subregion of Asia and is also the most dynamic region in the world. The countries in East Asia include Japan, North Korea, South Korea, Mongolia, and China. Japan is a world leader in fundamental scientific research[6]. South Korea is one of the new industrial economic countries as well as a leader in scientific research[7,8]. Due to the rapid socioeconomic development that has occurred in China, scientific and medical fields have undergone tremendous changes in the past decade[9,10]. Japan, South Korea and China are non-English-speaking countries that adhere to traditional East Asian cultural practices, and they are well-developed, developed and developing countries, respectively. Scientific publication provides a connection between the production and use of scientific knowledge and is a widely accepted method for evaluating public health and academic achievement. Nonetheless, little is known about the relative contributions of the three major East Asian countries to the field of orthopedics. The quantity and quality of scientific literature can be used to analyze the history and current status of science and technology and to forecast trends. Hence, it is crucial to accurately estimate global and regional productivity in ongoing orthopedic research. The present study was designed to investigate the characteristics and trends in orthopedic research studies from Japan, South Korea and China over the past 10 years.

MATERIALS AND METHODS

This retrospective study investigated 86 journals from the ''Orthopedics'' category of the Science Citation Index

Expanded for 2021[11]. Resources in this category include general orthopedics publications and specialized research on musculoskeletal disorders, spine diseases, injury, arthroplasty, arthroscopy, hand surgery, sport medicine, traumatology, foot and ankle surgery, connective tissue diseases, osteoarthritis and physical therapy. Based on the selection criteria, a total of 86 orthopedics journals were selected, and the journals included in the search are shown in Supplementary Table 1. The selection criteria, which were described in previous studies[12-14], were as follows: (1) The journal was indexed in the PubMed database; and (2) the journal had impact factors (IFs) in accordance with the Journal Citation Reports (JCR) for 2021[15]. On September 1, 2022, the PubMed and Web of Knowledge databases were searched for articles published in the 86 selected journals between January 1, 2012, and December 31, 2021, and written by researchers from Japan, South Korea, and China[16]. The databases were searched using the full journal titles or the ISSN numbers of the journals. The search terms used were "0001-5415 OR 1745-3674 OR 0001-6462 OR 1017-995X OR 1413-7852 OR 0363-5465 OR 0936-8051 OR 1862-3522 OR 0749-8063 OR 2049-4394 OR 2046-3758 OR 1413-3555 OR 1947-6035 OR 0268-0033 OR 1050-642X OR 0009-921X OR 2380-0186 OR 2005-291X OR 0891-8422 OR 0300-8207 OR 1935-973X OR 2396-7544 OR 1473-2262 OR 0940-6719 OR 1071-1007 OR 1083-7515 OR 1268-7731 OR 0966-6362 OR 2151-4585 OR 2192-5682 OR 0749-0712 OR 2468-1229 OR 1120-7000 OR 1556-3316 OR 0019-5413 OR 0020-1383 OR 0341-2695 OR 0959-3020 OR 2687-4784 OR 2572-1143 OR 0883-5403 OR 1053-8127 OR 0021-9355 OR 1863-2521 OR 1067-2516 OR 0363-5023 OR 1753-1934 OR 0894-1130 OR 2054-8397 OR 1538-8506 OR 0190-6011 OR 0736-0266 OR 0949-2658 OR 1022-5536 OR 1749-799X OR 2214-031X OR 0890-5339 OR 1590-9921 OR 0271-6798 OR 1060-152X OR 1836-9553 OR 2000-656X OR 1058-2746 OR 1067-151X OR 8750-7315 OR 0968-0160 OR 0942-2056 OR 0934-6694 OR 0085-4530 OR 0744-6020 OR 1757-7853 OR 1877-0568 OR 0030-5898 OR 0147-7447 OR 1063-4584 OR 0031-9023 OR 0091-3847 OR 0309-3646 OR 0364-2348 OR 0362-2436 OR 1529-9430 OR 0932-0555 OR 1864-6697 OR 2325-9671 OR 1757-1146 OR 1471-2474" AND "Japan [ad]," "South Korea [ad]," and "China [ad]".

The author's institutional affiliation was used to identify the country of the scientific publication. The publication type categories in the PubMed database were used to compile clinical trials, randomized controlled trials (RCTs), and case reports. In accordance with previous studies[12-14], four methods were used to evaluate publication quality. First, the annual total and average IFs were determined according to JCR 2021[15]. Second, the distribution and citation patterns of articles written by researchers from these three countries were analyzed using *Reference Citation Analysis* (https://www.referencecitationanalysis.com/)[17]. Third, we calculated the number of clinical trials, RCTs, systematic reviews/meta-analyses and case reports. Fourth, we quantified the articles published in the top 10 high-IF orthopedic journals and identified the top 10 popular orthopedic journals in the three countries based on the number of articles published in each journal. Moreover, we assessed global trends in orthopedic publications and ranked the top 10 countries with the highest number of publications worldwide over 10 years. Two reviewers (WC and XX) independently extracted the articles. Disagreements between the two reviewers were resolved by consulting a third reviewer (HJ).

RESULTS

Global trends in orthopedic publications

A total of 144518 articles were published in 86 orthopedics journals from 2012 to 2021. The global number of annually published orthopedic research articles showed an increasing trend during the study period. The United States was the highest ranked country in terms of the number of published orthopedic research articles (39017 articles), followed by China (14939), Japan (11525), the United Kingdom (11203), Germany (10080), Canada (7887), South Korea (7664), France (7138), Australia (6849), and the Netherlands (5941). The top 10 countries in the world with the highest number of annual publications are shown in Table 1.

Number of articles in the orthopedic field in Japan, South Korea and China

A total of 27164 articles from Japan, South Korea and China were published in the 86 selected journals between 2012 and 2021 (Figure 1). 44.32% (12040/27164) were from China, 32.98% (8959/27164) were from Japan, and 22.70% (6165/27164) were from South Korea ($P < 0.05$). From 2012 to 2021, the annual number of articles published in the orthopedic field increased noticeably in South Korea (459 to 899, annual rate of increase = 6.95%, $R^2 = 0.798$, $P < 0.001$), China (552 to 2661, annual rate of increase= 17.03%, $R^2 = 0.823$, $P < 0.001$) and Japan (622 to 1620, annual rate of increase = 10.05%, $R^2 = 0.728$, $P < 0.05$) (Figure 2A).

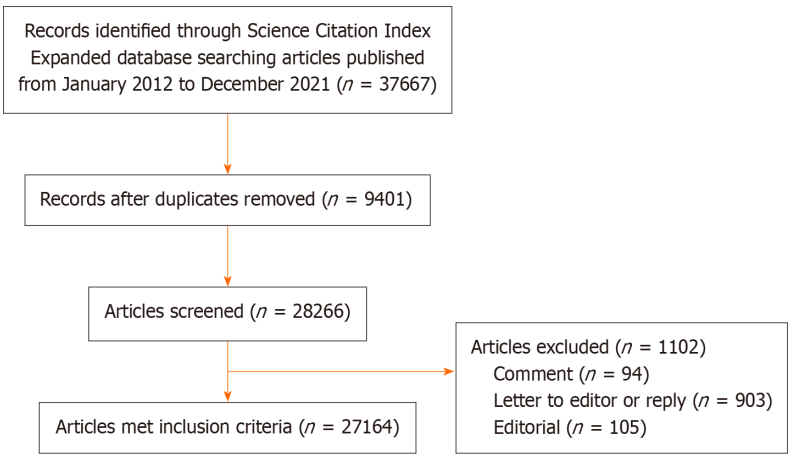
The worldwide share of articles increased remarkably over time in South Korea (3.37% to 6.53%, annual rate of increase = 6.85%, $R^2 = 0.988$, $P < 0.001$) and China (5.29% to 9.61%, annual rate of increase = 6.16%, $R^2 = 0.995$, $P < 0.001$). However, the worldwide share of articles decreased dramatically in Japan (5.22% to 3.80%, annual rate of increase =-3.14%, $R^2 = 0.878$, $P < 0.001$) (Figure 2B). In 2021, China accounted for 11.20% of all articles in the orthopedics field, followed by Japan (6.82%) and South Korea (3.78%) ($P < 0.05$).

Clinical trials, RCTs and case reports

Researchers from China published more clinical trials than researchers from Japan and South Korea [China (634) > South Korea (426) > Japan (330), all P values were less than 0.05] (Figure 3). Between 2012 and 2021, Chinese researchers published 512 RCTs, South Korean researchers published 353 RCTs ($P < 0.05$). Compared to China and South Korea, Japan had a distinctly higher number of case reports ($P < 0.05$) (Figure 3).

Table 1 Top 10 countries according to the annual number of articles from 2012-2021

Year	1	2	3	4	5	6	7	8	9	10
2012	United States	United Kingdom	Japan	China	Germany	South Korea	Canada	France	Netherlands	Australia
2013	United States	United Kingdom	Japan	China	Germany	South Korea	Canada	Netherlands	France	Australia
2014	United States	United Kingdom	China	Japan	Germany	Canada	South Korea	France	Australia	Netherlands
2015	United States	China	United Kingdom	Germany	Japan	Canada	South Korea	Australia	France	Turkey
2016	United States	China	United Kingdom	Japan	Germany	France	Canada	Australia	South Korea	Netherlands
2017	United States	China	Japan	United Kingdom	Germany	Canada	South Korea	France	Australia	Netherlands
2018	United States	China	Japan	United Kingdom	Germany	Canada	South Korea	France	Australia	Netherlands
2019	United States	China	Japan	United Kingdom	Germany	Canada	South Korea	France	Australia	Netherlands
2020	United States	China	Japan	United Kingdom	Germany	Canada	South Korea	France	Australia	Switzerland
2021	United States	China	Japan	United Kingdom	Germany	Canada	France	South Korea	Australia	Switzerland



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Figure 1 Flow chart for study selection.

IFs

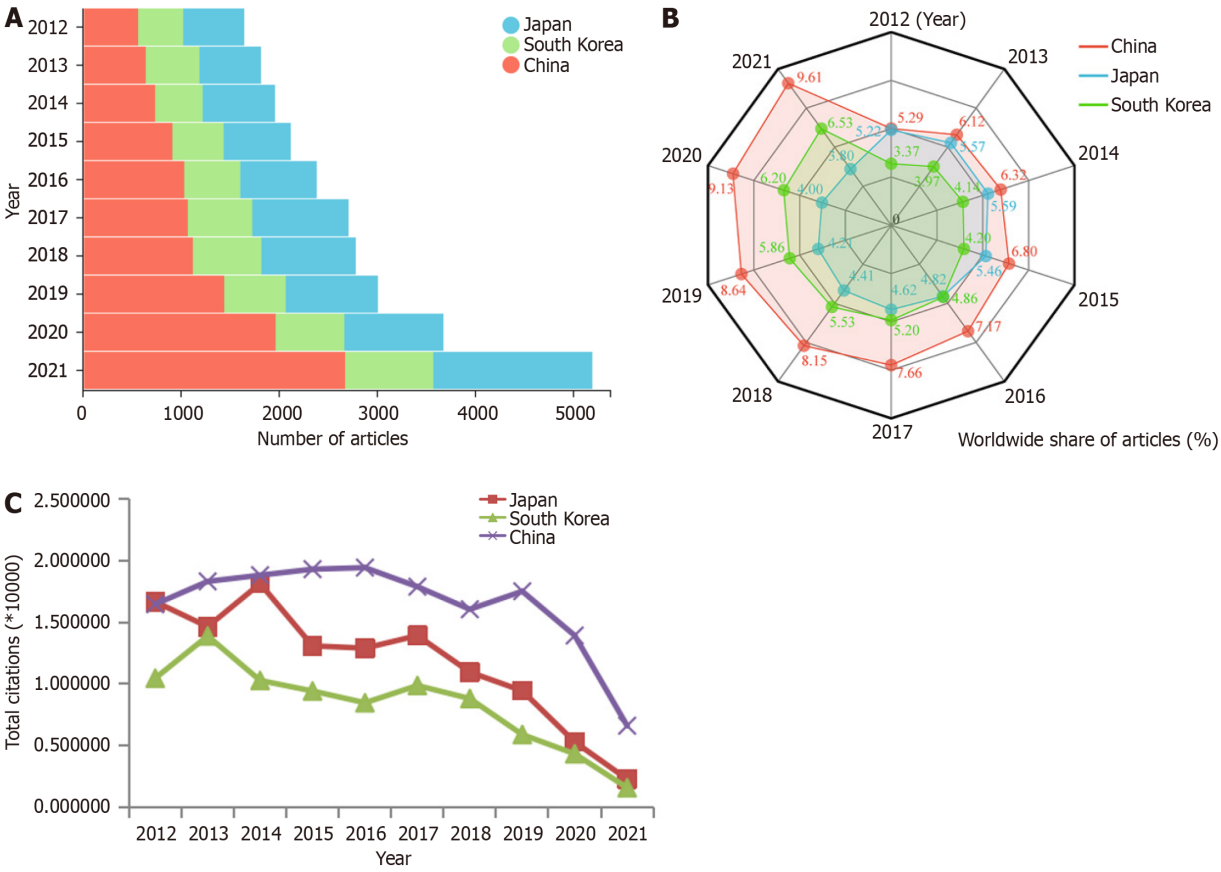
During the past 10 years, the annual total IFs were ranked in the following order: China, Japan and South Korea (36597.69 *vs* 27244.48 *vs* 20657.83, $P < 0.05$) (36597.69 *vs* 27244.48 *vs* 20657.83, $P < 0.05$). The annual total IFs of articles from China were markedly higher than those from South Korea. For the past 10 years, there were no discernible variations in the annual total IFs between Japan and the other two countries ($P > 0.05$). The average IFs of articles from Japan or China were significantly lower than those of articles from South Korea. (2.81 *vs* 2.94 *vs* 3.21; all P values were less than 0.05) (Figure 4). However, there was no significant difference in the average IF between Japan and China ($P > 0.05$).

Citations of articles published in orthopedics journals

Articles from China had the highest number of citations (164175 citations), followed by those from Japan (117323 citations) and South Korea (83118 citations). There was a significant difference in the number of citations between China and the two other countries ($P < 0.001$), but there was no statistically significant difference in the number of citations between Japan and South Korea ($P > 0.05$) (Figure 2C).

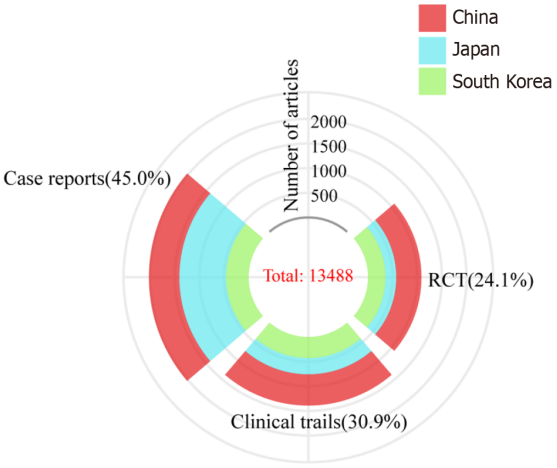
Articles in the top 10 high-IF orthopedics journals

The top 10 high-IF orthopedic journals with 2642 articles from the three countries. Among them, 41.75% (1103/2642) were



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Figure 2 The articles published in the 86 orthopedics journals by researchers from Japan, South Korea and China (2012-2021). A: Annual numbers; B: Annual proportion; C: Annual citations.



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Figure 3 Number of clinical trials, randomized controlled trials and case reports published by researchers from Japan, South Korea and China from 2012 to 2021. RCT: Randomized controlled trials.

in the top three journals: Journal of Physiotherapy, Osteoarthritis and Cartilage, and American Journal of Sports Medicine. Researchers from Japan published 770 (29.14%) articles in the top 10 high-IF orthopedics journals, those from South Korea published 847 (32.06%) articles, and those from China published 1025 (38.80%) articles (Table 2).

Popular orthopedics journals

The journals with the highest number of articles published by researchers from these three countries are shown in Table 3. Over the past 10 years, most of the orthopedic research studies from China were published in the Journal of Orthopaedic Surgery and Research (1680), most of the articles from Japan were published in the Journal of Orthopedic

Table 2 Articles published in the top 10 high IF orthopedics journals by researchers from Japan, South Korea and China from 2012 to 2021

Rank	Journal	2021 JIF	Japan (%)	South Korea (%)	China (%)	Total
1	*J PHYSIOTHER*	10.714	1 (33.33)	0 (10.00)	2 (66.67)	3
2	*OSTEOARTHR CARTILAGE*	7.507	124 (30.31)	47 (11.49)	238 (58.20)	409
3	*AM J SPORT MED*	7.01	234 (33.86)	290 (41.97)	167 (24.17)	691
4	*J BONE JOINT SURG AM*	6.558	99 (32.57)	112 (36.84)	93 (30.59)	304
5	*J ORTHOP SPORT PHYS*	6.276	5 (38.46)	4 (30.77)	4 (30.77)	13
6	*ARTHROSCOPY*	5.973	166 (28.28)	286 (48.72)	135 (22.99)	587
7	*BONE JOINT J*	5.385	122 (38.00)	94 (29.28)	105 (32.71)	321
8	*J ORTHOP TRANSL*	4.889	13 (4.36)	10 (3.36)	275 (92.28)	298
9	*EFORT OPEN REV*	4.775	2 (25.00)	1 (12.50)	5 (62.50)	8
10	*BRAZ J PHYS THER*	7.507	4 (50.00)	3 (37.50)	1 (12.50)	8
Total			770 (29.14)	847 (32.06)	1025 (38.80)	2642

Table 3 The top 10 popular orthopedics journals publishing the articles written by researchers from Japan, South Korea and China

Rank	Japan	IF	*n*	South Korea	IF	*n*	China	IF	*n*
1	*JOS*	1.805	1427	*COS*	2.503	492	*JOSR*	2.677	1680
2	*Spine*	3.269	622	*KSSTA*	4.114	394	*BMCMD*	2.562	1296
3	*KSSTA*	4.114	506	*AJSM*	5.973	290	*OS*	2.279	920
4	*BMCMD*	2.562	444	*ARTH*	7.01	286	*ESJ*	2.721	759
5	*ESJ*	2.721	421	*Spine*	3.269	261	*Spine*	3.269	691
6	*JA*	4.435	288	*JA*	4.435	241	*IO*	3.479	587
7	*JOR*	3.102	276	*BMCMD*	2.562	241	*Injury*	2.687	378
8	*JOSHK*	2.423	276	*JSES*	3.507	221	*TSJ*	4.297	326
9	*Knee*	1.482	242	*AOTS*	2.928	221	*JOT*	4.239	275
10	*AJSM*	7.01	234	*TSJ*	4.297	199	*AOTS*	2.928	272

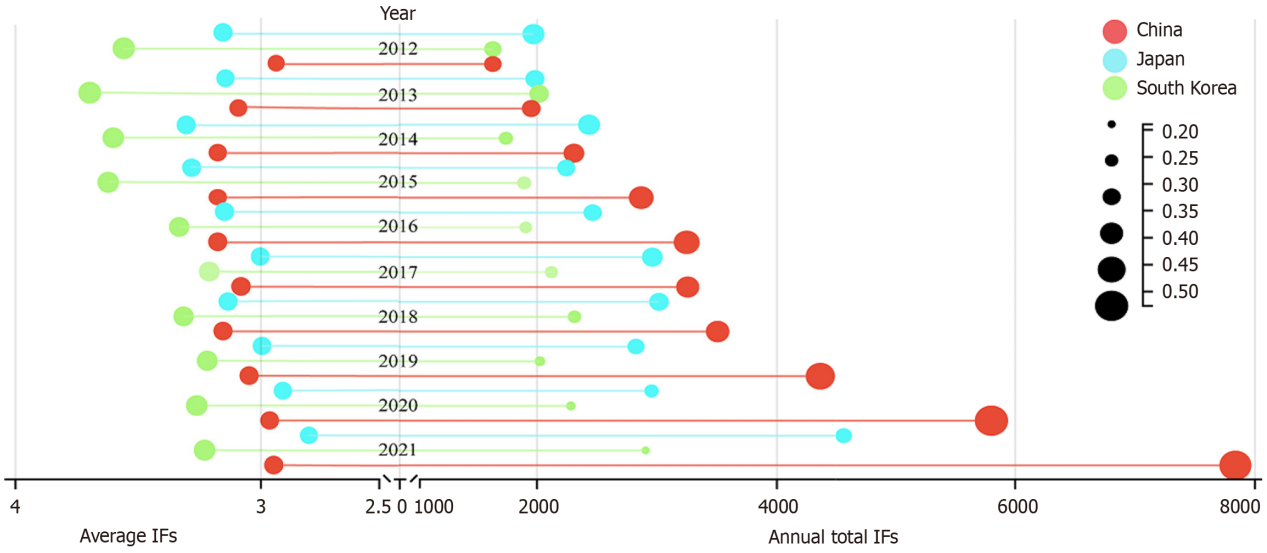
AJSM: Am J Sports Med; AOTS: Arch Orthop Traum Surg; ARTH: Arthroscopy; BMCMD: BMC Musculoskelet Disord; COS: Clin Orthop Surg; ESJ: Eur Spine J; IO: Int Orthop; JA: J Arthroplasty; JOR: J Orthop Res; JOSHK: J Orthop Surg (Hong Kong); JOS: J Orthop Sci; JOSR: J Orthop Surg Res; JSES: J Shoulder Elbow Surg; JOT: J Orthop Translat; KSSTA: Knee Surg Sport Tr A; OS: Orthopaedic Surgery; TSJ: The Spine J.

Science (1427), and most of the articles from South Korea were published in Clinics in Orthopedic Surgery (492). Spine, BMC Musculoskeletal Disorders appeared among the top 10 popular journals for all three countries.

DISCUSSION

To the best of our knowledge, this is the first study to investigate the characteristics of and trends in orthopedic studies from Japan, South Korea and China. The number of worldwide orthopedic publications showed an upward trend from 2012 to 2021. Unquestionably, the United States ranks first in the world in terms of total and annual number of orthopedic publications. Over the past 10 years, there has been a steady increase in the number of articles published each year in highly developed countries, including the United Kingdom, Japan, Germany and France[18,19]. Notably, there has been drastic growth in the annual number of articles published in China and Japan. Their articles disseminate a wealth of scientific knowledge and make significant contributions to the countries' profound emphasis on academic research, as well as active global engagement. Therefore, these countries have contributed to the development of orthopedics over the past 10 years.

During the past 10 years, a considerable increase in the total number and percentage of articles in orthopedic journals from Japan has been observed. Despite substantial growth in the annual number of orthopedic research articles published in Japan (622 in 2012 to 1620 in 2021), the country's worldwide share of articles decreased from 5.22% in 2012 to 3.80% in



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Figure 4 The average impact factors and annual total impact factors of articles published in the 86 orthopedics journals by researchers from Japan, South Korea and China from 2012 to 2021. IF: Impact factors.

2021. This decrease may be attributed to a decrease in government funding allocated for research endeavors[20]. Nevertheless, Japan still has a considerable international impact on scientific research and is a leader in the field of orthopedics. The large amount of research funding and the vast number of well-trained researchers might account for the objective reality that Japan has attained a continuously dominant position. Furthermore, Japan enjoys an efficient and competitive system of scientific research, which may be considered a reference model for some developing countries in Asia.

In the past 10 years, the annual number and worldwide share of orthopedic publications from South Korea have also increased (annual number: 459 in 2012 to 899 in 2021; worldwide share: 3.37% in 2012 to 6.53% in 2021). The rise of scientific research may be ascribed to the aging population. As the population progressively ages, there is a pronounced increase in the prevalence of orthopedic disorders[21]. In response, researchers have redirected their focus toward gaining a better understanding of this situation and advancing the treatment of orthopedic disorders. Consequently, South Korea has emerged as a noteworthy contributor to the development of orthopedic science, gradually gaining recognition for its prowess and innovative approaches.

There has been a strong positive trend in orthopedic publications from China. Our study suggests a 5-fold increase in the absolute number of articles from China in orthopedic journals (from 552 papers in 2012 to 2661 paper in 2021, $P < 0.001$), and the market share of articles in China has increased markedly (from 5.29% in 2012 to 9.61% in 2021, $P < 0.001$). In the orthopedics field, China's scientific research has been growing rapidly in the past decade[14,18,19]. In 2013, articles originating in China (629) surpassed those originating in Japan (627) and South Korea (548). Between 2012 and 2021, researchers from China published 634 orthopedic clinical trials, outpacing those from South Korea ($n = 426$, $P < 0.05$) and Japan ($n = 330$, $P < 0.05$). Only 1083 RCTs were found among all 27164 articles originating in these three countries (Japan 218 *vs* South Korea 353 *vs* China 512; $P < 0.05$). RCTs are considered to be a higher grade of scientific evidence that influences health care policy. Thus, researchers in East Asia should prioritize more RCTs and consider these findings.

The average number of citations to articles in the publications is indicated by the IF. Although the IF has many limitations[22,23], it remains one of the optimal tools for assessing the relative significance of scientific studies. Researchers from South Korea made the most qualitative contributions to orthopedic research, as evidenced by the number of papers they published in high-IF journals and the highest annual average IFs. Researchers from South Korea published more articles in high-IF journals and had the highest annual average IFs, indicating that they contributed the majority to orthopedic research in terms of quality. Throughout the past 10 years, there has been steady growth in the total annual IF of articles originating from China. However, the annual average IFs still lagged behind South Korea. Undoubtedly, the quality of the articles and the international presence from China requires improvement. Citations are another valuable indication of article quality, revealing the extent to which the article has been accepted by other authors in the same field. In this study, we revealed that articles from China had a fairly high number of citations, followed by those from Japan and Korea. The average number of citations for Chinese studies ranked behind Japan and South Korea. In fact, newly published articles have less time to be cited, and thus, old articles of high quality are usually more often cited. In the past 3 years, China published 6042 articles, accounting for 50.18% (6042/12040) of the total number of articles published from 2012 to 2021, which could explain this phenomenon.

Regarding the orthopedic journals with a top-ten IF, researchers from China (1025) and South Korea (847) published more articles in these journals than researchers from Japan (770), but there was no significant difference among the three countries ($P > 0.05$). It should be noted that IF is not always the optimum parameter for identifying the quality of journals. Sometimes, a high IF represents a journal with high visibility, prestige, and influence. Researchers with well-designed studies tend to submit their articles to journals with these characteristics. In this study, spine and *BMC Musculoskeletal*

Disorders were considered the most popular journals, ranking among the top 10 popular journals in the three countries. The most popular journals in this study were *Spine* and *BMC Musculoskeletal Disorders*, which were ranked among the top 10 most popular publications in each of the three nations. These two journals mainly publish high-quality clinical and basic research articles, which results in their widespread international influence. However, there were differences in the most popular journals for authors among the three countries. Researchers from Japan publish most in *Journal of Orthopedic Science*. This journal is the official journal of the Japanese Orthopedic Association and has a lengthy and illustrious history of publishing outstanding scientific papers in the field[24]. The top three popular journals for South Korea were *Clinics in Orthopedic Surgery, Knee Surgery Sports Traumatology Arthroscopy and Arthroscopy-The Journal of Arthroscopic and Related Surgery,* suggesting that arthroplasty surgery in South Korea is developing rapidly and has achieved great advances in recent years. On the other hand, the top three popular journals for China were *Journal of Orthopaedic Surgery and Research*, *BMC Musculoskeletal Disorders and Orthopaedic Surgery,* demonstrating that China has markedly improved its research in the field of orthopedic surgery during the past 10 years.

Orthopedic research in China is experiencing a period of immense growth, which is due to several factors. First, numerous newly established institutions and hospitals in China already conduct scientific research and surgical treatment in orthopedics, with recent advances in China's economy[9,25,26]. Second, the continual development of international cooperation might benefit Chinese orthopedic researchers to strengthen their clinical orthopedic practice and research abilities[27-29]. Third, the number and IF of articles indexed in the SCIE database were recently regarded as important indicators to evaluate the performance and achievements of a researcher or an institution in China. Importantly, SCIE papers are tightly linked to authors' academic status, income, funding and other key benefits[30,31]. However, these policies seem to have resulted in an increase in the number of articles and not in their quality, as indicated by the current citation rates for Chinese-authored articles.

There are some limitations to this study. First, only 86 orthopedic journals included in the SCIE database were analyzed. There were some orthopedic research articles published in general medical journals that were not included in our study. Second, the JCR database was restricted to include studies published in English, which may lead to publication bias. For that reason, we may have neglected the contribution of non-English publications.

CONCLUSION

In summary, some useful information about scientific research in orthopedics is provided in this study. China has maintained an increasing trend of scientific publication in orthopedics journals over the past 10 years and has exceeded Japan and South Korea in some aspects of orthopedics publications. Given the relative size of the populations, China still lags behind Japan and South Korea in terms of quality. Chinese orthopedic researchers must improve their research activities and produce high-quality research.

ARTICLE HIGHLIGHTS

Research background

Orthopedic research in East Asia has made significant strides over the past 10 years. However, the current status of orthopedic research in the three major East Asian countries of Japan, South Korea, and China remains uncertain.

Research motivation

To explore the current state of orthopedic research in Japan, South Korea, and China and provide informative findings in the field of orthopedic science.

Research objectives

To visualize the publication quantity, global share, publication types, impact factor (IF), and citation trends of orthopedic studies from Japan, South Korea, and China during the period of 2012-2021 and to analyze the developmental trends in orthopedic research in East Asia over the past decade.

Research methods

According to the selection criteria, which include: (1) The journal was indexed in the PubMed database; and (2) the journal had IFs in accordance with the Journal Citation Reports for 2021, a total of 86 orthopedic journals were included. The PubMed and Web of Knowledge databases were searched from January 1, 2012, to December 31, 2021, to retrieve articles published in the selected 86 journals by researchers from Japan, South Korea, and China. The publication quantity, global share, publication types, IF, and citation patterns of these papers were then analyzed and visualized. Statistical analyses were performed using SPSS 20.0 software.

Research results

Between 2012 and 2021, a total of 27164 orthopedic studies were published by Japan, South Korea, and China, showing a steady increase over the years. Among them, 44.32% were from China, 32.98% were from Japan, and 22.70% were from South Korea. Over time, the global share of articles significantly increased in South Korea (from 3.37% to 6.53%, $P < 0.001$)

and China (from 5.29% to 9.61%, $P < 0.001$), while it decreased significantly in Japan (from 5.22% to 3.80%, $P < 0.001$). The annual total IFs of articles from China were well above those of articles from Japan and South Korea (36597.69 *vs* 27244.48 *vs* 20657.83, $P < 0.05$). There was no significant difference in the number of top 10 high-IF orthopedics journals published among these three countries [South Korea (800) > China (787) > Japan (646), $P > 0.05$].

Research conclusions

China's orthopedic publications have seen consistent growth in the past decade, but when considering their population scales, Japan and South Korea still outpace China with respect to quality.

Research perspectives

The authors aim for this article to contribute toward the assessment and enhancement of academic productivity in orthopedic research in East Asia. In the future, it is imperative to foster stronger international cooperation and increase financial support for orthopedic research to produce a high level of evidence research and foster the sustained development of orthopedic research.

FOOTNOTES

Author contributions: Jiang H conceived and designed the study; Chen WY was involved in data retrieval and data selection, analyzed the data, and wrote the manuscript; Xiao X was involved in statistical analysis and manuscript revision; Pan C, Xu HY, and Huang FH were involved in data search; Jiang H and Wei QJ were involved in the selection of data and contributed analysis tools; All authors read and approved the final manuscript.

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CASE REPORT

Metallosis with spinal implant loosening after spinal instrumentation: A case report

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Abstract

BACKGROUND

Spinal metallosis is a rare complication following spinal instrumentation whereby an inflammatory response to the metal implants results in the development of granulomatous tissue.

CASE SUMMARY

We describe the case of a 78-year-old woman who had recurrence of back pain 5 years after lumbar spine posterior decompression and instrumented fusion. Lumbar spine radiographs showed hardware loosening and magnetic resonance imaging showed adjacent segment disease. Revision surgery revealed evidence of metallosis intraoperatively.

CONCLUSION

Spinal metallosis can present several years after instrumentation. Radiography and computed tomography may demonstrate hardware loosening secondary to metallosis. Blood metal concentrations associated with spinal metallosis have yet to be established. Hence, metallosis is still an intraoperative and histopathological diagnosis. The presence of metallosis after spinal instrumentation likely indicates a more complex underlying problem: Pseudarthrosis, failure to address sagittal balance, infection, and cross-threading of set screws. Hence, identifying metallosis is important, but initiating treatment promptly for symptomatic implant loosening is of greater paramount.

Key Words: Metallosis; Spine; Instrumentation; Implant loosening; Corrosion; Case report

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Core Tip: This paper describes a rare case of metallosis after spinal instrumentation and discusses the methods of diagnosing and risk factors contributing to spinal metallosis. A review of the current literature as presented in this paper demonstrates the scarcity of studies on spinal metallosis after spinal instrumentation, despite the fact that a diagnosis of spinal metallosis should be promptly identified and treated by revision surgery. It is also important to understand that the presence of metallosis after spinal instrumentation likely indicates a more complex underlying problem, such as instability of the spinal implants.

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INTRODUCTION

Metallosis is postulated to occur due to the corrosion of metal implants leading to metal debris build-up in periprosthetic soft tissue and bone. This precipitates a granulation-type reaction involving phagocytosis of metal particles resulting in osteolysis and local reactions, namely, aseptic fibrosis, local tissue necrosis, and implant loosening, as well as systemic toxicity such as cardiomyopathy and abnormal thyroid function[1]. Posterior spinal fusion involves the placement of metallic rods and screws and these fixtures are not routinely removed except for reasons such as localised pain over implant site, prominent hardware, implant failure, or infection[2]. Metallosis is not uncommon following joint arthroplasties but only a few cases of spinal metallosis have been described in the literature. Hence, we report a case of spinal metallosis with implant loosening after posterior spinal instrumentation.

CASE PRESENTATION

Chief complaints

A 78-year-old woman was admitted in 2019 to the Department of Orthopaedic Surgery in Changi General Hospital, a tertiary hospital in Singapore, for a 4-mo duration of worsening lower back pain with claudication and right lower limb radiculopathy, with onset 5 years after a spinal surgery.

History of present illness

The patient's past medical history was significant for well-controlled hypertension and type 2 diabetes mellitus, gout, gastroesophageal reflux disease, and obesity [body mass index (BMI) of 31.2].

She also had a significant past surgical history of L3 to S1 posterior decompressive laminectomy, stabilisation with pedicle screws, and posterolateral fusion with local bone grafting performed at the same hospital 5 years ago. The surgery was performed for a diagnosis of lumbar spondylosis with central canal stenosis, for which she presented with chronic lower back pain radiating down her bilateral lower limbs. Titanium polyaxial screws (DePuy Synthes) were used in that surgery. The patient's symptoms were relieved after the surgery and she recovered. Postoperative lumbar spine radiographs showed the proper positioning of the spinal implants (Figure 1).

History of past illness

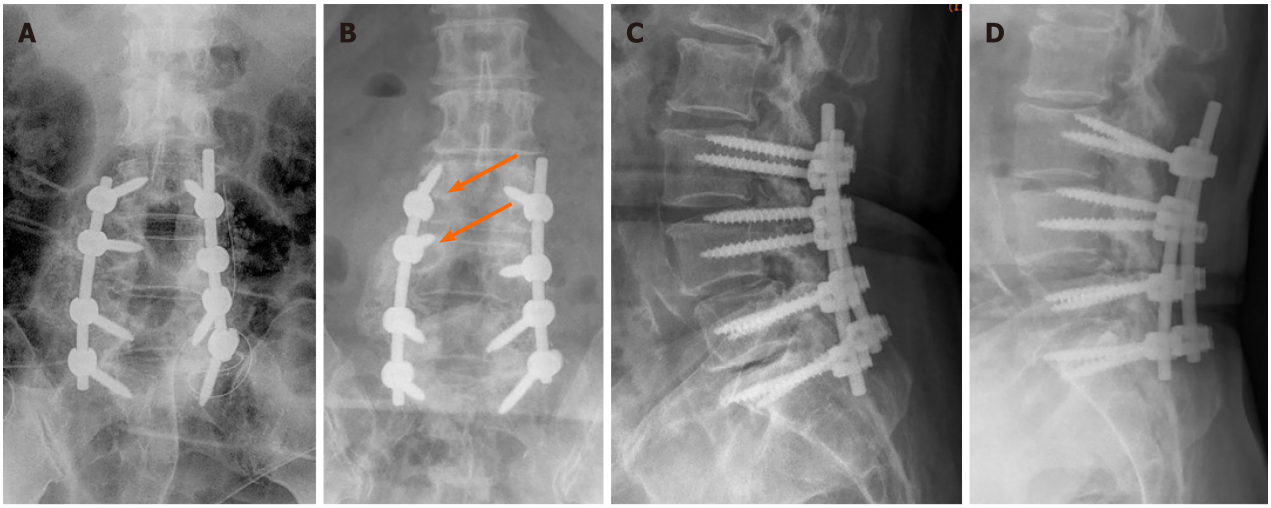
The patient was followed up in the orthopaedic surgery specialist outpatient clinic regularly after her spine surgery. Five years after the surgery, she started to develop progressively worsening lower back pain which radiated to her right lateral thigh and calves. Four months later, her symptoms had slowly deteriorated to the point where she required a motorized wheelchair as she was unable to ambulate long distances due to pain.

Personal and family history

The patient had no relevant personal and family history.

Physical examination

The most significant finding on examination was reduced power in the right L2 and L3 myotomes [grade 4 out of 5 on the Medical Research Council (MRC) scale for muscle strength]. The rest of the myotomes from L2 to S1 were normal, with a grade 5 out of 5 power on the MRC scale. She also had a large body habitus. Her gait was slow but steady over a short distance. The rest of the physical examination was unremarkable: There was no spinal tenderness or significant muscle wasting of her back or lower limbs. The range of movement of her cervical and thoracolumbar spine was normal. Sensation was intact over all dermatomes. Bilateral knee and ankle reflexes were normal. The straight leg raise test was negative as well.



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Figure 1 Postoperative lumbar spine radiographs showing the proper positioning of the spinal implants. A: Lumbar spine antero-posterior radiograph after initial surgery for posterior decompression and instrumented fusion; B: Lumbar spine antero-posterior radiograph at 5 years after initial surgery, showing stable periprosthetic radiolucencies (indicated by arrows) surrounding the right L3 and L4 screws suggestive of instrumentation loosening; C: Lumbar spine lateral radiograph after initial surgery; D: Lumbar spine lateral radiograph at 5 years after initial surgery.

Laboratory examinations

Laboratory blood tests showed normal values, including a white blood cell count of 8.2 × 10^9/L and C-reactive protein level of 4.1 mg/L. Other biochemical parameters were within the normal range. Serum metal concentrations were not performed for the patient due to cost issues.

Imaging examinations

Lumbar spine radiographs and magnetic resonance imaging (MRI) were performed prior to the revision surgery. Lumbar spine anteroposterior and lateral radiographs revealed stable periprosthetic radiolucency surrounding the right upper two screws (L3 and L4 pedicle screws) that suggested loosening of the instrumentation (Figure 1). There was no evidence of fracture of the pedicle screws and rod instrumentation. Narrowing of the L4-L5 and L5-S1 intervertebral disc spaces was noted but vertebral body heights were largely maintained. Spondylotic changes and facet arthropathy were seen. There was no instability noted in the flexion and extension views.

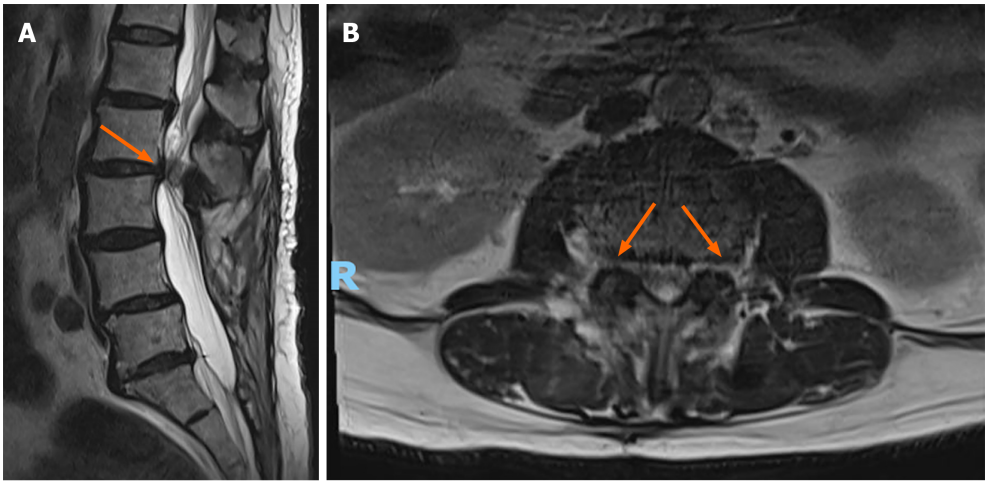
Lumbar spine MRI revealed severe spinal canal stenosis at the L2-L3 level with compression of the cauda equina nerve roots, severe bilateral lateral recess, and neural foraminal stenosis (Figure 2). There was moderate spinal canal stenosis with crowding of the cauda equina nerve roots at L1-L2. Mild peri-screw bony edema was observed around the left L4 screw (Figure 3), otherwise there was no significant evidence of peri-screw edema and screw loosening around the rest of the L3 to S1 screws.

FINAL DIAGNOSIS

Histopathology of the stained tissues that were excised revealed fibroadipose tissue and occasional striated muscle bundles exhibiting degenerative changes. There were aggregates of non-refractile, non-polarisable black granular foreign material mostly in a perivascular location, that were consistent with metallosis. There was no evidence of malignancy. Intra-operative tissue cultures were negative for bacterial growth.

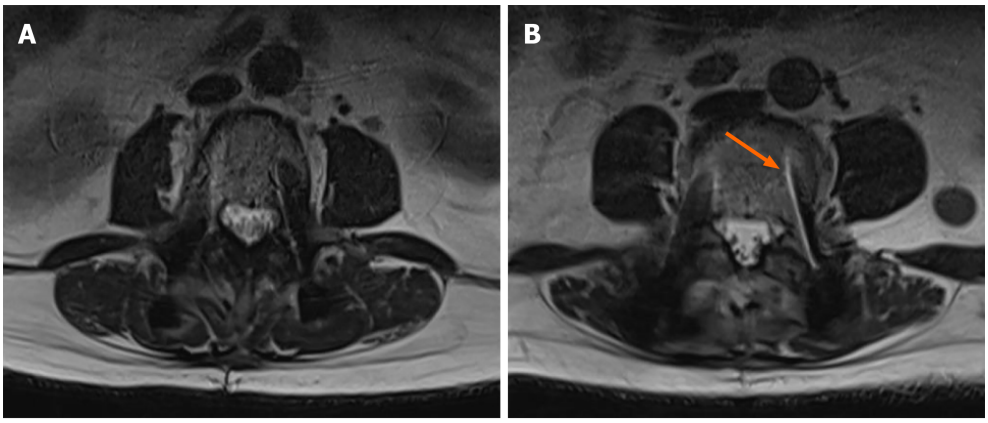
TREATMENT

L2 to S1 posterior decompression and instrumented fusion with O-Arm computer-guided navigation (Medtronic, StealthStation® S7®) were performed. Posterior elements were exposed from L2 to S1, revealing loosened L3 to L5 screws bilaterally, at both the set screw-rod interface and the bone-implant interface. The tissues surrounding the bilateral L3 to L5 polyaxial screw heads and tulips were observed to be stained dark grey (Figure 4). All previous DePuy Synthes screws were removed uneventfully. The loosened screws showed evidence of fretting at the contact surfaces. Newtitanium pedicle screws (Medtronic, CD Horizon® Solera®) were inserted with new trajectories under O-Arm computer-guided navigation. L2 and L3 Laminectomy was carried out. The thecal sac was well decompressed at L2-L3 where there was severe stenosis. A drain was inserted, and the surgical site was closed in layers.



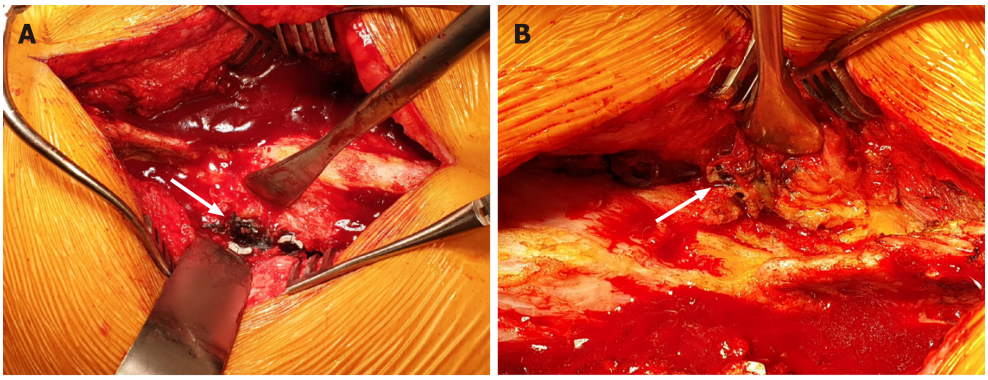
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Figure 2 Lumbar spine magnetic resonance imaging (T2 weighted) 5 years after initial surgery. A: Sagittal view. The arrow indicates herniated disc at L2-L3 level with severe spinal canal stenosis and compression of the cauda equina nerve roots; B: Coronal view demonstrating severe spinal cord compression at L2-L3 level. Arrows indicate protruded disc with bilateral lateral recess and neural foramina stenosis.



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Figure 3 Lumbar spine magnetic resonance imaging (T2 weighted) 5 years after initial surgery. A: Coronal view showing L3 level with no significant peri-screw bony edema; B: Coronal view showing L4 level with the arrow indicating mild left L4 peri-screw bony edema.



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Figure 4 Intraoperative photographs during revision surgery showing metallic grey-stained tissue surrounding bilateral L3 to L5 polyaxial screw heads. The most prominent staining occurred at A: Left L4 screw (indicated by the arrow); B: Right L4 screw (indicated by the arrow).

OUTCOME AND FOLLOW-UP

The patient's postoperative recovery was uneventful. At the 2-mo follow up, her back pain and lower limb weakness had

almost completely resolved. Her postoperative lumbar spine radiographs showed that the new implants were intact (Figure 5).

DISCUSSION

Literature review

Metallosis was first identified as a complication of metal-on-metal total hip arthroplasty[1]. The incidence of metallosis following total hip arthroplasty has been described to be 5.3% and 0.3% after lumbar arthroplasty[3], but the incidence following spinal instrumentation such as posterior spinal fusion is not well estimated currently due to the scarce literature. A literature search detailing other cases of metallosis after spinal instrumentation revealed that it is a rare occurrence. A detailed look of the reported cases of metallosis after spinal instrumentation is summarised in Table 1.

The earliest cases of metallosis following spinal instrumentation were reported by Takahashi *et al*[4]. The authors described two cases of delayed neurological deficits secondary to intraspinal metalloma adjacent to loosened infralaminar hooks. One of the patients had undergone posterior correction and stabilisation and the other had undergone posterior correction and arthrodesis for degenerative scoliosis. Radicular symptoms resolved entirely after revision surgery. The authors speculated that metallosis was caused by abnormal implant movements and chemical reactions from the metal particles. Tezer *et al*[5] then described a case whereby paraparesis secondary to intraspinal metallosis adjacent to the pedicular hook occurred 3 years after posterior spinal instrumentation and fusion for a vertebral compression fracture. The patient's neurological symptoms resolved completely following the excision of the metalloma and removal of the affected instrumentation. The authors concurred with the pathophysiology of metallosis described by Takahashi *et al*[4], and recommended using transpedicular screws sufficiently while carrying out further research to improve the corrosive resistance of spinal instrumentation. Goldenberg *et al*[6] also reported a case of spinal metalloma 18 mo after lumbar laminectomy, posterior spinal instrumentation, and fusion using titanium instead of stainless-steel alloy components. The authors concluded that the metallosis in their case occurred due to the interaction between titanium and the surrounding tissue structures rather than as a result of implant failure, corrosion, or infection as described in previous cases. Li *et al*[7] described another case of metalloma attributed to the wear and loosening of implant. A 2-cm large metalloma could be visualised on MRI. Prior to this study, MRI had not demonstrated much utility in the investigation of metallosis. Subsequently, Ayers *et al*[8] described three more cases of spinal metallosis, two of which had undergone multiple previous spine surgeries complicated by pseudarthrosis and infection and the last had undergone single-level lumbar stabilisation. Neurological symptoms improved in all three cases following revision surgery. The authors hypothesised that biologic mechanisms such as bacterial growth could influence fretting and corrosion of spinal instrumentation leading to metallosis. Richman *et al*[9] then described a young patient with acute onset pain and neurological deficits that progressed quickly. Previous instrument made of stainless steel was removed. They also noted high serum chromium levels. Most recently, Mazur-Hart *et al*[10] reported a case of unilateral metalloma from mixed-metal (titanium and cobalt chrome) instrumentation that resulted in progressive neurological deficit, but not hardware failure. Another unusual finding was the absence of metallosis on the side where the patient had also undergone a hip arthroplasty comprising of the same materials.

Clinical presentation and diagnosis of spinal metallosis

Metallosis is often diagnosed incidentally through intraoperative findings of grey-stained local tissue[8], and definitively through histopathological evidence of macrophages containing metal debris[11]. This is because of the non-specificity of clinical presentations, such as pain, symptoms of infection, and neurological deficits[9]. Based on case studies in the literature (summarised in Table 1), patients with spinal metallosis most commonly presented with lower back or radicular pain. Other symptoms included neurogenic claudication and progressive paraparesis of the lower limbs. It is also challenging to visualise metallosis through standard radiographic evaluation[8]. MRI and computed tomography (CT) are not able to definitively diagnose spinal metallosis due to the presence of artifacts around the metal implants[4,5]. Ayer *et al*'s study showed that all three cases did not have evidence of metallosis on CT prior to surgery[8]. This differs from the usefulness of CT in the diagnosis of metallosis in total hip arthroplasties, in which metallic debris or a high-density material outlining the joint capsule or bursa can be visualised[12]. On the other hand, CT myelography has been the diagnostic imaging modality of choice in a number of studies on spinal metallosis, showing stenotic lesions adjacent to previous instrumentation[4,5,6,9]. In our case, lumbar spine radiographs showed evidence of loosening of pedicle screws. Screw loosening can be secondary to a variety of factors including metal wear debris, microfracture, infection, tumour, and metabolic diseases, with a greater incidence in patients with osteoporosis[13]. Our patient had type 2 diabetes mellitus but was not known to have osteoporosis. She did not have constitutional symptoms and her preoperative routine blood tests were unremarkable. Therefore, osteolysis secondary to fretting of instrumentation was a more probable mechanism for the loosening of screws in this case. MRI was not useful in identifying hardware loosening or spinal metallosis in our case. In a recent clinical trial by Spirig *et al*[14], CT was more sensitive and specific in detecting screw loosening despite applying metal artifact reduction techniques with MRI. However, MRI may be of utility in cases where the metalloma is large enough with compression or extension into surrounding structures, such as in the cases reported by Li *et al*[7] and Mazur-Hart *et al*[10]. Comparing plain radiographs and CT findings of previous studies (Table 1), we suggest adopting a high index of suspicion of metallosis when screw loosening is evident on radiographical imaging in a patient with persistent postoperative back pain or radiculopathy but otherwise medically well. If plain radiographs do not show hardware abnormalities, it may be prudent to proceed with a CT scan or myelogram instead.

Table 1 Summary of the literature

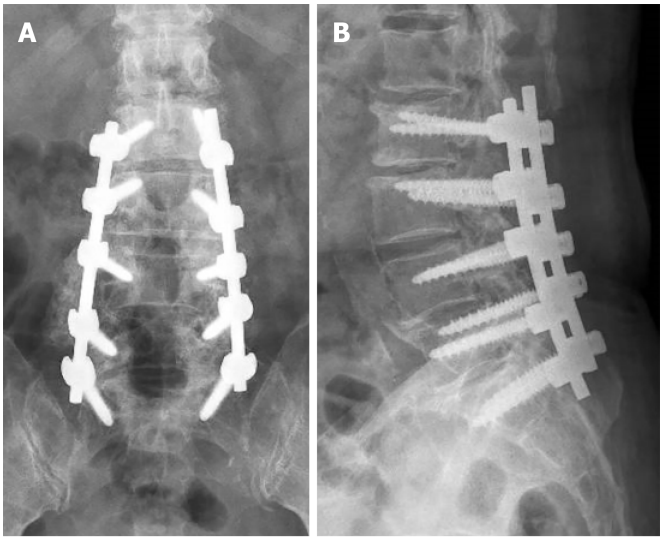
Ref.	Patient biodata	Type of surgery undergone	Instrumentation	Symptoms leading to revision surgery	Radiological findings	Revision surgery	Intraoperative findings	Histopathological findings	Patient outcome
Takahashi *et al*[4], 2001 (case series)	1 Female, aged 58	Posterior correction and stabilisation T10-L3 (no decompression) for degenerative thoracolumbar scoliosis	Stainless steel Cotrel-Dubousset	Left L4-L5 radicular pain several months post-op	Plain radiographs: No implant dislodgement or spinal instability; myelography: Shadow defect adjacent to the tip of the L3 infralaminar hook and dura mater was compressed from the posterior	11 mo post-op; removal of L3 pedicular screws and left L3 infralaminar hook, L3 laminectomy, excision of metallotic mass, instrumentation elongated to L4 with connecting pieces, posterolateral fusion	L3 hook loose from rod, macroscopic metallosis (8 mm mass of dark grey granulation tissue) at hook-rod junction extending to surrounding fibrous tissues, L2-L3 pseudarthrosis	Not described	Immediate resolution of radicular pain, but continued to have slight low back pain during active trunk motion
	2 Female, aged 54	Posterior correction and arthrodesis T12-L4 for symptomatic degenerative lumbar scoliosis	Stainless steel Cotrel-Dubousset	Right L5 sciatic pain 4 yr post-op	Plain radiographs: No implant dislodgement or spinal instability; myelography: Stenotic lesion at lowest level of instrumented lumbar spine but undisplaced implants; myelotomography: No migration of the hooks in the spinal canal, stenotic lesion adjacent to tip of L4 supralaminar hook	5 yr post-op; L4 and L5 laminectomy, excision of metallotic mass, instrumentation elongated down to sacrum	1 cm × 1 cm × 2 cm dark grey granulation tissue under L4 lamina continuous with fibrous membrane of the same colour surrounding right L4 supralaminar hook and compressing right L5 root, loosening implant connection and wear of rod at hook-rod junction, no pseudarthrosis	Granulation tissue consisting of metallic debris – iron staining showed widespread intracellular iron, spectrometry analysis of metal concentrations showed presence of iron, nickel and chromium	Radicular symptoms resolved
Tezer *et al*[5], 2005 (Case report)	Male, aged 57	Posterior spinal instrumentation for T8-9 compression fracture	Stainless steel pedicle screw-hook combination system	Progressive paraparesis 3 yr post-op	Myelography and myelo-CT: Focal image of a mass at T6-7 antero- laterally displacing the dural sac and spinal cord; CT and MRI could not be done due to diffuse metal artefacts	Posterior surgical procedure, complete removal of implants, excision of mass, all metallic debris cleaned	Corroded, black-coloured pedicle hook, no loosening or colour change of other implanted parts, construct stable and strong, fusion complete, granuloma formation in centre of metallic construct, metallic debris had pushed dural sac and spinal cord to anterior and contralateral side resulting in defect of 1.5 cm in diameter in lamina and pedicle	Hematoxylineosin stained sections of paraffin-embedded material showed dense fibrotic tissue heavily stained with black metal debris, foreign body giant cells seen around metallic debris, iron staining by Perls method showed widespread iron within macrophages	Symptom-free 3 mo post-op
Goldenberg *et al*[6], 2016 (Systematic review)	Male, aged 75	Single-level lumbar laminectomy, posterior instrumentation and fusion	Bilateral L4 and L5 titanium alloy pedicle screws, dual interconnecting vertical rods, single interconnecting horizontal rod using the	Persistent and progressive severe lower back pain since the surgery, associated with severe left-sided sciatica	CT myelography: Posterior epidural mass causing canal stenosis, no features suggestive of corrosion or loosening of metalwork; SPECT:	Explorative lumbar canal decompression and nerve root neurolysis, dissected down to area of previous surgery, removal of scar tissue and rostral part of L5	Scar tissue in area of previous surgery, intermixed dark brown and pale pink roughened firm tissue compressing thecal sac,	Dense fibrohistiocytic reaction and cystic change associated with granulomas and calcification, multinucleated giant cells both encasing and adjacent to	Satisfactory clinical improvement in back pain and sciatica

			DENALI K2M system, interbody device containing bone graft admixed with bone morphogenetic protein, high speed burr used but no contact between metalwork and drill		Increased uptake in keeping with discovertebral disease; MRI not done as incompatible cardiac pacemaker	lamina and spinous process, debulking of mass	no implant loosening or corrosion	foreign black pigmented particles, presence of degenerate bone, cartilaginous material and skeletal muscle, no microorganisms identified	
Li *et al*[7], 2016 (Case report)	Male, aged 58	Posterior decompression and instrumented fusion	Titanium implant (surgery was done at another institution)	Recurrent lower back pain radiating to left lower limb, dysesthesia, neurogenic claudication	MRI: Severe adjacent stenosis at L3-4, intraspinal extradural tumor-like mass with compression of the neurological elements	Spinal decompression, excision of mass, and extension of instrumented fusion	Metallic soft tissue and a well-capsulated tumor-like mass	Hematoxylin and eosin staining of mass showed many spindle-shaped; fibroblasts. Many macrophages containing dark metallic wear particulates with phagocytosis	Follow-up not reported
Ayers *et al* [8], 2017 (Case series)	Male, aged 74	Multiple previous spinal surgeries including limited lumbar fusion complicated by pseudarthrosis, revision with extension of fusions and infection at subsequent operations	Mix of alloy rods (CoCrMoC, ASTM F-1537 specification) and titanium alloy (Ti6Al4V ASTM F-136 specification) screws	Continued mechanical back and radicular pain	CT: Hardware failure with bilateral fractured L5 screws and sagittal plane deformity	Staged revision surgery; (1) Initial surgery - removal and cleaning of T10-S1 hardware, evacuation of fluid collection, wound debridement, intra-op cultures, and exploration of the fusion, subfascial drains inserted; (2) then 2 further irrigation and debridement procedures until cultures negative and tissues appeared viable; and (3) after 6 wk, final stage – evacuation of smaller fluid collection, revision posterior instrumentation with L3 pedicle subtraction osteotomy	(1) Initial surgery: Large fluid pocket containing approximately 500 mL of grey-black fluid, black discolouration of posterior soft tissues, all rods showed significant evidence of fretting, galling, pitting and crevice corrosion; and (2) final stage: Smaller fluid collection of 300 mL in posterior soft tissues, gram stain negative	Excised tissue consisted of necrotic fibrous tissue with areas of viable fibrous tissue and particle laden histiocytes. Soft tissue, pseudomembrane from L3-S1 consisted of fibrous tissue with refractile material and calcification. Cell culture of infected tissue/fluid showed presence of propionibacterium acnes and staphylococcus aureus	Significant reduction in pain and symptoms 1 yr post-op
	Male, aged 47	Multiple previous lumbar spine procedures complicated by pseudarthrosis and infection	Titanium alloy (Ti6Al4V) components	Recurrent pulmonary infections and continued back and radicular leg symptoms	CT: Likely pseudarthrosis at multiple lumbar spine levels	2 yr post-op; Staged surgery; (1) Initial surgery – wound exploration, removal of hardware, formal irrigation-and-debridement, deep drains placed; (2) another irrigation-and-debridement with post-op antibiotics × 6 wk; (3) after 6 wk, instrumented fusion from T10-Ilium with revision TLIF at L2-3 and Smith-Petersen Osteotomy; (4) irrigation-and-debridement; and (5) removal of right S1 screw as	(1) Initial surgery: Significant fluid collection, soft tissues stained black, all rods showed significant evidence of fretting, galling, pitting and crevice corrosion	(1) Initial surgery: Excised tissue comprised of necrotic adipose and fibrotic connective tissue; and (2) instrumented fusion stage: Cultures grew Mycobacterium phlei	No back or leg pain at follow up (recent to when paper was written)

						it was causing right nerve root irritation			
	Female, aged 61	Single level lumbar stabilisation procedure including instrumentation with pedicle screws and PEEK rod	Titanium alloy (Ti6Al4V) components	Significant sagittal plane deformity and significant back/radicular leg symptoms	CT: Significant sagittal plane deformity	Instrumentation from T4-pelvis with hardware removal and pedicle subtraction osteotomy, including removal of L2-3 disc to allow greater correction	Significant black staining of the posterior soft tissues, all rods showed significant evidence of fretting, galling, pitting and crevice corrosion	Tissues not submitted to pathology	Complete symptomatic relief at 6 mo post-op
Richman *et al*[9], 2017 (Case report)	Male, aged 19	Posterior spinal fusion	Stainless steel implants	Low back pain, urinary hesitancy, and parasthesias on bilateral anterior thighs, that quickly progressed to flaccid paraparesis, hypoesthesis, and urinary retention	CT: Cavitation around right L1 pedicle screw CT myelogram: Irregular and inadequate opacification of the thecal sac at L1	(1) Initial surgery: Removal of screw; and (2) posterior laminectomy and decompression from T12 to L2 with removal of all instrumentation	(1) Initial surgery: Black and yellowish corrosive film and tissue around right L1 screw; and (2) subsequent surgery: Gritty yellow-black material tracking through the L1 foramen around left L1 pedicle screw, causing thecal saccompression at T12-L2	Pathologic diagnosis was consistent with metallosis	Pain and urinary retention resolved, complete motor and sensory recovery, but presence of bilateral clonus 3 yr post-discharge
Mazur-Hart *et al*[10], 2022 (Case report)	Male, aged 79	2 previous lumbar decompression, posterior instrumentation and fusion 2 yr apart. Right hip arthroplasty 1 yr later	First surgery: Cobalt chrome rods and titanium screws. Second surgery: PEEK spacer and titanium screws and plates	Worsening falls, ataxia and pseudo-claudication	CT and MRI: T1 and T2 hypointense non–enhancing mass around right-sided paraspinal rod extending into spinal canal and surrounding bones and muscle on the same side	L4-S1 biopsy and subtotal resection of paraspinal mass with removal of hardware at L2-S1	Dense fibrotic tissue, black granular material on screws and rods, black staining of adjacent soft tissues and lumbar bone	Extensive necrosis with surrounding inflammation and fibrosis with focal deposition of black pigment of exogenous origin (metallic *vs* carbonaceous), lymphohistiocytic reaction with giant cell formation in rare areas. Gram stain and culture negative	Weaned off walker, reduced dysesthesia but leg weakness still present 3 mo post-op. Leg strength and ambulation continued to improve 7 mo post-op

CT: Computed tomography; MRI: Magnetic resonance imaging; PEEK: Polyetheretherketone.

In regards to the relationship between serum metal concentrations and the development of metallosis, Richman *et al*[9] noted that in asymptomatic patients, serum chromium levels of more than 0.6 ng/mL and more than 3.75 μg/L were indications of implant malfunction and corrosion, respectively. Fernández Bances *et al*[15] found a significant rise (P = 0.00049) in serum titanium concentrations from the levels prior to posterior spinal fusion using titanium instrumentation, similarly to previous studies; however, the correlation of serum titanium concentrations and metallosis was not explored in their study. Cundy *et al*[16] found that serum titanium and niobium levels in children 2 years after instrumented spinal fusion were significantly increased but their clinical significance was not explored. Ayers *et al*[8] reported that muscle concentrations of various metals, namely, aluminium, cobalt, vanadium, and molybdenum, were higher than normal levels in their cases with spinal metallosis due to observed wear and corrosion of the metal instrumentation. However, none of the patients had elevated concentrations of metal in blood. So far, serum metal levels indicating metallosis have yet to be well-defined. We did not check serum metal concentrations in our patient as she did not have symptoms of metal poisoning, there was no baseline data prior to her previous spinal surgery, and investigating metal concentrations



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Figure 5 Lumbar spine antero-posterior and lateral radiographs showing proper positioning of the implants after revision L2-S1 surgery.

this time would be costly and purely academic. However, in patients exhibiting symptoms of metal poisoning, serum metal concentrations will be helpful in confirming a diagnosis of metallosis, potentially leading to timely intervention.

Effect of implant material and factors contributing to metallosis

The mechanism for the development of metallosis following spinal instrumentation is yet to be well-ascertained. It has been postulated that the rigidity that results from instrumentation leads to accelerated degeneration at adjacent spinal levels[7]. The metallic debris from the degeneration of the spinal implants in turn results in a chronic inflammatory process involving a foreign-body granulation-type reaction[1,7]. Spinal metallosis has been described in studies that involved titanium or stainless steel implants[3]. Spinal instrumentation of different metals is commonly used in combination as each metal has a particular mechanical and physical property; for example, cobalt chromium rods have been described to provide stronger correctional forces for scoliotic curves as compared to rods made of other materials [17]. Titanium may be more resistant to crevice corrosion than stainless steel but it has less mechanical resistance and may even stimulate osteolysis[4]. Singh *et al*[18] demonstrated that posterior spinal fusion constructs made of stainless steel were more prone to fretting corrosion as compared to those made with a combination of cobalt chrome with titanium alloy or pure titanium with titanium alloy in a simulated *in vitro* experiment using normal saline. However, the study was unable to account for the actual inflammatory environments present in the human body. Panagiotopoulou *et al*'s study on retrieved spinal implants demonstrated that the risk of corrosion was not increased when two dissimilar metals, namely, cobalt chromium alloy rods and titanium screws, were used in combination[17]. The authors suggested that metallosis may be more dependent on patient factors rather than the corrosiveness of the metals. However, the main limitation of that study was its small sample size, whereby a combination of metals was employed only in two out of seven patients [17].

Vieweg *et al*[19] in an early study on the corrosion of the internal spinal fixator system described that corrosion occurred due to not only the metallurgical composition but the specific construction of the instrument as well. Cundy *et al* [16] described that crevice corrosion was more likely to occur at rod junctions with increased metal-on-metal sites, contributed by micromovements prior to spinal fusion. Takahashi *et al*[4] noted that the lower end of an instrumented fusion was subjected to greater stress hence predisposing the release of metal debris from the hook-rod junction during flexion-extension movement of the lumbar spine. Comparatively, Tezer *et al*[5] felt that metallosis occurred at the middle levels of the spinal construct in their case because of the unequal distribution of chemical properties and degeneration of micromovements in the long term. Interestingly, metallosis occurred at the upper levels of the spinal construct in our patient, where the burden of flexion-extension is not particularly high in day-to-day activities.

Patient factors such as a high BMI as evident in our patient could have accelerated the wear of the titanium screws. As described in the literature review, previous studies have postulated that metallosis results from abnormal micromovements of hardware and a continuous inflammatory reaction[4-6]. Obesity has been associated with the development of spinal disease through both a chronic low-grade inflammatory response as well as biomechanical alterations in the lumbar spine that lead to increased shear forces and torque on the discs and joints[20], hence potentially predisposing to metallosis. However, it is currently difficult to demonstrate an association between patient demographics and spinal metallosis due to the limited number of case reports and case series in the literature so far.

Metallosis is also likely to be a by-product of unstable spinal instrumentation. The increased cyclical loading as a result of implant loosening causes increased fretting at the contact surfaces. This not only produces the characteristic metal debris in metallosis, but ultimately can lead to implant failure. Pseudarthrosis after lumbar spine fusion is a common cause of spinal implant loosening requiring revision surgery[21]. Chronic low-grade spinal surgical site infection is another potential cause for instrumentation loosening, hence stressing the importance of sterile instrumentation[22,23].

Several procedure-related risk factors for implant loosening have also been described. First, inadequate correction of sagittal imbalance has been associated with a negative prognosis for implant anchorage in bone[24], increasing the risks of screw loosening in posterior spine fusion[25]. Inadequate set screw tightening or cross-threading of screw tulips due to improper insertion of set screws into the screw tulip can also predispose to coupling failure, which can occur at any level of a spinal construct[26]. Hence, spinal surgery should be performed only by well-trained spinal surgeons with vast experience and undertaking these operations regularly to minimise these mechanical risk factors. Other possible risk factors for instrumentation loosening are osteoporosis and cobalt chromium rods[23]. Our patient was not known to have osteoporosis, but it may be prudent to commence osteoporosis treatment prior to surgery in patients who have been diagnosed with osteoporosis so as to improve bone density and potentially increase the strength of screw fixation. Utilising a material that is less rigid than cobalt chromium rods may reduce the risk of implant loosening; however, current options are limited, and cases of metallosis including our patient have mainly involved titanium or stainless steel instrumentation. Our patient's symptoms of progressive lower back and radicular pain were due to severe spinal stenosis and compression of the cauda equina nerve roots. Although implant loosening may present similarly even in the absence of metallosis, there was both intraoperative (corrosion of screws and grey-stained surrounding tissues) as well as histopathological (metallic debris in macrophages) evidence of metallosis at the same spinal levels. Ultimately, it is important to recognise symptoms of spinal implant instability and initiate treatment for patients timely.

CONCLUSION

Identifying metallosis prior to surgical exploration is challenging. Clinical presentation tends to be non-specific, most commonly being lower back or radicular pain. CT appears to be the modality of choice to observe for aseptic hardware loosening and pseudarthrosis, while myelography and MRI are able to suggest the presence of a metalloma. A definitive diagnosis of metallosis can only be made from histopathological results, where metallic debris is seen in macrophages.

To date, the relationship between serum metal levels and the presence of metallosis has yet to be established. Currently, implants of various metallic compositions are used, but the individual metallic properties confer theoretical benefits and disadvantages and no particular material has been identified to be least likely to cause metallosis thus far. Furthermore, patient factors may contribute to metallosis but further studies are required to establish an association.

Finally, we would like to highlight that the presence of metallosis after spinal instrumentation likely indicates a more complex underlying problem. Metallosis can occur due to instability of the spinal implants, which may be secondary to pseudarthrosis, failure to address sagittal balance, infection, and cross-threading of set screws. Spinal implant instability manifests commonly as pain and weakness, which were present in most cases involving instrumentation loosening described within this report to varying degrees. However, regardless of the cause for metallosis, the only definitive treatment to date for symptomatic implant loosening is the removal and replacement of the implants. The rate at which metallosis progress and the onset of symptoms is not known. However, it undoubtedly can lead to significant pain and mobility issues. Hence, it is prudent to identify the underlying cause of implant loosening early and commence treatment promptly.

FOOTNOTES

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MINIREVIEWS

Silver nanoparticle technology in orthopaedic infections

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Abstract

The irrational and prolonged use of antibiotics in orthopaedic infections poses a major threat to the development of antimicrobial resistance. To combat antimicrobial resistance, researchers have implemented various novel and innovative modalities to curb infections. Nanotechnology involves doping ions/metals onto the scaffolds to reach the target site to eradicate the infective foci. In this connotation, we reviewed silver nanoparticle technology in terms of mechanism of action, clinical applications, toxicity, and regulatory guidelines to treat orthopaedic infections.

Key Words: Antimicrobial resistance; Biofilms; Silver; Nanoparticles; Orthopaedics

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Core Tip: To overcome antimicrobial resistance, researchers explored the alternate technology to curb infections in musculoskeletal disorders. Nanotechnology forms an eye opener in the usage of silver nanoparticles to eradicate infections in osteoarticular system.

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INTRODUCTION

Globally, Orthopaedic infections pose a great challenge among orthopaedic surgeons and orthopaedic researchers. In the literature, the incidence of infection after orthopaedic surgeries was 1% to 2% in closed fractures and approximately 30% in open fractures[1]. Universally, there is no accepted classification for infection after orthopaedic surgeries. To overcome these infections, antibiotics were used irrationally which led to antimicrobial resistance (AMR) due to the development of biofilm by the micro-organisms[2,3]. Jefferson reported that biofilm formation is due to (1) protection from host defense; (2) colonization; (3) local environment benefits; and (4) planktonic cultures as *in vitro* artifacts[4]. Aparna *et al*[5] gave 5 stages of the growth cycle of a biofilm namely stage 1 – attachment phase, stage 2 – irreversible binding phase, stage 3 – maturation 1 phase, stage 4 – maturation 2 phase, and stage 5 – cellular dispersion phase.

In humans, 80% of microbial infections are due to non-healing chronic wounds, osteomyelitis, prosthesis- and implant-related infections, endocarditis, rhinosinusitis, and cystic fibrosis[6-9]. Literature states that both gram-positive and gram-negative bacteria form biofilms on the surface of medical devices which are *E. faecalis, S. aureus, S. epidermidis, S. viridans, E. coli, K. pneumoniae, P. mirabilis*, and *P. aeruginosa*[10]. Out of all these organisms, *S. aureus* and coagulase-negative staphylococci pose a greater risk of forming biofilms in orthopaedic implants[11,12], whereas *P. aeruginosa* sustain and survive in harsh environments and forms a resistant biofilm[13].

With the rise of AMR, antibiotic prophylaxis has become ineffective in curbing infections. Novel techniques such as nanomedicine, bacteriophage therapy, antimicrobial peptides, sonic therapies, scaffold-loaded nanoparticles, antimicrobial adjuvants in the form of silver, electrical and electromagnetic methods, bioacoustic effects, surface modification of biomaterials, antimicrobial photodynamic therapies, biosensors, hyperbaric oxygen, and fecal microbiota transplantation have been introduced to combat AMR[10,14,15]. With the profound literature evidence of the antimicrobial property of silver (Ag), nanotechnology experts doped nanoparticles (NP) with Ag for targeted drug delivery and enhanced interaction with the surrounding environment to curb biofilm-producing organisms[16]. In this article, the usage of AgNP in curbing orthopaedic infections is narrated.

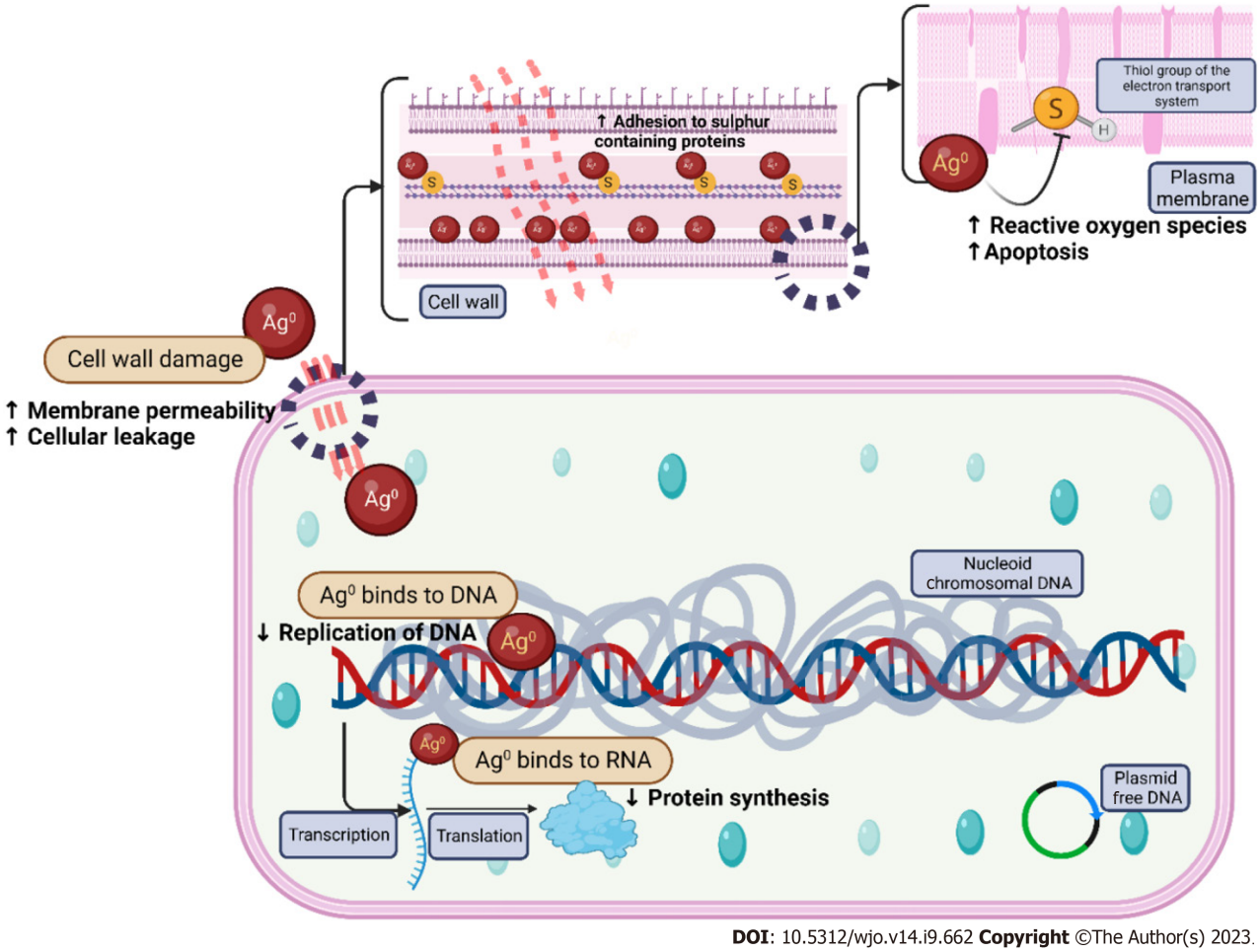
AGNP TECHNOLOGY

In literature, Ag has been identified to have antimicrobial properties[17-19], but in recent years clinicians have demonstrated this property in various clinical conditions. The oligodynamic action of Ag refers to the toxic nature of metal ions on microbes by integrating with microbial deoxyribonucleic acid (DNA)[20-22]. Few studies have emphasized the precipitation of DNA within the microbial cell[23]. Ag exerts antibacterial action by inhibiting cell wall synthesis[24,25].

Recent technologies use NP to load Ag ions which may be used as an antimicrobial agent in a target-specific manner [23]. AgNP permeates into cells and interferes with the enzymes of bacterial respiratory chains to inhibit ATP production and growth of the bacteria[16,26]. The particle size of AgNP determines the bactericidal activity. 10-nm Ag demonstrates the complete bacterial interaction, henceforth AgNP exerts a higher bactericidal effect[27]. The mechanism of action of AgNP in infections is as follows (as depicted in Figure 1).

Direct contact with microbes through leakage of cellular contents and bacterial death due to the damage of cell membrane and higher production of reactive oxygen species and free radical species, release of Ag+ ions through interaction with sulfhydryl groups (cysteine) in cell wall proteins and enzymes, induction of bacterial death when Ag^+ ions in AgNPs by bombarding the electron transport chain in bacterial mitochondria. Entering of Ag+ ions into periplasmic space which leads to the separation of the cytosol from the cell membrane, occurrence of cellular pits after the exposure of Ag+ ions, inhibition of ribosomal functions leading to enhanced ROS production, malformation of proteins resulting in improper DNA function, antibiofilm activity of AgNPs, and dose-dependent cytotoxic and genotoxic effects of AgNP on osteoblasts and impaired cellular viability of AgNPs at 10 μg/g.

To impart biocompatibility of AgNP in musculoskeletal tissues: (1) Biosynthesis process from bacteria, yeast, and fungi; (2) physical property adjustment; and (3) biomolecule combinations can be tried.



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Figure 1 Mechanism of action of silver nanoparticles. DNA: Deoxyribonucleic acid.

AGNP IN ORTHOPAEDIC INFECTIONS

Recently, the modification of orthopaedic implants with the application of AgNPs on the surface leads to the prevention of implant-associated infections. With the availability of AgNP-coated external fixators, mega prostheses, and AgNP-coated bone cement, orthopaedic infections are showing a downtrend. Since AgNP-coated orthopaedic implants demonstrate antimicrobial activity, the specific molecular mechanism of osteogenic-related cells warrants an understanding. Due to dose-dependent cytotoxicity, the effect of AgNP on osteoblast and osteoclast is controversial. Aurore *et al*[28] demonstrated the bactericidal effect of AgNP against non-virulent E.coli and virulent MRSA at non-toxic concentrations. Macrophage polarization towards the M1 phenotype enables the cells to kill the engulfed microorganisms. Elevated reactive oxygen species (ROS) responses were found in AgNP-treated osteoclasts. The modification of orthopaedic implants by using AgNPs enhances antimicrobial effects through plasma immersion ion implantation (PIII), magnetron sputtering, plasma electrolytic oxidation, and 3DP-Ag-containing scaffolds[16].

Tumor prosthesis: In orthopaedic oncology, peri-prosthetic infection rates from 9% to 29%. Due to the immunosuppressive environment, this group of patients is more prone to infection than arthroplasty patients. Gosheger *et al*[29] demonstrated a superior antimicrobial effect with a silver-coated mega prosthesis (7% infection rate) than titanium prosthesis (47% infection rate) in a rabbit model. Ag coated group showed fewer signs of inflammation as measured by ESR, CRP, and neutrophil count. In sarcoma patients, Hardes *et al*[30] observed 17.6% of infection in the non-silver coated mega prosthesis group than 5.6% of infection in silver coated mega prosthesis group. About 38.5% of cases of amputation in the non-silver-coated mega prosthesis group were due to deep infections whereas no case of amputation was reported in the silver-coated mega prosthesis group. Hence, silver-coated mega prosthesis reduces the risk of further infection in oncology cases as they are already in an immunocompromised state. However, large-scale blinded controlled trials have to prove the safety and efficacy of infection prevention with the silver-coated prosthesis in orthopaedic oncological cases.

External fixator pins: Pin tract infections mount for 42% of orthopaedic infections which results in loosening of the implant, fracture non-union, and osteomyelitis. An in-vitro study demonstrated a 3-log step reduction of *S. epidermidis* biofilm producers when incubating the stainless steel pins coated with AgNP compared with titanium and copper pins for 20 h (9). Wassall *et al*[31] revealed the antimicrobial effects of Ag in Ag-coated pins with the significant reduction of adhesion of *E. coli, P. aeruginosa*, and *S. aureus* when compared with normal stainless steel pins. Loosening of external fixator pins was less frequently found with Ag-coated pins. Hence silver inhibits microbial adhesion by inhibiting the formation of the glycocalyx on the surface of the pins.

Osteomyelitis and infected non-union: Ag ionophoresis act as an adjunct treatment option for osteomyelitis and infection in non-union of fractures. The continuous inflow of electrically driven Ag into the infective foci curbs the infection and promotes the environment for tissue regeneration. At the end of 3 mo follow-up, radiographic and histological analysis revealed neo-osteogenesis in a 6 mm critical bone defect in the femoral diaphysis of rats managed with bone graft with BMP-2 coupled with AgNP and poly lactic-co-glycolic acid (PLGA) scaffold injected with 10 CFUs of vancomycin-resistant MRSA[32]. Microbial elimination with 2% Ag NP coupled with composite bioscaffold resulted in fracture union.

Bone cement: Alt *et al*[33] proved that nanosilver-coated cement produced a high index of antimicrobial activity against *S. epidermidis*, MRSE, and MRSA. Tiopronin, a stabilizing agent, coupled with AgNP in bone cement expressed a good antimicrobial efficacy without displaying any cement-related cytotoxicity[34]. AgNP coated bone cement resulted in antibacterial activity against MRSA and decrease the formation of polymer debris in joint replacement[35].

TOXICITY OF AGNP

Though nanotechnology poses a greater advantage in clinical applications, a considerable note of precautions and toxic effects are observed with AgNP. The interaction of AgNP with biological media leads to Ag agglomeration and dissolution. Doping of Ag into NP results in the induction of toxic responses. The failure of protective coatings on NPs to prevent aggregation in biological fluids leads to AgNP instability. In vitro and *in vivo* AgNP studies demonstrated the induction of lung fibroblasts, genotoxicity, chromosomal aberrations, DNA damage, and apoptosis of cells. There is only limited evidence for carcinogenicity in any biological tissues.

The interaction of human alveolar basal epithelial cells with AgNP results in the generation of reactive oxygen species, reduction of mitochondrial membrane potential and cellular viability, and enhance cellular apoptosis. Exposure to higher concentrations of AgNP in human cell lines induces not only cellular apoptosis but also induces cellular morphology and genetic mutations. The toxicity of AgNP has been demonstrated in microbes ranging from bacteria, viruses, fungi, and algae. AgNP molecules penetrate the skin and blood tube of zebrafish larvae in aggregate form whereas it induces heat shock, oxidate stress, and DNA damage in *Drosophila melanogaster*.

AgNP technology is associated with developmental abnormalities in zebrafish embryos, cytotoxic, and genotoxic effects with systemic immunosuppression. AgNP-mediated cytotoxicity with 10 μg/g is observed on primary human MSCs and osteoblast cells[36]. In zebrafish, AgNP induced neurotoxicity and persistent abnormal behavior[36]. Cytotoxicity of AgNP depends on the particle size of Ag. Literature has documented the cytotoxic effects of Ag of 24 nm causing an intrinsic pro-inflammatory response and apoptosis of surrounding cells[36].

Drake *et al*[37] and Lansdown[38] have done an extensive review of the exposure-related health effects of silver and its related compounds in health. The evidence of toxic effects and complications of AgNP in human studies is limited. Silver represents occupational health hazards like argyria in long-term exposure[37]. The critical oral dosage of silver varies for every individual. The accumulation of silver and nanosilver particles occur in the liver, spleen, kidney, nails, and mucous membranes[39]. With the topical application of Ag, the risk of percutaneous absorption is very low as the epidermis is a relatively impenetrable barrier[40]. Munger *et al*[41] performed a cross-over time exposure study with oral AgNP (5-10 mm) and demonstrated no change in metabolic, hematologic, physical, or morphological findings. However, the toxicity of AgNP in humans is understudied.

Due to the increase of AgNP usage in the market, governmental regulations in the United States [Environment Protection Agency on the nanomaterials regulation], European Union [European Strategy for Nanotechnology], and Canada [Health Canada and Environment Canada] have been implemented[42]. These agencies mentioned that the size of AgNP must be ranging from 1–100 nm in at least one spatial dimension[42]. No specific occupational exposure limits have been laid by these governmental agencies on AgNPs. Global organizations focus on the safety and sustainability of AgNPs in the market for optimal benefits in the community.

RECENT ADVANCES IN AGNP TECHNOLOGY

With the introduction of new fabricating methods, the toxic effects of AgNP are minimized in the microenvironment[43]. Doping of copolymers and growth factors with AgNPs is more effective in hastening wound healing. Green-synthesized AgNPs are cheaper and eco-friendly for the desired environment. The phytochemicals to be doped with AgNPs have to be characterized and seek appropriate regulatory approvals before commercializing the product for preclinical and clinical studies[44,45]. The addition of electrospun nanofibers along with AgNP offers a great advantage in curbing the infection along with debridement and antibiotics. Once the wound is healed, such electrospun nanofibers provide a naïve extracellular matrix in the newly regenerated tissues[46].

With the evolution of 3-D printing technology, the fabrication of scaffolds with Ag coating prevents infections in complex orthopaedic cases[47,48]. 3D scaffolds with porous structures are ideal for loading biomolecules and ions for targeting the desired site. Doping of AgNP into scaffolds with antimicrobial activity and biocompatibility properties in musculoskeletal tissues aids in curbing infection and promoting tissue regeneration as depicted in Figure 2.

3D bioprinting technology dispenses “bio-inks” which contain cells with regenerative potential, scaffolds doped with metal/ion nanoparticles, and biomicromolecules in a temporospatial controlled fashion[49,50]. Such bio-inks with antimicrobial properties aim at uprooting the infection and facilitating the regeneration of tissues. Damle *et al*[51] proved the proliferation and differentiation of mesenchymal stromal cells when doped with AgNPs which gave further insights in

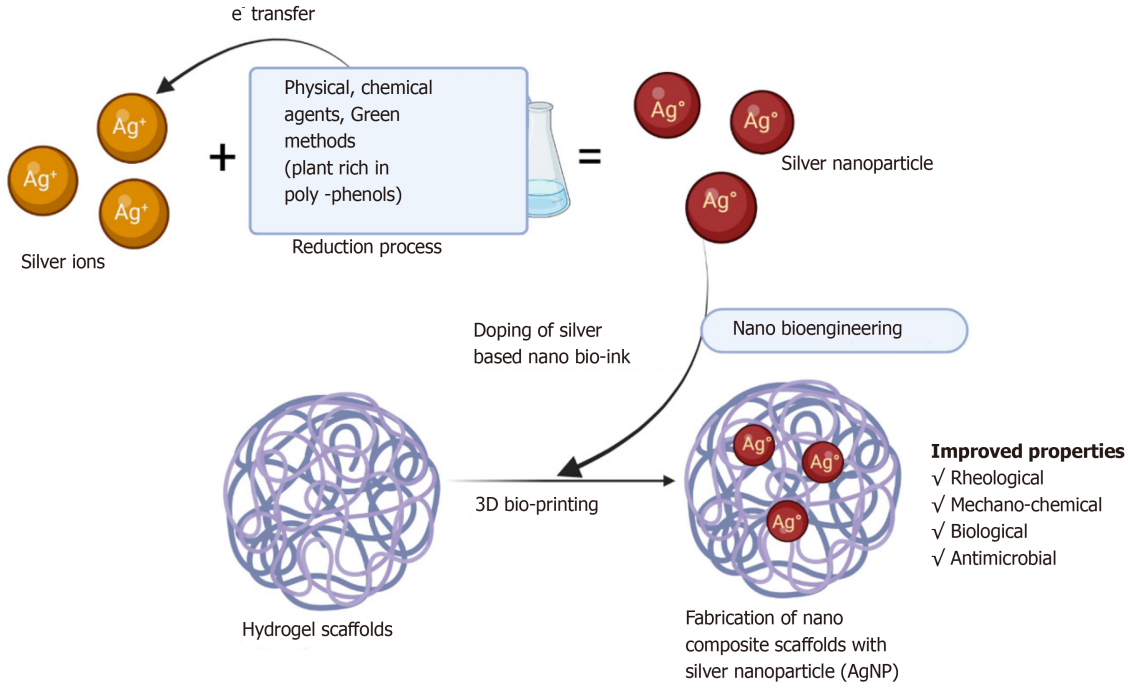


Figure 2 Doping of silver nanoparticles in scaffolds.

osseous tissue engineering. The concept of "Smart Coating" depends on light responsiveness, temperature responsiveness, pH responsiveness, and piezo responsiveness for improving osseous integration, inhibting biofilm formation, and preventing post-operative complications associated with orthopaedic infections[52].

CONCLUSION

In orthopaedics, AgNP technology has the potential to reduce implant-related orthopaedic infections. Doping AgNP with scaffolds and bio-inks must adhere to the regulatory guidelines to avoid toxicity in clinical applications. With the evidence of preclinical studies, large-scale blinded controlled trials on AgNP in orthopaedic infections have to be assessed for further validation.

FOOTNOTES

Author contributions: Jeyaraman M conceptualized the study; Jeyaraman M, Jeyaraman N, Nallakumarasamy A, Iyengar KP and Jain VK contributed to writing, reviewing, and editing the manuscript; Jeyaraman M, Iyengar KP, Potty AG, and Gupta A supervised the study; All authors contributed to the article and approved the submitted version.

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Formation process of extension knee joint contracture following external immobilization in rats

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Abstract

BACKGROUND

Current research lacks a model of knee extension contracture in rats.

AIM

To elucidate the formation process of knee extension contracture.

METHODS

We developed a rat model using an aluminum external fixator. Sixty male Sprague-Dawley rats with mature bones were divided into the control group (n = 6) and groups that had the left knee immobilized with an aluminum external fixator for 1, 2, and 3 d, and 1, 2, 3, 4, 6, and 8 wk (n = 6 in each group). The passive extension range of motion, histology, and expression of fibrosis-related proteins were compared between the control group and the immobilization groups.

RESULTS

Myogenic contracture progressed very quickly during the initial 2 wk of immobilization. After 2 wk, the contracture gradually changed from myogenic to arthrogenic. The arthrogenic contracture progressed slowly during the 1st week, rapidly progressed until the 3rd week, and then showed a steady progression until the 4rd week. Histological analyses confirmed that the anterior joint capsule of the extended fixed knee became increasingly thicker over time. Correspondingly, the level of transforming growth factor beta 1 (TGF-β1) and phosphorylated mothers against decapentaplegic homolog 2 (p-Smad2) in the anterior joint capsule also increased with the immobilization time. Over time, the cross-sectional area of muscle fibers gradually decreased, while the amount of intermuscular collagen

and TGF-β1, p-Smad2, and p-Smad3 was increased. Unexpectedly, the amount of intermuscular collagen and TGF-β1, p-Smad2, and p-Smad3 was decreased during the late stage of immobilization (6-8 wk). The myogenic contracture was stabilized after 2 wk of immobilization, whereas the arthrogenic contracture was stabilized after 3 wk of immobilization and completely stable in 4 wk.

CONCLUSION
This rat model may be a useful tool to study the etiology of joint contracture and establish therapeutic approaches.

Key Words: Knee joint; Immobilization; Contracture; External fixator; Rats

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Core Tip: Current research lacks a model of knee extension contracture in rats. The study elucidated the formation process and therapeutic strategies of knee extension contracture. To this end, we developed a rat model using an aluminum external fixator. The results showed that the myogenic contracture was stabilized after 2 wk of immobilization, whereas the arthrogenic contracture was stabilized after 4 wk of immobilization. This rat model may be a useful tool to study the etiology of the joint contracture and establish therapeutic approaches.

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INTRODUCTION

Knee contracture is currently one of the most common clinical diseases and is characterized by joint capsule fibrosis and a restricted range of motion (ROM) secondary to periarticular intermuscular connective tissue hyperplasia[1]. The signature pathology of joint contracture is the proliferation of myofibroblasts (active fibroblasts) and the deposition of proteins in the extracellular matrix in the joint capsule and intermuscular connective tissue[2]. The most common cause of knee contracture is prolonged immobilization, which is clinically used as an acute treatment for musculoskeletal disease to relieve knee pain and reduce inflammation[3,4]. Knee contracture is unsightly and has adverse effects on function and quality of life, affecting daily activities such as ascending and descending stairs, walking, and toileting. Furthermore, knee contracture is very difficult to treat[5]. Despite a large amount of rehabilitation, conservative treatment, and even surgical treatment, it is difficult to completely restore the joint mobility, and this loss of mobility seriously decreases the quality of life of patients and adversely affects the distribution of medical resources in society[6,7]. It is therefore very important to investigate the mechanisms leading to knee contracture.

The contracture mechanism has been explored in many studies. As early as 1993, a rat flexion contracture model was successfully established by fixing the tibia and fibula in complete flexion (150) for up to 7 wk without damaging the joints [8]. In recent years, various immobilization methods have been introduced to create flexion contracture models by fixing the animal knee joint at about 150 of flexion, including hook buckle (a hook-and-loop fastener) immobilization and helix (spiral wire) immobilization[9,10]. By contrast, extension contracture models are rare. However, the extension contracture model is of clinical relevance because it better mimics fracture and bed-associated immobilization than the flexion contracture model.

According to the general international standard, the neutral position of the knee joint is the straightened or extended position, which is defined as 0. The functional position of the knee joint is from 15 to 20 of flexion, while the ROM of the normal knee is 120 to 150 for flexion and 5 to 10 for overextension. Knee injury usually requires immobilization in a straightened or functional position, but this type of immobilization may result in limited knee flexion motion (knee extension contracture); therefore, knee extension contracture is the most common type of knee contracture. Different fixation methods have different effects on muscles. If the muscle is fixed under the condition of being lengthened, its atrophy and the decrease of muscle contraction force will be less, and the ratio of fast and slow muscles of biceps femoris, which is often selected as the detection index of flexion knee contracture model, is also different from that of quadriceps femoris; however, the current literature describes several animal knee contracture models, most of which involve flexion knee contracture. The structure of the knee joint of rats is similar to that of humans and is easier to obtain compared to other animals. Thus, it is necessary to establish a convenient and reliable rat model of knee extension contracture.

In the present study, we studied the process of knee extension contracture formation during external fixation of the knee in a straightened position in a rat model that we developed. To the best of our knowledge, this is the first report of a rat model of knee extension contracture.

MATERIALS AND METHODS

A rat model of knee extension contracture

Male Sprague-Dawley (SD) rats (age 8 wk and weight 350 g +) were used in this experiment. Aluminum splints (6061; Longkai, Suzhou, China), sponge (33 d; Changzhou, China), and woodworking (BND-2815; Bonida, Guangdong, China) were prepared. The rats were kept under the same conditions without intervention for 2 wk before the experiment (free diet, day and night balance, temperature 20-25 ℃, humidity 50% ± 5%). Each rat was placed on the operating table in the supine position and fixed. The fixing device and fixing schematic diagram is shown in Figure 1. Figure 2A shows the results of applied fixation. Figure 2B shows the anterior X-ray of the rat knee joint, while Figure 2C shows the lateral X-ray of the rat knee joint. Immobilization was performed under general anesthesia achieved with an intraperitoneal injection of 10% chloral hydrate (0.03 mL/kg). A patent application has been made for the self-made aluminum splint (Patent No. ZL202120470158.0).

Measurements of the knee joints of 8-wk-old male rats (n = 15) revealed that the average thigh width was 3.23 cm ± 0.21 cm (range 6.38 ± 0.41 to 7.21 cm ± 0.43 cm) and the average calf width was 4.86 cm ± 0.27 cm (range 2.34 ± 0.13 to 5.11 cm ± 0.36 cm). In accordance with the anatomical characteristics of the rats, the immobilization device was shaped using a wire cutting process with an aluminum plate and bonded with a 0.5-cm-thick sponge on the skin to prevent excessive immobilization. The shape of the aluminum plate is shown in Figure 1. The fixation device placed the knee joint in the straightened position and ensured complete external immobilization of the knee joint. The animal experiments described in this study were authorized by the Experimental Animal Ethics Committee of Anhui Medical University (No. LLSC20221126).

Grouping and specimen collection

Sixty rats were randomly divided into 10 groups (n = 6 in each group). The control group did not do any intervention. while the immobilization groups had the left hindlimb fixed for 1 d (immobilization-1 d group), 2 d (immobilization-2 d group), 3 d (immobilization-3 d group), 1 wk (immobilization-1 wk group), 2 wk (immobilization-2 wk group), 3 wk (immobilization-3 wk group), 4 wk (immobilization-4 wk group), 6 wk (immobilization-6 wk group), and 8 wk (immobilization-8 wk group). All groups were reared in the same environment, and the ROM of the knee joint was measured on the same day as the 8-wk-fixed group after controlling the fixed time. The rats in the appropriate group were euthanized by an excessive intraperitoneal injection of 10% chloral hydrate. After euthanasia, the fixed left hindlimb of the rat was removed at the hip joint. The skin was separated, and the knee mobility was measured using the measurement device designed for this experiment (Figure 3). Then the muscles were separated. The rectus femoris was divided into two parts: one part was frozen at -80 ℃ for protein molecular weight detection, while the other part was fixed in 4% paraformaldehyde for Sirius red staining. Knee mobility was measured after the separation of the muscles. The anterior joint capsule was divided into two parts: one part was frozen at -80 ℃ for protein molecular weight detection, while the other part was fixed in 4% paraformaldehyde for hematoxylin and eosin (H&E) staining. During the experiment, the rats were free to move within the cage with the immobilization device attached.

Measurement of joint mobility

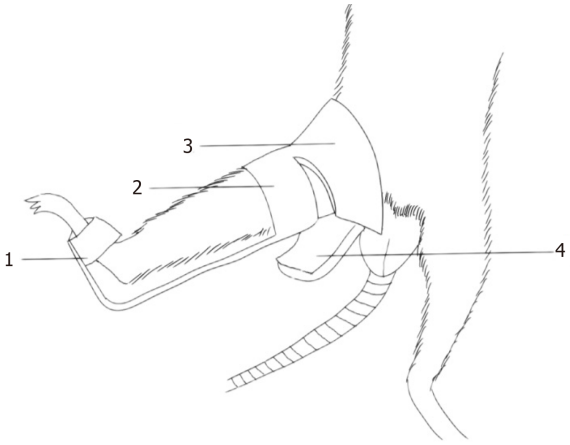
A joint mobility meter was used to measure the joint motion of the left knee of 60 SD rats (Figure 3). The Kirschner wire was penetrated from the femoral neck parallel to the femur. Fixed the cruzi needle by magnetic suction removable metal clamp. The distal tibia was secured to the turntable with disposable plastic ties. The digital force gauge was secured to the slide. On the base of the equipment was a rope attached to the groove of the turntable and a digital dynamometer. The turntable moved when the drive wheel was turned to indirectly turn the tibia while the femur was stationary. The applied force was displayed on the screen of the digital force meter, and the angular change between the femur and tibia (the disk radius, the force arm) was constant and was calculated according to the scale of the turntable. Therefore, the force moment and the force size showed a linear relationship. The moment size and the angle also had a corresponding relationship. The applied torque was calculated by multiplying the force by the constant radius of the disk. Knee ROM was measured with 5.3 N-cm as the standard torque. This torque brings the knee close to its physiological limit but does not damage the soft tissue[11-13]. The mobility of each left knee was measured three times by two researchers, giving six measurements. The knee ROM before and after myotomy was measured to yield the total, myogenic, and arthrogenic contracture using a previously described method[14]. (1) Degree of total contracture = ROM before myotomy (knee joint in the control group)-ROM before myotomy (knee joint in the immobilization group); (2) degree of arthrogenic contracture = ROM after myotomy (knee joint in the control group)-ROM after myotomy (knee joint in the immobilization group); and (3) degree of myogenic contracture = degree of total contracture-degree of arthrogenic contracture. A patent application has been made for the self-made joint mobility meter (Patent No. ZL202120996643.1).

Histological evaluation

Specimens used for joint mobility assessment were used to evaluate the histology of the knee joint. After the ROM measurements, the left rectus femoris and anterior knee joint capsule were fixed in 4% paraformaldehyde (pH 7.4) at 4 ℃ for approximately 36 h. The specimens were embedded in paraffin. The rectus femoris specimens were cut into 5-μm coronal sections, while the joint capsule specimens were sectioned into 5-μm sagittal sections.

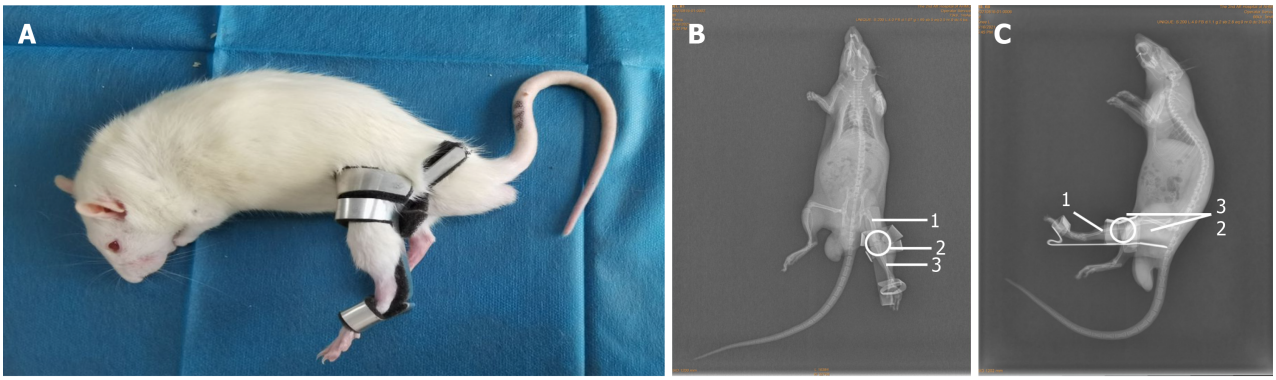
Sirius red staining

Rectus femoris sections were stained with Sirius red solution for 1 h (2610-10-8; Solarbio Life Science, Beijing, China) and rinsed with running water to remove the surface dye. Nuclei were stained with Mayer's hematoxylin solution for 8 to 10



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Figure 1 Knee joint fixation device. Immobilize the back of the rat's distal foot to prevent the rat's lower limb from slipping out of the immobilization device. Immobilize the periphery of the rat knee joint. Above the knee joint of the rat is an inverted conical structure, and this design fixes the periphery of the femur of the rat. Appropriate bending under the rat femur provides a lever fulcrum action. (1) Immobilize the back of the rat's distal foot to prevent the rat's lower limb from slipping out of the immobilization device. (2) Immobilize the periphery of the rat knee joint. (3) Above the knee joint of the rat is an inverted conical structure, and this design fixes the periphery of the femur of the rat. (4) Appropriate bending under the rat femur provides a lever fulcrum action.



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Figure 2 Fixed schematic diagram. A: Fixed picture; B: X-ray orthotopic slice of rat knee joint after immobilization; C: X-line lateral tablet of rat knee joint after immobilization. [1]Femur; [2]Knee; [3]Tibia.

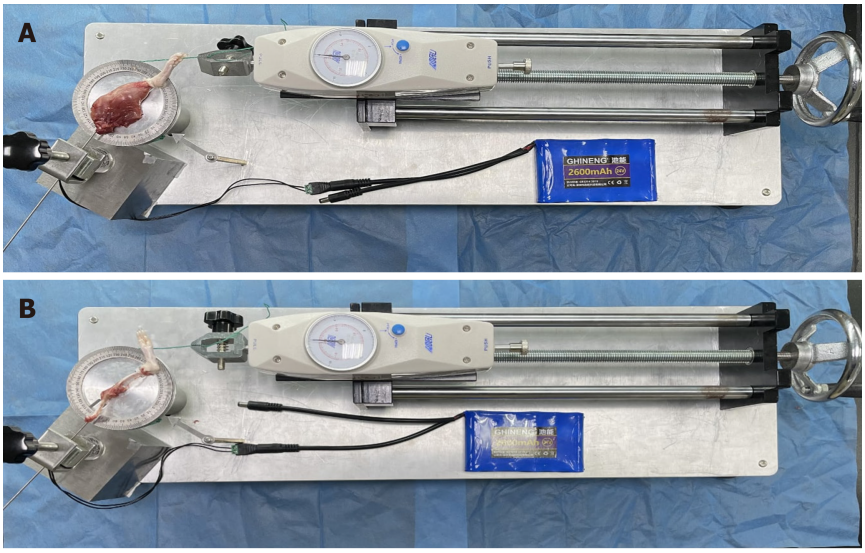
min and flushed with running water for 10 min. Sections were then conventionally dehydrated and sealed with neutral gum. The muscle collagen fiber density and muscle fiber cross-sectional area for each region were assessed using ImageJ software version 1.53a (National Institutes of Health, Bethesda, MD, United States, available at https://imagej.nih.gov/ij/). Histological analysis was performed on six rats in each group, with three slides for each rat.

H&E staining

The joint capsule sections were stained with H&E using the following steps. (1) Paraffin sections were dewaxed and then placed in xylene I for 10 min, xylene for 10 min, anhydrous ethanol I for 5 min, anhydrous ethanol for 5 min, 95% alcohol for 5 min, 90% alcohol for 5 min, 80% alcohol for 5 min, 70% alcohol for 5 min, and finally washed with distilled water; (2) Sections were stained with harris hematoxylin for 3-8 min, rinsed with tap water and differentiated with 1% ethanol hydrochloride for several seconds, and then rinsed with tap water again. The sections were returned to blue with 0.6% ammonia and rinsed with running water; (3) Sections were stained in eosin solution for 1-3 min; (4) To attain the dehydration seal, the sections were placed in 95% alcohol I for 5 min, 95% alcohol II for 5 min, anhydrous ethanol I for 5 min, anhydrous ethanol II for 5 min, xylene I for 5 min, and xylene II for 5 min; the sections were then removed from the xylene to dry and were sealed with neutral gum; and (5) Microscopic examination, image acquisition, and histological analysis were performed on six rats in each group, with three slides for each rat.

Immunohistochemistry

The following steps were used to prepare the articular capsule sections by immunohistochemistry. (1) Paraffin sections were dewaxed in the same way as H&E staining; (2) The 3% hydrogen peroxide was dropped onto the slice tissue, incubated at room temperature for 15 min, and washed with phosphate-buffered saline (PBS) for 3 times, 3 min each time; (3) After wiping the slide dry, the diluted normal goat serum was added and the slide was sealed at room temperature for



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Figure 3 Joint mobility meter. A: Peeling range of motion (total contracture) measurement; B: Measuring range of motion after muscle separation (arthrogenic contracture).

30 min; (4) The first antibody was added and incubated in a wet box at 4 ℃ overnight (15 h); (5) After PBS washing, the sections were dried with absorbent paper, and streptavidin-horseradish peroxidase conjugate labeled goat anti rabbit/mouse secondary antibody was added and incubated at 37 ℃ for 30 min; (6) After PBS washing, the PBS solution was removed and 3,3'-diaminobenzidine color developing solution was freshly prepared and added to each slice; (7) Mayer's hematoxylin re-staining was performed; and (8) Finally, dehydration and sealing, microscopic examination, image collection and histological analyses were performed the same way as H&E staining.

Proteomics analysis of muscle and joint capsule

Protein immunoblotting (western blotting) was performed as follows. Total protein was extracted from the retained muscle and joint capsule samples. When 50-60 mg rectus femoris muscle was taken, the total tissue protein was extracted with 600 mL radio immunoprecipitation assay (RIPA) reagent (Tris-HCl [pH 7.4], 150 mmol/L NaCl, 1 mmol/L ethyleneiamineetraacetic acid, 1% Triton X-100, 1% sodium deoxycholate, 0.1% sodium dodecyl sulfate [SDS], and 1 mmol/L PMSF), and a protease inhibitor was added to the RIPA. Total proteins were separated by SDS-polyacrylamide gel electrophoresis and transferred to the polyvinylidene difluoride (PVDF) membrane. The PVDF was washed and immersed in 5% skim milk for 4 ℃ overnight. Membranes were incubated with anti-rat monoclonal antibody (1:10000-50000, cell signaling, United States) for 2 h at room temperature, and then washed three times with a Tris-buffered saline with 0.1% Tween 20 (TBST) solution (10 min/wash). The washed PVDF membrane was incubated with horseradish peroxidase-labeled goat anti-rat immunoglobulin G antibody (1: 10000-50000; Cell Signaling, Danvers, MA, United States) for 1 to 2 h at room temperature, washed with TBST (as described above), and then detected with enhanced chemiluminescence light-emitting liquid colored with energy autoexposure. The developing bands were analyzed by IPP software.

Statistical analysis

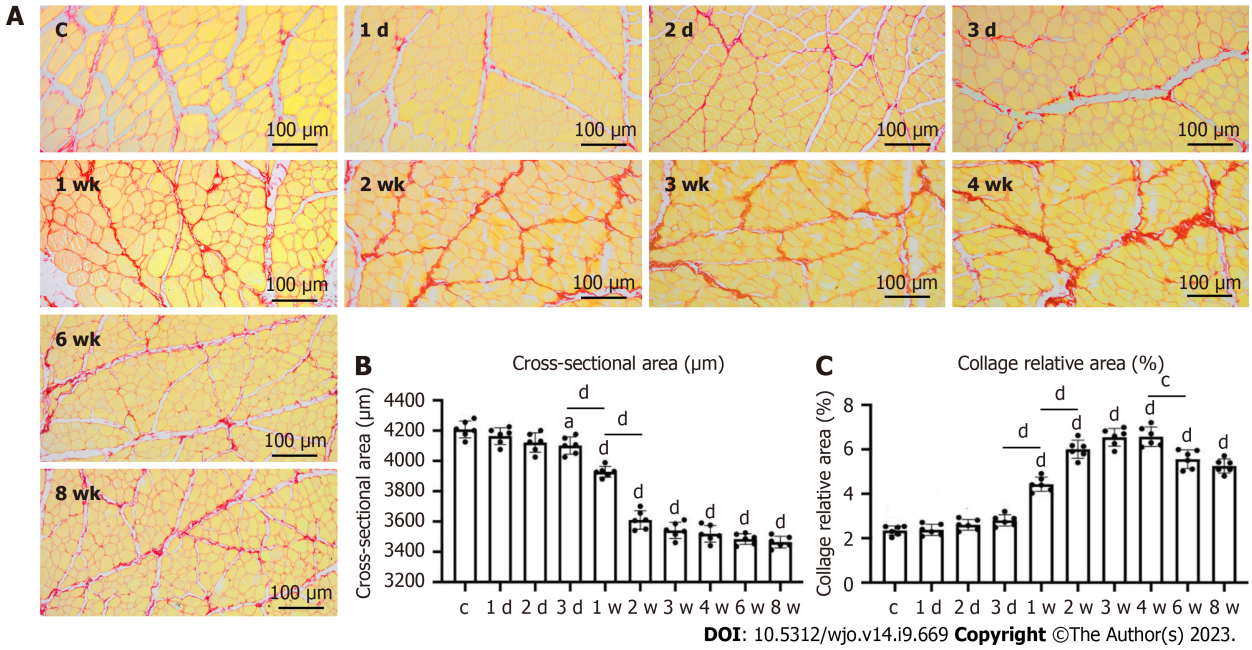
The results are expressed as the mean ± standard deviation. One-way analysis of variance was used to test the difference between groups. $P < 0.05$ was statistically significant. Statistical analyses were performed using IBM SPSS statistics software, version 22 (IBM Corp., Armonk, NY, United States).

RESULTS

Three rats in the immobilization-6 wk group experienced slippage of the immobilization device in the 2nd week of immobilization; the immobilization device was fixed the same day as the slippage occurred, and there was no further slippage until the end of the immobilization period. There was no death, lower limb necrosis, or other complications in any group.

Total contracture, myogenic contracture, and arthrogenic contracture

After 1 wk of immobilization, the degree of total contracture significantly differed between the control group and the immobilization groups (all $P < 0.05$). Compared with the immobilization-1 d, -2 d, and -3 d groups, the degree of total contracture was significantly greater in the immobilization-1 wk, -2 wk, -3 wk, -4 wk, -6 wk, and -8 wk groups (all $P < 0.05$). Total contracture degree was not significantly different between certain adjacent immobilization groups, *i.e.* between the immobilization-1 d and -2 d, immobilization-2 d and -3 d, immobilization-3 wk and -4 wk, immobilization-4



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Figure 4 Sirius red staining findings. A: Morphological changes of rectus femoris after Sirius red staining, group C (control), 1 d, 2 d, 1 wk, 2 wk, 3 wk, 4 wk, 6 wk, and 8 wk; B and C: Cross-sectional value of rectus femoris fibers. $^{a}P < 0.05$; $^{c}P < 0.001$; $^{d}P < 0.0001$.

wk and -6 wk, and immobilization-6 wk and -8 wk groups. The degree of total contracture was increased with the immobilization time (Table 1).

The degree of myogenic contracture was significantly greater in the immobilization-1 wk group than the immobilization-3 d group ($P < 0.05$). The degree of myogenic contracture also significantly differed between the immobilization-1 wk and -2 wk groups ($P < 0.05$), but not between any other adjacent immobilization groups ($P > 0.05$). The results suggested that myogenic contracture occurred after 1 wk of immobilization and gradually stabilized after 2 wk of immobilization, whereas the subsequent joint contractures were mostly arthrogenic (Table 1).

After 1 wk of immobilization, the degree of arthrogenic contracture was significantly greater in the immobilization groups than the control group ($P < 0.05$). The degree of arthrogenic contracture significantly differed between the immobilization-3 d and -1 wk, immobilization-1 wk and -2 wk, and immobilization-2 wk and -3 wk groups (all $P < 0.05$), but not between the other adjacent groups ($P > 0.05$). The results suggested that arthrogenic contracture progressed from 1 to 3 wk of immobilization. However, the progression amplitude of the arthrogenic contracture began to weaken after 3 wk of immobilization, after 4 wk, the arthrogenic contracture is basically stable (Table 1).

Histological evaluation of the Sirius red-stained sections

Compared with the control group, the mean diameter of the rectus femoris was significantly decreased with the duration of immobilization in all immobilization groups except the immobilization-1 d and -2 d groups ($P < 0.05$). From 1 d to 3 wk of immobilization, the proportion of collagen fibers in the rectus femoris of the immobilization groups increased with the fixation time. The proportion of collagen fibers significantly differed between the control group and all immobilization groups except the immobilization-1 d, -2 d, and -3 d groups ($P < 0.05$). The proportion of collagen fibers in the rectus femoris stabilized in the immobilization-4w group, but was decreased in the immobilization-6 wk and -8 wk groups ($P < 0.05$ in all cases; Figure 4).

Evaluation of the hematoxylin-eosin-stained sections and immunohistochemistry

The largest synovial area in the sagittal plane was analyzed. H&E staining showed that the degree of synovial hyperplasia of the anterior joint capsule in the immobilization groups increased with the fixation time, with significant differences between adjacent groups, *i.e.* between the immobilization-1 d and -2 d, immobilization-3 d and -1 wk, immobilization-1 wk and -2 wk, and immobilization-2 wk and -3 wk groups ($P < 0.05$). The degree of synovial hyperplasia of the anterior joint capsule also significantly differed between the control group and all immobilization groups, except the immobilization-1 d group ($P < 0.05$; Figure 5). Immunohistochemistry showed that the change trend of phosphorylated mothers against decapentaplegic homolog (p-Smad2) was consistent with the degree of synovial hyperplasia of the anterior joint capsule, but the percentage of p-Smad2 in each group was significantly different from that in the control group immobilization-2 d ($P < 0.05$; Figure 6).

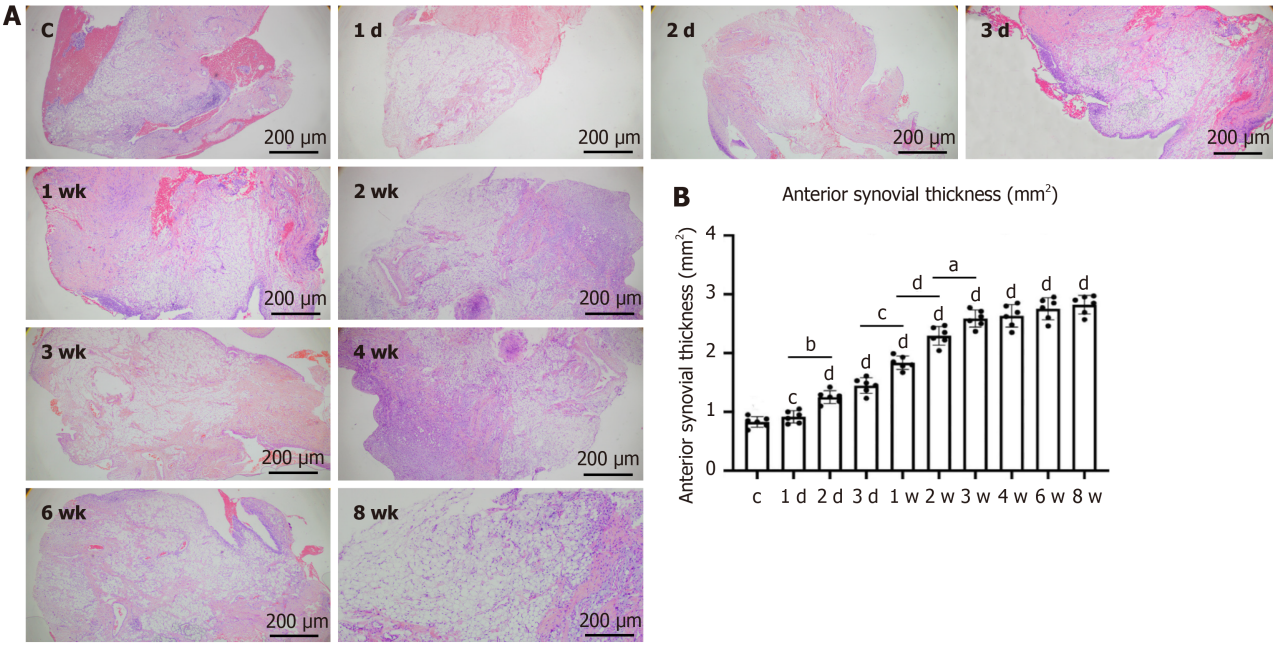
Protein expression in the muscle and joint capsule

After early joint immobilization, the expression level of transforming growth factor beta 1 (TGF-β1) was significantly increased in the joint capsule and muscles. The expression level of TGF-β1 in the joint capsule was significantly higher in the immobilization-1 wk group than in the immobilization-3 d group. TGF-β1 expression of joint capsule continued to

Table 1 Total, myogenic, and arthrogenic contracture after knee immobilization for various time periods in 60 SD rats (mean ± SD)

Grouping	Quantity	Degree of contracture		
		Total contracture	Myogenic contracture	Arthrogenic contracture
Control	6	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Immobilization-1 d	6	1.1 ± 0.6	0.6 ± 0.4	0.5 ± 0.3
Immobilization-2 d	6	2.4 ± 0.7	1.5 ± 0.4	0.9 ± 0.2
Immobilization-3 d	6	5.9 ± 1.0	4.0 ± 1.0	1.9 ± 0.5
Immobilization-1 wk	6	23.5 ± 2.0[a,b,c,d]	15.9 ± 1.9[a,b,c,d]	7.6 ± 0.7[a,b,c,d]
Immobilization-2 wk	6	51.8 ± 1.8[a,b,c,d,e]	32.7 ± 1.1[a,b,c,d,e]	19.1 ± 1.3[a,b,c,d,e]
Immobilization-3 wk	6	78.7 ± 2.2[a,b,c,d,e,f]	33.9 ± 2.1[a,b,c,d,e]	44.5 ± 1.9[a,b,c,d,e,f]
Immobilization-4 wk	6	79.9 ± 2.8[a,b,c,d,e,f]	34.2 ± 2.2[a,b,c,d,e]	44.9 ± 2.2[a,b,c,d,e,f]
Immobilization-6 wk	6	80.8 ± 3.5[a,b,c,d,e,f]	35.5 ± 2.9[a,b,c,d,e]	45.3 ± 2.9[a,b,c,d,e,f]
Immobilization-8 wk	6	82.5 ± 3.0[a,b,c,d,e,f]	35.9 ± 2.5[a,b,c,d,e]	46.6 ± 2.3[a,b,c,d,e,f]

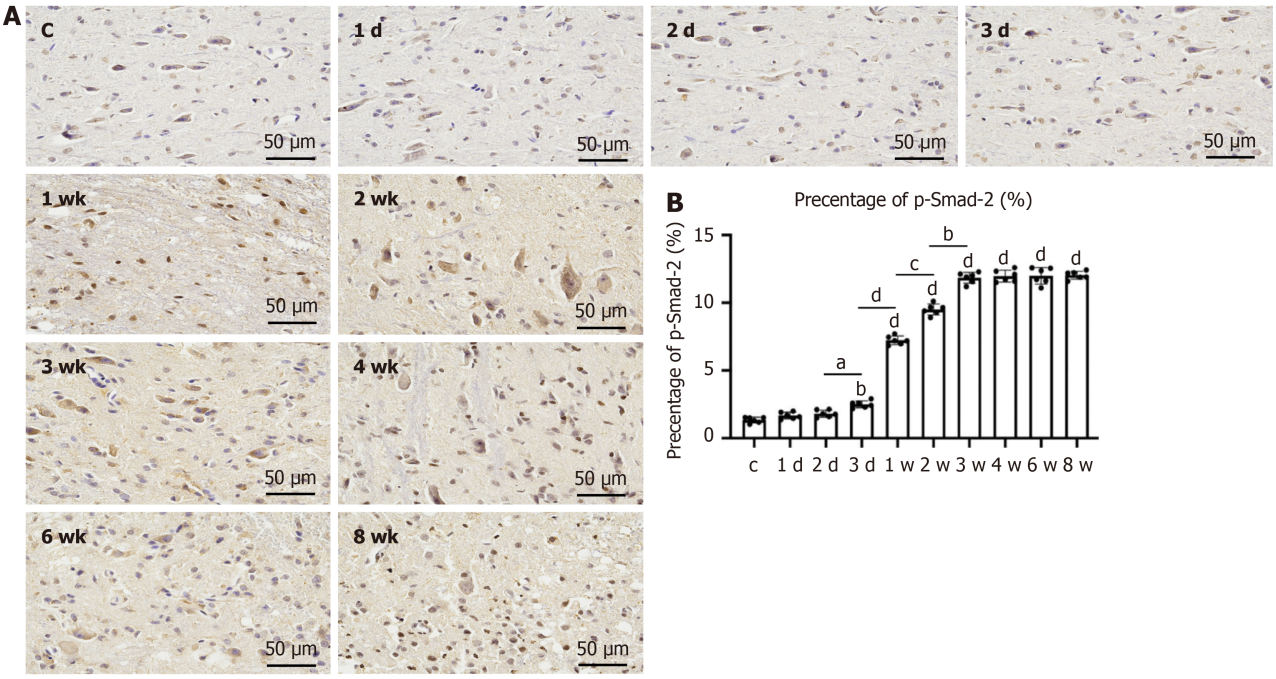
[a]$P < 0.05$ *vs* control group.
[b]$P < 0.05$ *vs* immobilization-1 d group.
[c]$P < 0.05$ *vs* immobilization-2 d group.
[d]$P < 0.05$ *vs* immobilization-3 d group.
[e]$P < 0.05$ *vs* immobilization-1 wk group.
[f]$P < 0.05$ *vs* immobilization-2 wk group.



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Figure 5 Hematoxylin and eosin staining findings. A: Morphological changes of the anterior joint capsule; B: The anterior joint capsule thickness value. [a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$; [d]$P < 0.0001$.

increase after immobilization for up to 8 wk. There were significant differences in TGF-β1 levels in the joint capsule between the immobilization-2 d and -3 d, immobilization-1 wk and -2 wk, and immobilization-2 wk and -3 wk groups ($P < 0.05$). The TGF-β1 content of the anterior joint capsule increased with the immobilization time, with a slight downward trend in the immobilization-8w group that did not reach statistical significance ($P > 0.05$). TGF-β1 expression in the anterior joint capsule was significantly increased in the control group compared with the immobilization groups ($P < 0.05$), except the immobilization-1 d and -2 d groups. Western blot analysis showed that the TGF-β1 content in the quadriceps muscle first increased and then decreased. The TGF-β1 content in the muscle significantly differed between the immobilization-2 d and -3 d, immobilization-3 d and -1 wk, immobilization-1 wk and -2 wk, and immobilization-6 wk and -8 wk groups ($P < 0.05$); The contents of Smad2 and Smad3 and TGF-β1 in quadriceps femoris had the same trend of



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Figure 6 Immunohistochemistry findings. A: Immunohistochemical staining of the anterior joint capsule; B: Percentage of the anterior articular joint capsule phosphorylated mothers against decapentaplegic homolog 2. [a]*P* < 0.05; [b]*P* < 0.01; [c]*P* < 0.001; [d]*P* < 0.0001.

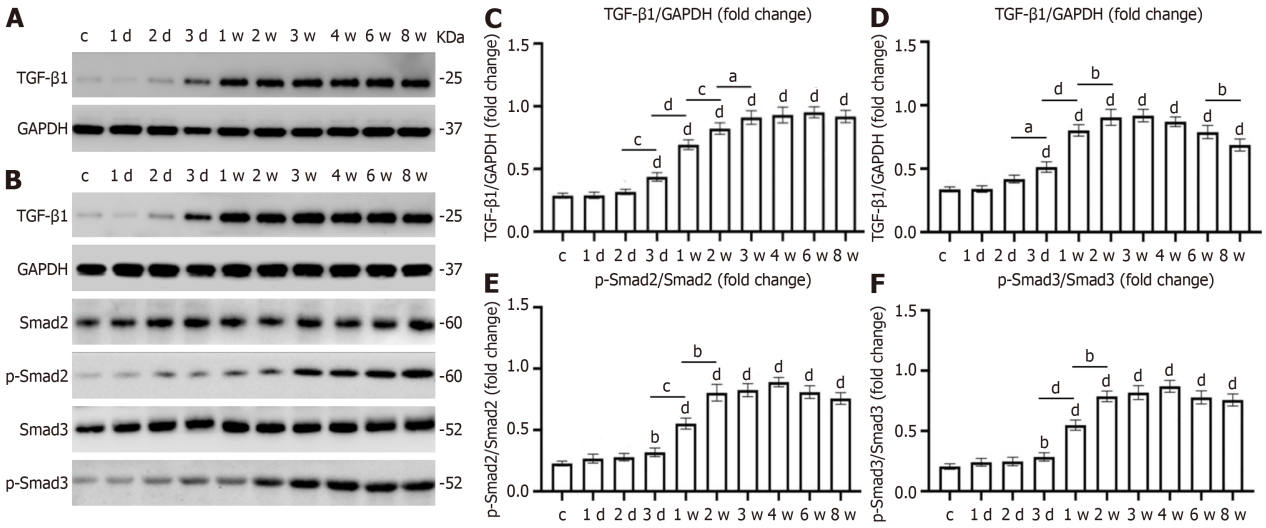
change, but there were significant differences only between the groups of immobilization-3 d and -1 wk, immobilization-1 wk and -2 wk ($P < 0.05$). In all of the results, with the exception of the fixed-1 d and-2 d groups, there was also a significant difference between the control group and the fixed group ($P < 0.05$) (Figure 7).

DISCUSSION

Joint contracture is a relatively common condition that is mainly caused by fibrosis of the joint capsule and skeletal muscle after long-term immobilization, and shows the pathological features of excessive deposition of collagen and connective tissue components[15]. Numerous animal models have been developed to simulate knee flexion contracture; however, few animal models of knee extension contracture have been reported. A previous study successfully established a model of knee extension contracture in New Zealand white rabbits and reported in detail the characteristics of plaster immobilization and the relevant mechanisms[16]. However, it is beneficial to model knee extension contracture in rats rather than rabbits because of the lower cost of studying the pathogenesis of joint contracture and evaluating therapeutic efficacy. Therefore, the present study described a method to establish a model of knee extension contracture in the rat. We demonstrated that this model had significantly limited knee flexion motion and altered expressions of histological and fibrosis-related proteins in the skeletal muscle and anterior joint capsule.

Wang *et al*[17] directly assessed the muscle limitations of rats with immobilized ankle joints and found that the initial flexion contracture of the knee is mainly due to muscle structures and is reversible and can spontaneously resolve. By contrast, long-term contracture is mainly caused by the joint structures and is irreversible[14]. Such arthrogenic contracture cannot be improved, even by aggressive rehabilitation[18]. Several reports suggest that joint contractures occur within 1 wk of immobilization and progress in a time-dependent manner[19,20]. Chimoto *et al*[21] reported that 2 wk of muscle limitation mainly causes myogenic contracture, while long-term contracture (more than 4 wk of immobilization) results in joint contracture. Therefore, prolonged immobilization for longer than 4 wk should be avoided to prevent irreversible joint contracture[22]. In the present study, myogenic contracture was the predominant type of contracture during the first 2 wk of immobilization. From 2 to 3 wk of immobilization, the joint contracture changed from myogenic to arthrogenic. The contracture initiation time in the present study was consistent with previous studies; however, in contrast with previous studies, the arthrogenic contracture stabilized at 3 wk and completely stable at 4 wk. Arthrogenic contracture is primarily a fibrotic response within the joint capsule. The posterior joint capsule is the main contributor to the formation of immobilization-induced knee flexion contracture, while the anterior joint capsule has the greatest impact on knee extension contracture[21]. The synovial layer of the anterior joint capsule is the widest and most complex in the knee joint[23]. In the present study, the degree of synovial hyperplasia continuously increased with the immobilization time; this may explain why knee extension contracture forms earlier than knee flexion contracture.

In the histologic assessment of the present study, the myofiber cross-sectional area, intermuscular collagen deposition, and extent of hyperplasia in the anterior joint capsule supported the biological findings. As the decreased skeletal muscle mass caused by an imbalance in protein metabolism is characterized by a significantly smaller muscle fiber area[24-26].



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Figure 7 Western blot findings. A: Changes in the intensity of transforming growth factor beta 1 (TGF-β1) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) bands in the anterior joint capsule; B: Changes in the intensity of TGF-β1/GAPDH, phosphorylated mothers against decapentaplegic homolog 2 (p-Smad2)/Smad2, p-Smad2/Smad2 bands in the quadriceps; C: Graphical representation of the expression level of TGF-β1 in the anterior joint capsule relative to GAPDH; D-F: Graphical representation of the expression level of TGF-β1/GAPDH, p-Smad2/Smad2, p-Smad2/Smad2. $^{a}P < 0.05$; $^{b}P < 0.01$; $^{c}P < 0.001$; $^{d}P < 0.0001$.

The amount of intermuscular collagen deposition was significantly greater in the immobilization-1w group than the control group, but did not significantly differ between the immobilization-2 wk and -3 wk groups. Furthermore, there was significantly less intermuscular collagen deposition in the immobilization-6w group compared with the immobilization-4w group. This indicates that intermuscular collagen deposition began to increase in the 1st week of immobilization, but decreased after 4 wk of immobilization. Previous studies have shown that this may be associated with gradual resolution of the inflammatory and fibrotic response after immobilization[11]. This was demonstrated by the reduction in collagen content and TGF-β1 protein expression over time. The anterior joint synovial proliferation was significantly greater in the immobilization-2 d group than the control group, but did not differ between the immobilization-3 wk and -4 wk groups, indicating that the anterior joint synovial proliferation significantly increased during the first 3 wk of immobilization and completely stabilized from 4 wk onwards. Wang *et al*[27] analyzed changes in the synovial membrane caused by anterior articular capsule fibroblasts, microvasodilation, and congestion due to plaster immobilization. Li *et al*[28] and Yao *et al*[29] reported that intra-articular tissue adhesion does not completely cover the cruciate ligament in and around the knee, but originates from synovial fibrosis. The proliferation of intra-articular synovial tissue was responsible for the limited ROM found in the present study.

To further characterize the altered fibrosis of skeletal muscle and the joint capsule, we evaluated the expression of the TGF-β1 and p-Smad protein. There are three subtypes of TGF-β family: TGF-β1, TGF-β2, and TGF-β3. A large number of studies have demonstrated that the expression of TGF-β1 is the most important in fibrosis changes. TGF-β1 can cause differentiation, proliferation and extracellular matrix production, promote the transformation of fibroblasts to myofibroblasts, cause the deposition of collagen and increase the expression of alpha smooth muscle actin (α-SMA), and then cause tissue fibrosis[30,31]. Zhang *et al*[32] found that the expression level of TGF-β1 in the posterior joint capsule was significantly increased *in vivo* experiments. *In vitro* experiments showed that the expression level of TGF-β1 was increased, and the expression of α-SMA and type I collagen was also increased. Mao *et al*[33] applied a TGF-β inhibitor to treat a traumatic rat knee joint contracture animal model and found that after the activity of TGF-β was inhibited, the degree of joint contracture was alleviated, while the protein expression of collagen type I, collagen type III, α-SMA, and p-Smad2 was decreased. Therefore, we used the TGF-β1 and Smad signaling pathway as indicators to prove the formation of contracture. The aggravation of contracture enhances the fibrosis response, characterized by increases in profibrotic genes and proteins (*e.g.*, cytokine TGF-β1 genes, type I and type III collagen genes and proteins), leading to increases in collagen density and joint capsule thickness[34]. Hildebrand *et al*[35] reported the increased expression of type I and III collagen, TGF-β1, p-Smad2, and p-Smad3 in a rabbit post-traumatic flexion contracture model compared with control joint cysts. The increased mRNA levels of TGF-β1 may be related to collagen deposition inside and outside the articular capsule. Joint capsule fibrosis may be associated with the development of joint contracture. Similarly, the present study showed that the expression of fibrosis-related genes increased with prolonged immobilization, but the expression of TGF-β1, p-Smad2, and p-Smad3 in the rectus femoris decreased slightly after 3 wk of immobilization and was significantly decreased at 8 wk. The altered expression levels of TGF-β1 may be due to hypoxia or a reduction in collagen turnover or degradation rates[36]. Among several other roles, one of the adaptive responses of hypoxic cells is the upregulation of hypoxia-inducible factor 1 alpha (HIF-1α). The expression of TGF-β1 and HIF-1α is significantly upregulated during the transformation of fibroblasts to myofibroblasts, leading to the promotion of vascular endothelial growth factor (VEGF) gene expression[37]. The HIF-1α signaling pathway in turn regulates angiogenesis by inducing VEGF expression, thereby improving circulation and reducing the inflammatory response[38].

In the present study, ordinary gypsum and polymer gypsum were initially used to establish the extended knee contracture model. However, the rats inevitably gnawed the gypsum and there was also gypsum slippage. In the process of switching to an aluminum splint, we found that the knee joints of the rats could not be wrapped when fixed because the proximal lower limbs were short and strong. The present shape of the external immobilization device was determined after multiple improvements. The immobilization device comprised of aluminum plate pressurized at the distal end on the back of the foot that was plantarflexed at 60. After the first proximal rectangular aluminum plate was used to fix the knee joint, the second inverted trapezoidal aluminum plate was wrapped around the knee to ensure that the knee was completely immobilized. Although this immobilization method is simple, the pressure strength must be carefully controlled. A pressure that is too high will easily cause poor limb circulation in rats. As aluminum is easy to shape, we were able to adjust the tightness of the external immobilization to resolve any swelling. Tokuda *et al*[39] successfully created a model of flexion contracture outside the knee joint; however, the external immobilization device used in the present study had less effect on the overall activity of the rats and better reflected the clinical situation in which the knee joint is usually fixed in extension after injury, leading to limited knee flexion after long-term immobilization. Therefore, to more closely mimic the clinical situation, we chose to create a model of knee extension contracture.

We demonstrated that the present model is as reliable as other animal models in reproducing the features of human joint contracture, including limited joint mobility, changes in the joint and muscle histology, and changes in the expression of fibrosis-associated proteins in the joint capsule *vs* muscle. The advantage of the present model is that it is easy to replicate because it does not require complex surgical procedures, the tools are easy to use, and the rat anesthesia and immobilization can be performed in a very short period of time. We described the detailed process of establishing a rat model of knee extension contracture, with photographs. The model closely replicates joint contracture caused by complications of immobilization, enabling researchers to investigate the etiology of joint contracture and establish new treatments. This model is a reliable tool, as described earlier. Contractures caused by long-term fixation are mainly caused by joint structure and are irreversible. Moreover, the mechanism by which movement after fixation may exacerbate joint contracture has not been fully explored[40]. As the external fixator is easy to shape and can be removed at any time. Therefore, this model can be used to study the prevention and treatment of knee extension contracture in rats, at the same time, it is possible to change the dressing and keep the wound dry during the fixation of traumatic knee joint contracture.

The present study had some limitations. First, in this model, the ankle joint and the knee joint were inevitably fixed together. Because the lower limb of the rat is shaped like a cone, the ankle joint was plantarflexed at 60 and fixed with the knee joint to prevent slippage of the aluminum splint. Second, the longest immobilization time in the present study was 8 wk. We plan to explore the continuous longer-term changes in fibrosis-related proteins in a future study. Finally, the state of the extension contracture after the removal of the external fixator was also studied and will be reported.

CONCLUSION

The results in this study suggest that the myogenic contracture is stabilized after 2 wk, whereas the arthrogenic contracture is stabilized after 3 wk and completely stable in 4 wk.

ARTICLE HIGHLIGHTS

Research background

There is currently no research on establishing a model of knee joint extension contracture in rats.

Research motivation

The extension contracture model is of clinical relevance because it better mimics fracture and bed-associated immobilization than the flexion contracture model.

Research objectives

Clarify the formation process of knee joint extension contracture in rats.

Research methods

Verify the formation process of extension contracture by observing pathology, detecting fibrotic proteins, and measuring joint range of motion.

Research results

All results show that the myogenic contracture tends to stabilize after 2 wk, and the arthrogenic contracture tends to stabilize after 3 wk and completely stable in 4 wk.

Research conclusions

The extension contracture model is of clinical relevance because it better mimics fracture and bed-associated immobilization than the flexion contracture model.

Research perspectives

This rat model may be a useful tool for studying the etiology of joint contracture and establishing new treatment methods.

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FOOTNOTES

Author contributions: Zhou CX conceived the study, participated in its design and coordination, and drafted the manuscript; Wang F participated in the design of the study and performed the statistical analyses; Zhou Y participated in its design and coordination, and helped to draft the manuscript; Fang QZ drew the pictures in the manuscript; Zhang QB performed the statistical analysis in the revised manuscript; All authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Basic Study

Comparative study *in vivo* of the osseointegration of 3D-printed and plasma-coated titanium implants

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Abstract

BACKGROUND

Total hip arthroplasty is a common surgical treatment for elderly patients with osteoporosis, particularly in postmenopausal women. In such cases, highly porous acetabular components are a favorable option in achieving osseointegration. However, further discussion is needed if use of such acetabular components is justified under the condition of normal bone mass.

AIM

To determine the features of osseointegration of two different types of titanium implants [3-dimensional (3D)-printed and plasma-coated titanium implants] in bone tissue of a distal metaphysis in a rat femur model.

METHODS
This study was performed on 20 white male laboratory rats weighing 300-350 g aged 6 mo. Rats were divided into two groups of 10 animals, which had two different types of implants were inserted into a hole defect (2 × 3 mm) in the distal metaphysis of the femur: Group I: 3D-printed titanium implant (highly porous); Group II: Plasma-coated titanium implant. After 45 and 90 d following surgery, the rats were sacrificed, and their implanted femurs were extracted for histological examination. The relative perimeter (%) of bone trabeculae [bone-implant contact (BIC%)] and bone marrow surrounding the titanium implants was measured.

RESULTS
Trabecular bone tissue was formed on the 45th day after implantation around the implants regardless of their type. 45 d after surgery, group I (3D-printed titanium implant) and group II (plasma-coated titanium implant) did not differ in BIC% (83.51 ± 8.5 *vs* 84.12 ± 1 .73; P = 0.838). After 90 d, the BIC% was higher in group I (87.04 ± 6.99 *vs* 81.24 ± 7.62; P = 0.049), compared to group II. The relative perimeter of the bone marrow after 45 d did not differ between groups and was 16.49% ± 8.58% for group I, and 15.88% ± 1.73% for group II. Futhermore, after 90 d, in group I the relative perimeter of bone marrow was 1.4 times smaller (12.96 ± 6.99 *vs* 18.76 ± 7.62; P = 0.049) compared to the relative perimeter of bone marrow in group II.

CONCLUSION
The use of a highly porous titanium implant, manufactured with 3D printing, for acetabular components provides increased osseointegration compared to a plasma-coated titanium implant.

Key Words: Rats; Hip arthroplasty; Femur; Porosity; 3-dimensional printing; Microscopy

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Core Tip: The use of porous titanium materials was shown to be the most favorable solution for osseointegration for total hip arthroplasty, especially in the case of osteoporosis. Is the use of highly porous acetabular components justified under the condition of normal bone mass? We conducted a study on rats, in which we compared the osseointegration of 3-dimensional (3D)-printed or plasma-coated titanium implants into femoral bone defect by assessing the relative perimeter (%) of bone trabeculae. The highly porous titanium implant, manufactured with 3-dimensional printing, for acetabular components provides increased osseointegration compared to a plasma-coated titanium implant.

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INTRODUCTION

Titanium has long been used for the manufacture of medical implants. Among them, highly porous titanium created using additive technologies [used, in particular, for acetabular component manufacturing for total hip arthroplasty (THA)] was shown to be the most favorable material for osseointegration[1-3]. This is due to the similarity of the structure and biomechanical qualities of this material with bone tissue[4,5]. THA is a common surgical treatment for elderly patients, women are equally represented among THA patients. A common challenge is matching the structure of the material to the structure of the bone, this becomes even more important due to the possibility of osteoporosis[6] or slowing of bone tissue formation due to age changes, endocrine diseases, menopause, hormonal therapy, *etc.*[7,8]. The use of acetabular components with a porous surface formed by plasma spraying has also proven itself in clinical practice[9-11]. Previously, we reported the comparative osseointegration of four types of highly porous materials from which the acetabular components of endoprostheses are made[12]. No established difference was seen between them in healthy rats, in contrast differences were seen in postmenopausal osteoporotic animals[12]. Additionally, an *in vivo* study in sheep also showed that surface modification by chemical treatment of porous titanium can improve osseointegration[13]. It has been shown in clinical settings that the use of porous titanium cups was accompanied by a higher intensity of pain during the first 5 years after THA compared to cups made of titanium with plasma spraying[14]. Conflicting data has been published regarding better primary stability of porous titanium cups compared to plasma sprayed titanium cups[4,15]. The question arises: Is the use of highly porous acetabular components justified under the condition of normal bone mass?

Aim of the study was to establish the features of osseointegration of two different types of titanium implants [3-dimensional (3D)-printed and plasma-coated titanium implants] in a distal femoral metaphisial rat model.

MATERIALS AND METHODS

The study was conducted in compliance with the national guidelines, the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (1986, ETS 123) and Directive 2010/63/EU. The protocol of the study was approved by the local Bioethics Committee (protocol No. 211 dated February 01, 2021).

Experiment design

The experimental study was performed on 20 white male laboratory rats weighing 300-350 g of 6 mo of age (Figure 1A), which were kept under conditions of standard food for rodents, free access to drinking water, and 12-h light day/night. The rats were divided into two groups of 10 animals each depending on the type of implanted titanium material: Group I: 3D-printed titanium implant (highly porous); Group II: Plasma-coated titanium implant (Figure 1A).

Implants

The cylindrical implants (2 mm diameter and 3 mm length) were made from the material of one of the two types of acetabular cups from (AK Medical H.L. Beijing, China): AK 3D ACT Titanium Alloy Trabecular Acetabular Cup[16] or AK A Series Bio-Type Acetabular Cup[17]. The difference between the coatings was in the method of their production and the resulting structure. In particular, the AK 3D ACT Titanium Alloy Trabecular Acetabular Cup is a highly porous titanium cup with open controlled porosity (approximately 80%) manufactured using additive technologies (Figure 1B); AK A Series Bio-Type Acetabular Cup is created by plasma spraying of titanium on the surface of the cup and has closed porosity (Figure 1C).

Surgical intervention

Surgical interventions were performed under aseptic and antiseptic conditions under general anesthesia (aminazine 10 mg/kg and ketamine 50 mg/kg intramuscularly). After preparation of the operative field [shaving the hair on the left knee and thigh, treatment with Kodan® forte antiseptic (Schülke & Mayr GmbH, Germany)], the distal metaphysis of the femur was opened through an anterolateral approach (Figure 1D). In the animal distal femoral metaphysis, a hole defect with a diameter of 2 mm was created with a dental boron, where 3D-printed or plasma-coated titanium implants were installed (Figure 1E and F). After that, the soft tissues and skin were sutured with knotted sutures and treated with Kodan® antiseptic. The condition of the rats after surgery did not necessitate pharmacological treatment.

At 45 and 90 d after surgery, rats were euthanized with a lethal dose of anaesthetic (sodium thiopental, 90 mg/kg intramuscularly) and implanted femurs were removed for histological examination.

Histological examination

Removed femurs with titanium implants were cleaned of soft tissue, then fixed in 10% buffered formalin for 5 d. After fixation, the bones were transferred to 70° ethyl alcohol for dehydration. After a day, three longitudinal sections with a thickness of approximately 0.5 mm were made from each distal metaphysis of the femur in the area of implantation of the titanium cylinders with a diamond saw. The obtained slices were stored in 70° ethyl alcohol and dried with filter paper before taking measurements.

Histomorphometry

Bone sections together with the implant were photographed using an Olympus BX-63 microscope (Olympus, Japan) with × 4 magnification in fluorescent light (U-FBW filter, blue excitation; Olympus, Japan), X-Lite lamp (Olympus, Japan), camera DP73 (Olympus, Japan). The relative perimeter (%) of bone trabeculae [bone-implant contact (BIC%)] and bone marrow around titanium implants were measured using ImageJ software.

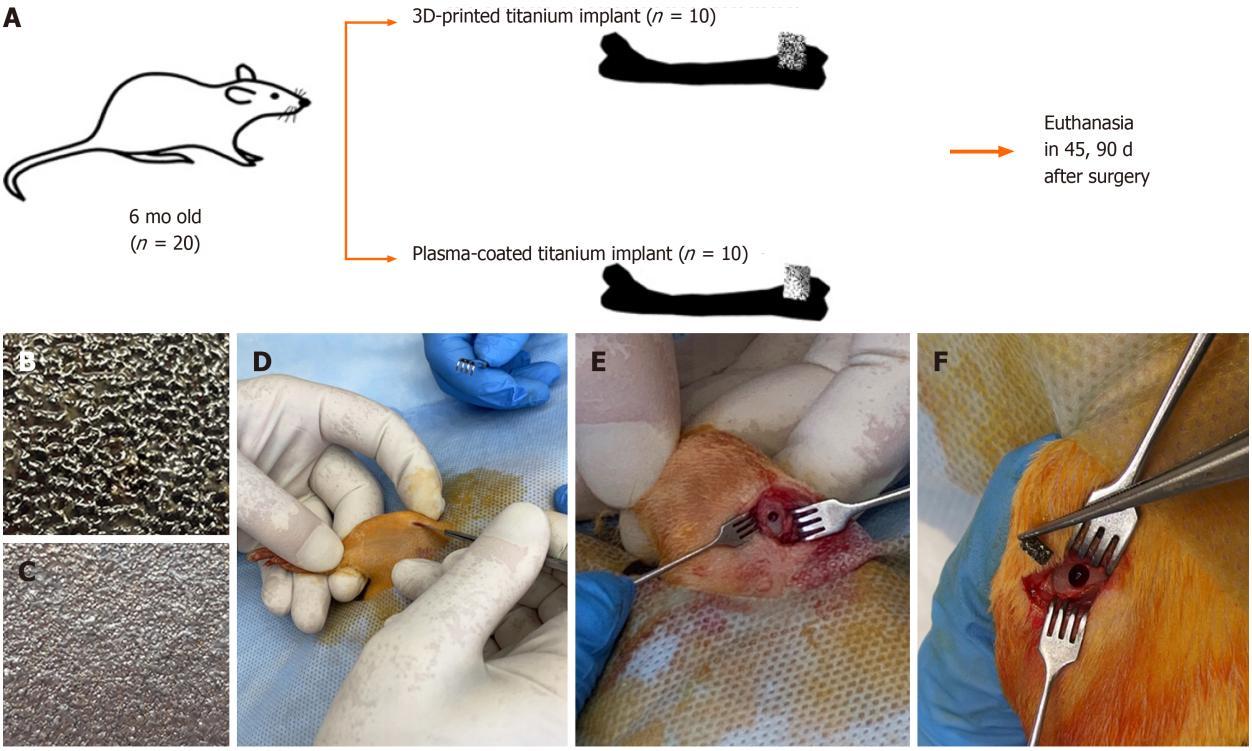
Statistical analysis

The obtained results are presented as mean and standard deviation. To detect the influence of the type of titanium material on tissue formation, as well as to detect changes in tissue formation during the experiment (45 and 90 d), Mann–Whitney U test was used. The difference between groups was considered statistically significant if $P < 0.05$. Statistical analysis was performed using IBM SPSS Statistics 19.0 software.

RESULTS

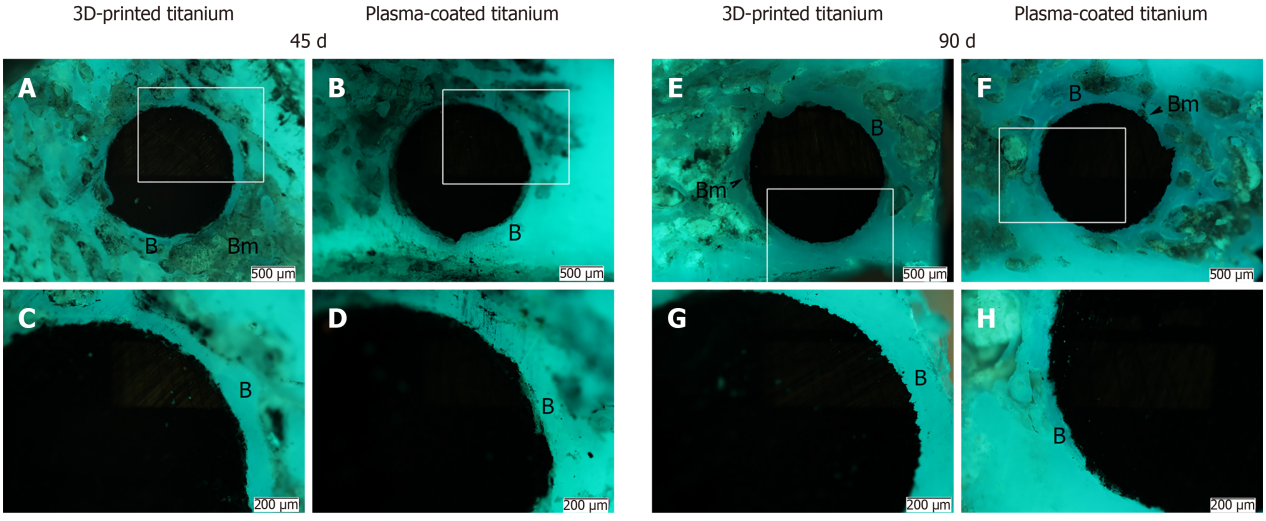
Forty-five days after the index surgery, both implant groups, formed spongy bone tissue of the lamellar type, in which lacunae with osteocytes were observed (Figure 2). 90 d after the index surgery, no qualitative changes in the structure of the bone tissue around both types of implants were detected.

Forty-five days after surgery, group I (3D-printed titanium implant) and group II (plasma-coated titanium implant) did not differ in BIC% (Figure 3) (83.51 ± 8.5 *vs* 84.12 ± 1 .73; $P = 0.838$). After 90 d, the BIC% was higher in group I (87.04 ± 6.99 *vs* 81.24 ± 7.62; $P = 0.049$), compared to group II (Figure 3). The relative perimeter of the bone marrow after 45 d did not differ between groups and was 16.49% ± 8.58% for group I, and 15.88% ± 1.73% for group II, respectively. In comparison after 90 d in group I, the relative perimeter of the bone marrow was 1.4 times smaller (12.96 ± 6.99 *vs* 18.76 ± 7.62; $P = 0.049$) compared to the relative perimeter of the bone marrow in group II.



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Figure 1 Design of study with characteristics of implanted material and stages of index surgery. A: Design of an experimental study on rats with a demonstration of the features of the implant materials used; B: 3D-printed titanium implant; C: Plasma-coated titanium implant; D-F: Stages of surgical intervention.



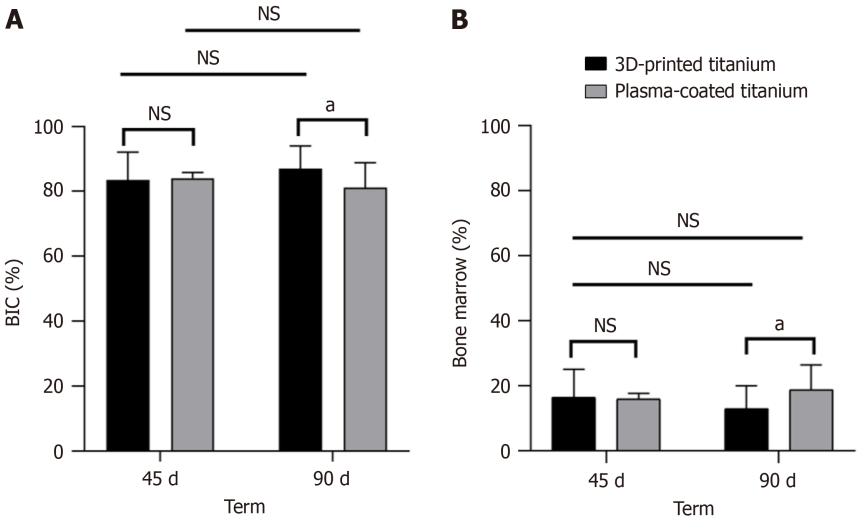
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Figure 2 Fluorescence microscopy of rat femoral sections after index surgery. Titanium implants (black color) with 3D-printed or plasma-coated titanium in the distal metaphysis of the rat femur. Bone trabeculae are formed along the perimeter of implants with areas of bone marrow. White rectangles show fragments of the corresponding photos taken at a higher magnification. Longitudinal sections. A-D: 45 d (*n* = 10) after implantation; E-H: 90 d (*n* = 10). B: Bone trabeculae; Bm: Bone marrow.

During the experimental study (45 d and 90 d after the index surgery), the BIC% indicator and the relative perimeter of the bone marrow did not significantly change in both groups of differing titanium implants (Figure 3).

DISCUSSION

The results of this study show that both types of cylindrical titanium implants (made by 3D printing with controlled open porosity and by plasma spraying with closed porosity) contribute to the formation of bone tissue, with corresponding



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Figure 3 Bone tissue formation (Bone-implant-contact%; Bone marrow%) around two types of titanium implants. 3D-printed and plasma-coated titanium implants 45 d (n = 10) and 90 d (n = 10) after implantation in the distal metaphysis of the femur of rats. Data are presented as mean ± SD. A: Bone-implant contact (Bone-implant-contact%) is significantly higher at day 90 for the implant with 3D-printed titanium; B: Bone marrow% is significantly lower at day 90 for the implant with 3D-printed titanium. NS: Not significant; $^{a}P < 0.05$.

structure, 45 d after installation in the femoral distal metaphysis in a rat model. The study shown that the BIC% in rats was more than 80% for both types of titanium implants and did not differ significantly between implant groups. The successful formation of bone tissue is primarily related to the chemical composition of the implants[18]. In addition, the surface structure of the implanted samples has an important influence on the osteointegration process. In particular, *in vitro* experiments have shown that cell adhesion and proliferation are slowed down on the rough surface of titanium plasma sprayed implants compared to the smooth surface of an identical titanium alloy[19,20]. However, based on the analysis of bone formation markers (type I procollagen peptide, alkaline phosphatase, osteocalcin, osteoprotegerin), a greater degree of differentiation of cultured cells into osteoblasts on the rough surface of titanium plasma sprayed implants was established[21]. On the other hand, as a result of the comparison of titanium samples with a porous surface (one created using plasma spraying, the other using additive technologies) in the culture of osteoblasts, no difference between them was found either in terms of cell adhesion, nor in the rate of their proliferation and alkaline phosphatase activity[21]. Other researchers[22] have shown both in *in vitro* and *in vivo* experiments the dependence of bone formation on the technology used to create a porous titanium surface. For this, they compared titanium samples with a porous titanium coating created using titanium plasma spray (TPS) and two 3D printing techniques: The powder bed fusion and direct energy deposition (DED). In human osteoblast cultures, after 14 d of cultivation, the largest number of cells and the highest activity of alkaline phosphatase were established in tested DED samples. In an *in vivo* study in rabbits, the best integration at 6 wk after implantation into the distal femoral metaphysis, as determined by BIC%, was found in the DED group, but the difference disappeared at 12 wk[22].

In our study, we observed bone formation around both titanium specimens 45 d after their implantation without statistical difference in BIC%. The time frame in a rat model for bone tissue formation is similar to bone recovery under conditions of a closed fracture, which is reported at 42 d[23].

At 90 d postoperatively, we found a significantly higher BIC% for the 3D-printed highly porous titanium implant group compared to the plasma-coated titanium implant group. This may be due to the fact that in rats, newly formed bone tissue covers titanium implants by the 30th day, but the process of rebuilding the regenerate may last up to the 90th day[24]. Results similar to ours were reported in a sheep model, where two different types of titanium implants, one etched sandblasted and the other a porous surface were, studied. Better results were found for the porous material but only for the final observation period (56 d after index surgery)[25]. In addition, the positive influence of the porous material created with the help of 3D printing was observed, one finding was the proliferation of human 1.19 fetal osteoblast-like cells and calcium production compared to a TPS coated surface in orthopedic spinal implants[26].

In our study, autofluorescence of bone tissue was used, which made it possible to distinguish between bone trabeculae and bone marrow around titanium implants in the rat femoral sections. Bone autofluorescence is associated with the content of type I collagen[27], which is absent in bone marrow. Due to the above mentioned characteristic structures can be distinguished and bone sections can be analyzed without additional staining.

Our study is not without limitations, first of all the conducted research is limited by it's methodological simplicity, which is stipulated by the goal: *In vivo* evaluation to substantiate the utility of the use of porous titanium implants as acetabular components for patients with normal bone mass, as such we can not answer study questions about different bone qualities. At the same time, despite the already known results of effective osseointegration of porous titanium materials compared to smooth ones, there is a paucity of *in vivo* studies comparing porous titanium materials with plasma sprayed titanium acetabular components.

CONCLUSION

The use of a highly porous titanium implant, manufactured using 3D printing, for acetabular components showed a larger amount of bone tissue integration around it, thus it may provide better osseointegration compared to a plasma-coated titanium implant.

ARTICLE HIGHLIGHTS

Research background

Total hip arthroplasty is a common surgical treatment for elderly patients with osteoporosis and further discussion is needed if use of such acetabular components is justified under the condition of normal bone mass.

Research motivation

There is a need to perform studies to compare of osseintegration of two different types of titanium implants [3-dimensional (3D)-printed and plasma-coated titanium implants].

Research objectives

To determine the features of osseointegration of two different types of titanium implants (3D-printed and plasma-coated titanium implants) in bone tissue of a distal metaphysis in a rat femur model.

Research methods

This study was performed in a rat femur model. Histological examination of the femur was carried out by measuring the relative perimeter of bone trabeculae [bone-implant contact (BIC%)] and bone marrow surrounding of 3D-printed titanium implant (highly porous) and plasma-coated titanium implant.

Research results

Trabecular bone tissue was formed on the 45th day after implantation around the implants regardless of their type. Forty-five days after surgery groups with different implants did not differ in BIC%, but after 90 d, the BIC% was higher in 3D-printed titanium implant group.

Research conclusions

The use of a highly porous titanium implant, manufactured with 3D printing, for acetabular components provides increased osseointegration compared to a plasma-coated titanium implant.

Research perspectives

Further research studies on the use of other histological and biomechanical methods will help to determine the optimal materials of acetabular implants in terms of structure and complexity of their manufacture to be used in patients with normal bone mass.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design; Bondarenko S, Maltseva V and Ashukina N wrote the first draft version of the manuscript; Filipenko V supervised the study and performed critical revision of the article; Maltseva V performed data analysis and interpretation; Ivanov G, Lazarenko I and Sereda D performed experimental surgery, collection and interpretation data; Schwarzkopf R performed critical revision of the article; all authors revised and approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Sytenko Institute of Spine and Joint Pathology Review Board.

Institutional animal care and use committee statement: All applicable national guidelines for the care and use of animals were followed. The *in vivo* study was approved by the Ethical Clearance Bioethics Committee State Institution (Sytenko Institute of Spine and Joint Pathology NAMS of Ukraine), Kharkiv, Ukraine (protocol number 211 of 01 Feb 2021).

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Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Epidemiology of shoulder dislocations presenting to United States emergency departments: An updated ten-year study

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Abstract

BACKGROUND

Glenohumeral dislocation is a common injury that may predispose patients to chronic pain and instability. However, there is a paucity of current data available regarding the epidemiological trends of this injury.

AIM

To provide an updated, comparative assessment of the epidemiology of shoulder dislocations presenting to emergency departments in the United States. We also sought to analyze patient demographic risk factors and consumer products associated with dislocation events.

METHODS

Data were obtained from the national electronic injury surveillance system database for glenohumeral dislocations between 2012 and 2021. Incidence, age, sex, and injury characteristics were analyzed using weighted population statistics as well as incidence rates and 95% confidence intervals (CI).

RESULTS

In total, an estimated 773039 shoulder dislocations (CI: 640598-905481) presented to emergency rooms across the United States during the study period. The annual

incidence rate was 23.96 per 100000 persons and the average patient age at the time of injury was 37.1 years. Significantly more male patients sustained dislocations than female patients (537189, 69.5%, *vs* 235834, 30.5%, $P < 0.001$). With regard to associated consumer products, sports and recreation equipment were involved in the highest proportion of incidents (44.31%), followed by home structures and construction materials (21.22%), and home furnishings, fixtures, and accessories (21.21%). Regarding product sub-groups, stairs, ramps, landings, floors was cited in the greatest number of cases (131745).

CONCLUSION

The national annual incidence rate of glenohumeral dislocations throughout the study period was approximately 23.92 per 100000 persons. Male adolescents sustained the highest proportion of dislocations, with a peak incidence in age group 15-20 years, predominantly secondary to participation in sporting and recreational activities. Conversely, women experienced a relatively consistent incidence of dislocation throughout their lifespan. After age 63, the incidence rate of dislocations in females was found to surpass that observed in males.

Key Words: Shoulder dislocation; Epidemiology; United States; Emergency department; Glenohumeral dislocation; national electronic injury surveillance system

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Core Tip: Shoulder dislocations occur in a bimodal distribution and are commonly seen in young men and older women. The national incidence of shoulder dislocations presenting to United States emergency departments has remained relatively stable compared to previous epidemiologic studies. Among young patients sustaining shoulder dislocations, sporting and recreational activities are the most involved activities.

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INTRODUCTION

The glenohumeral joint is the most mobile joint in the body, making it particularly vulnerable to dislocation[1]. This physiologic predisposition makes shoulder dislocation a common injury across age groups-especially in young, physically active men[2-5]. Existing studies have estimated the incidence of shoulder dislocation to be 23.9 per 100000 person-years in the general population, with rates as high as 169 per 100000 person-years among young, active, and military populations[3,5-7]. Patients with shoulder dislocations often experience lasting functional impairments and are known to be at high risk for recurrent injury[1,8]. Despite the high incidence of shoulder dislocations experienced in the United States, there is a paucity of current epidemiological data available regarding general population risk factors and etiology.

While young populations have the highest incidence of shoulder dislocation, these injuries have a bimodal age distribution, affecting both the young and elderly at higher rates[6,9]. Unsurprisingly, the etiology of shoulder dislocation varies with patients' age as the activities they routinely engage in change. Older patients classically sustain shoulder dislocations as the result of a fall, whereas younger patients are more likely to experience injury while participating in sporting and recreational activities[6]. Because of these observed differences in the mechanism of injury for shoulder dislocations across age groups, there is an interest in exploring the relationship between consumer products and patient demographics as it relates to shoulder dislocation events.

The purpose of this study is to provide an updated, comparative assessment of the epidemiology of shoulder dislocations presenting to emergency departments in the United States. We also sought to analyze patient demographic risk factors and consumer products as-sociated with dislocation events. We hypothesized that consumer products involved with shoulder dislocations would vary depending on patient age and gender, with male adolescents utilizing sports and recreation equipment representing the highest incidence of dislocations.

MATERIALS AND METHODS

Database and Query

Data for this cross-sectional, epidemiologic study of glenohumeral dislocations that present to United States emergency departments was obtained from the national electronic injury surveillance system (NEISS) database[10,11]. The NEISS database collects de-identified patient demographics, injury characteristics, and associated consumer product information

from approximately 100 emergency departments across the United States. Data was obtained by a hospital coordinator assigned to the facility and acquired from both clinical information and follow-up telephone communication as needed. These data points are then extrapolated to establish national estimates for each category after weighing each hospital. NEISS is managed by the Consumer Product Safety Commission, who have been responsible for collecting this data since 1999. This organization makes annual adjustments by weighting probabilities of each of the included emergency departments, then uses the number of annual emergency department visits to establish their calculated national estimates [12,13].

The NEISS database was queried for a 10-year period between 2012 and 2021. All age groups were included in the study. "Shoulder (30)" was selected for body part and "dislocation (55)" was selected for diagnosis for all queries. Information was further stratified by age, gender, product group, and product sub-group.

Statistical Analysis

When querying data from the NEISS database, 95% confidence intervals (CI) were calculated based on input requests. Following data acquisition, incidence rates were calculated per 100000 persons. Unstable data, characterized by a national estimate of less than 1200, number of cases less than 20, or coefficient of variation exceeding 33%, were excluded from data analysis, based on NEISS database outputs. Sub-group analysis was performed comparing ages over and under 40 years. This comparison essentially split life expectancy in half (currently approximately 79 years) and compared "early life" and "later life" with known bimodal distribution of patient age[14]. Chi-squared tests were used to compare categorical variables between cohorts. A P value < 0.05 was used to determine statistical significance.

RESULTS

In total, an estimated 773039 (CI 640598-905481) shoulder dislocations presented to emergency departments between 2012–2021 across the United States (Table 1). The annual incidence rate was 23.96 per 100000 persons (CI 19.86-28.07). Average age at time of injury was 37.1 +/- 22.0 years. Male patients accounted for a greater proportion of shoulder dislocations than female patients (537189, 69.5%, *vs* 235834, 30.5%, P < 0.001). Young males accounted for the highest proportion of dislocations, with 17.70% of all dislocations occurring in males aged 15-20 years. The incidence rate for this demographic was observed to be 106.91 per 100000 persons (95%CI: 84.24-129.57).

The largest number of dislocations occurred in patients 17 years old (national estimate 30796, 3.98%). The peak age for dislocation was 18 years in males (national estimate 26661, 4.96% of males) and 66 years in females (national estimate 4833, 2.05% of females). Young males experienced a higher dislocation rate and reached a relative plateau around age 40. Conversely, females had a relatively stable rate of dislocations throughout all age groups and the incidence increased in their later decades. The incidence rate of dislocations in females surpassed that of males at approximately age 63 years. The overall rate per year of shoulder dislocations by gender and age is seen in Figure 1.

The NEISS database divides consumer products into broad categories, which were analyzed to determine overall injury patterns (Table 2). Sports and recreation equipment were associated with 44.31% (365348) of dislocations, followed by home structures and construction materials (21.22%), and home furnishings, fixtures, and accessories (21.21%).

In an analysis of sub-groups, stairs, ramps, landings, floors were associated with the greatest number of dislocations (131745, 14.0%), with a predominance noted among patients ≥ 40 years (9.6% for ≤ 39 years, 28.4% for ≥ 40 years, P < 0.001) and females (12.0% for males, 28.6% for females, P < 0.001). Among sport and recreational activities, most dislocations occurred during basketball (56600) followed by football (45167). A more throughout breakdown of this information is seen in Table 3.

Specific analysis of males aged 15-20, previously identified as having the highest incidence of dislocation, was undertaken (Table 4). In this group of young males, 82.88% (113421) of dislocations were associated with sports and recreation equipment[3,6]. Specifically, basketball (18.60%) and football (18.59%) were involved in the greatest number and percentage of dislocations. Eight of the top ten subcategories for this age group involved sports and recreation equipment.

DISCUSSION

This study represents a current analysis of the epidemiology of shoulder dislocations presenting to emergency departments in the United States from 2012-2021. The national annual incidence rate throughout the study period held was approximately 23.92 per 100000 persons. Male adolescents sustained the highest proportion of dislocations, with 17.70% of all dislocations occurring in males aged 15-20 years, predominantly resulting participation in sports and recreation equipment. Conversely, women experienced a relatively consistent incidence of dislocation throughout their lifespan. After age 63, the incidence rate of dislocations in females surpassed that observed in males.

The findings of this study align with the existing literature. We observed an annual incidence rate of 23.92 per 100000 throughout the study period. Similarly, Zacchilli *et al*[6] noted an incidence of 23.9 per 100000 person-years in a study analyzing NEISS data between 2002 and 2006. Of note, a study by Owens *et al*[3] reported a much higher incidence rate of dislocations among United States Military Academy cadets at 169 per 100000 person-years, although their study was comprised of primarily young, physically active males. Additionally, other studies have reported dislocation rates among young, physically active patients to be as high as seven times greater than that observed in the general population[6,9]. These findings agree with the results of our analysis, which noted male adolescents to account for the greatest number of

Table 1 Total weighted national electronic injury surveillance system estimates, rate per year, national incidence, and demographics, for all United States shoulder dislocations between 2012 and 2021

	National estimate	95%CI
Total	773039	640598-905481
Rate per year	77304	64060-90548
Incidence per 100000	23.92	19.86-28.07
	Mean	St. Deviation
Age	37.1	22.0
Gender	National estimate	Percent
Male	537189	69.5%
Female	235834	30.5%

CI: Confidence intervals.

Table 2 Total weighted national electronic injury surveillance system estimates for all United States shoulder dislocations between 2012 and 2021, by consumer product categories

Consumer product category	National estimate	Percent of cases
Sports and recreation equipment	365348	44.31%
Home structures and construction materials	174975	21.22%
Home furnishings, fixtures, and accessories	174883	21.21%
Personal use items	32235	3.91%
Packing and containers, household	15511	1.88%
Home communication, entertainment and hobby	13940	1.69%
Yard and garden	8943	1.08%

shoulder dislocations presenting to emergency departments.

The current study found an estimated total reported cases of 136844 men 15-20 years old, which made up for 17.70% of the total cases reported in this study, with an annual incidence of 106.91 per 100000. These results are higher to those of similar studies in other countries which found men 16-20 years old to have an incidence of 80.5 per 100000 in the United Kingdom and 98.3 per 100000 in Canada[15,16]. Studies have attributed this difference in rates of injury to the prevalence of competitive contact sports played among men within this age range in the United States and Canada (American football and ice hockey) compared with their peers in the United Kingdom[15]. Further, it was observed that in this population, 113421 (82.88%) of the injuries occurred while using sports and recreational equipment. This finding is consistent with prior studies that have analyzed the incidence of this injury among young athletes and military populations[3,4,17,18].

During our study period, women were found to account for less than one third of dislocations presenting to emergency departments and previous studies have reported a similarly low incidence of this injury in women when compared to men[7,15,16]. However, the incidence of shoulder dislocation in women was noted to surpass that of men after the age of 63. This aligns with existing data demonstrating a higher dislocation rate in women after the sixth decade[7,15]. While this discrepancy is poorly understood, we hypothesize that it may be due to a combination of biological differences between men and women as they age, such as muscle bulk and tendon strength, as well differences in the rate of falls between sexes[19,20]. Interestingly, over 60% of dislocations events in female patients were associated with home furnishings, fixtures, or structures. This suggests a need for separate preventative measures and strategies for older female patients from the already established sports-related strategies directed at young males. Further research is necessary to fully understand underlying differences in risk between patient demographics and may assist in the development of preventative measures aimed at decreasing the burden of shoulder dislocations associated with falls in the elderly[21].

Of note, there were too few recorded cases of shoulder dislocation in children younger than 12 years to provide national estimates, suggesting that this is a relatively rare injury among this demographic. One existing study reporting on the epidemiology of pediatric shoulder dislocation in Italy demonstrated an incidence of 0.3 per 100000 inhabitants less than age 14[22]. The low incidence of shoulder dislocation in pediatric patients may be explained by skeletal immaturity as the mechanisms of injury generally associated with dislocation are more likely to cause proximal humerus fractures or physeal injury in patients whose physis has not yet closed[23].

Table 3 Total weighted national electronic injury surveillance system estimates for all United States shoulder dislocations between 2012 and 2021, for the top ten product sub-groups, with subgroup analysis for age ≤ 39 and ≥ 40 years, and gender

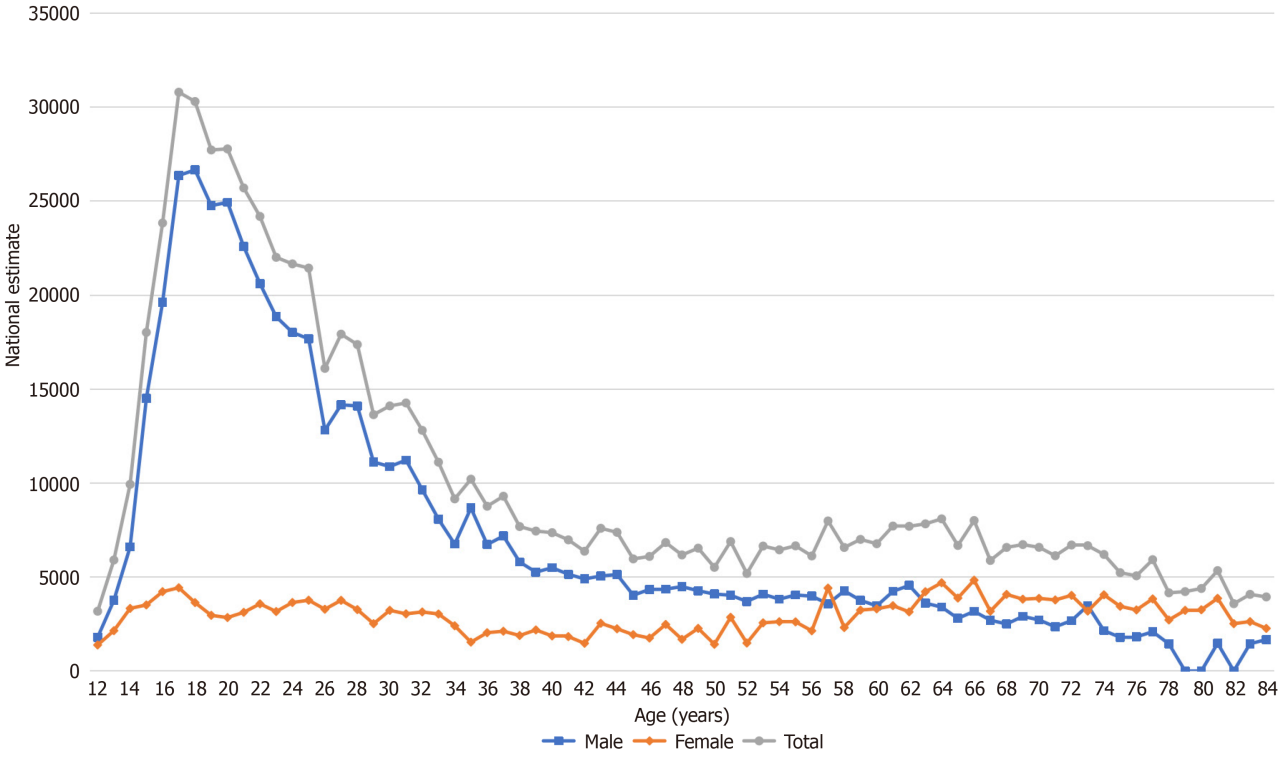
Rank	Product sub-group	National estimate	≤ 39	Percent (%)	≥ 40	Percent (%)	Male	Percent (%)	Female	Percent (%)
1	Stairs, ramps, landings, floors	131745	45193	9.6	86551	28.4	64235	12.0	67510	28.6
2	Beds, mattresses, pillows	76778	45200	9.6	31579	10.4	48119	9.0	28660	12.2
3	Basketball	55226	53619	11.4	1607	0.5	51081	9.5	4145	1.8
4	Football	43158	42172	9.0	[1]	[1]	42006	7.8	[1]	[1]
5	Exercise and equipment	39052	26388	5.6	12665	4.2	26836	5.0	12216	5.2
6	Bicycles and accessories	32789	15733	3.4	17040	5.6	28600	5.3	4189	1.8
7	Clothing, all	26832	12714	2.7	14118	4.6	13653	2.5	13180	5.6
8	Ladders, stools	22372	4930	1.1	17442	5.7	17529	3.3	4842	2.1
9	Bathtub and shower structures	21640	8861	1.9	12779	4.2	11076	2.1	10564	4.5
10	Chairs, sofas, and sofa beds	21193	8143	1.7	13050	4.3	10667	2.0	10526	4.5
Total		773039	468458		304566		537189		235834	

[1]Estimates denoted by have at least one of the following unstable characteristics and were not returned: Estimate is less than 1200, number of cases is less than 20, coefficient of variation exceeds 33%.
$P < 0.001$ age groups *vs* gender groups.

Table 4 Total weighted national electronic injury surveillance system estimates for shoulder dislocations among males aged 15-20 years between 2012 and 2021, including the top ten product sub-groups

		National estimate	95%CI
	Total	136844	107830-165857
	Rate per year	13684	10783-16586
	Incidence per 100000	106.91	84.24-129.57
Rank	Product sub-group	National estimate	Percent
1	Basketball	25448	18.60%
2	Football	25435	18.59%
3	Beds, mattresses, pillows	7314	5.34%
4	Exercise and equipment	6350	4.64%
5	Miscellaneous sports	5941	4.34%
6	Soccer	5772	4.22%
7	Skateboards, scooters, hoverboards	5771	4.22%
8	Stairs, ramps, landings, floors	5627	4.11%
9	Swimming activity, pools, equipment	5440	3.98%
10	Baseball/softball	5163	3.77%

CI: Confidence intervals.



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Figure 1 Total weighted national electronic injury surveillance system estimates per year for all United States shoulder dislocations between 2012 and 2021, by age in years and gender. There was insufficient data to provide national estimates for ages < 12 and > 84 years, as well as males ages 79, 80, and 82.

This study was not without its limitations. As with any database, the scope of this study is limited to variables obtained by data collectors and does not include patients who presented to primary care, urgent care, or sports medicine clinics. Because the provided totals are weighted estimates based on a probability sample of emergency room visits, the numerical estimates could be subject to sampling bias and therefore may not represent the true incidence of injury in the defined study population. Additionally, it is possible that errors were made while coding these injuries and their associated consumer products within the NEISS. Furthermore, logging products into broad categories relies on the coder's judgment and this carries bias. Due to the nature of the NEISS database, we were unable to retrieve more detailed information regarding specific consumer products associated with injury, nor where we able to retrieve exact mechanism of injury. Lastly, the database did not differentiate between anterior and posterior shoulder dislocations, nor did it indicate whether dislocation events were primary or recurrent. It is possible that the presence of patients with multiple recurrent dislocations may contribute to a falsely elevated incidence rate[6].

CONCLUSION

The national annual incidence rate throughout the study period was approximately 23.92 per 100000 persons. Male adolescents sustained the highest proportion of dislocations, with peak incidence occurring in age 15-20 years, predominantly secondary to participation with sports and recreation equipment. Conversely, women experienced a relatively consistent incidence of dislocation throughout their lifespan. After age 63, the incidence rate of dislocations in females was found to surpass that observed in males.

ARTICLE HIGHLIGHTS

Research background

This research was conducted to examine temporal trends regarding shoulder dislocations in the Untied States.

Research motivation

Shoulder dislocations are common among all populations, especially young men, and understanding the epidemiology is important for orthopedic surgeons.

Research objectives
To provide and updated assessment of the epidemiology of shoulder dislocations in the United States.

Research methods
Emergency department within the United States was collected using the national electronic injury surveillance system database between 2012 and 2021, and epidemiologic data was collected and analyzed for shoulder dislocations.

Research results
The national annual incidence of shoulder dislocations in the United States was approximately 23.92 per 100000 persons, with a predominance of dislocations occurring in male adolescents between the ages of 15-20.

Research conclusions
There is a bimodal distribution of shoulder dislocations in the United States. A large portion of male adolescent sustain these injuries between the ages of 15-20 secondary to participation in sporting events. Conversely, women have a relatively consistent incidence of dislocations in their lifespan with an increase in their later decades of life.

Research perspectives
Future studies should help create measures to help lower the incidence of shoulder dislocations in at risk population, particularly adolescent males participating in sports.

FOOTNOTES

Author contributions: Patrick CM performed the majority of the research, collected data, analyzed data, and contributed to the manuscript; Snowden J and Eckhoff MD contributed equally to this work by performing research, and contributing to the manuscript and background research; Green CK and Scanaliato JP oversaw manuscript revisions and project design; Dunn JC and Parnes N designed the research study, coordinated the research team, and oversaw final manuscript revisions; All authors have read and approve the final manuscript.

Institutional review board statement: All data used in the following manuscript are deidentified and available online through the United States Consumer Product Safety Commission.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Sclerotherapy as a primary or salvage procedure for aneurysmal bone cysts: A single-center experience

Kolja Sebastian Weber, Claus Lindkær Jensen, Michael Mørk Petersen

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Abstract

BACKGROUND

Aneurysmal bone cysts (ABC) are benign cystic bone tumors of an osteolytic and locally aggressive nature. As an alternative to the primary treatment of choice, which consists of curettage with bone grafting, alternative treatment methods with promising results have been described. At our department, we have, in recent years, used percutaneous sclerotherapy with polidocanol. The objective of this study was to identify the healing rate and safety of sclerotherapy with polidocanol.

AIM

To identify the efficacy and safety of sclerotherapy with polidocanol in primary and recurrent ABC.

METHODS

Twenty-two consecutive patients (median age 12.5 years; range 1-27) with 23 ABCs treated with sclerotherapy with polidocanol from 2016-2021 were included retrospectively. Eleven patients (48%) had undergone different forms of previous treatment with recurrence. Under general anesthesia and fluoroscopic guidance, repeated percutaneous injections of 4mg polidocanol/kg body weight were performed. Through review of the electronic medical records, the following were identified: healing and recurrence rate, number of treatments, gender, age, comorbidity, location of the tumor and side effects / complications, as well as any previous surgery for ABC. The median length of radiographic follow-up was 19.5 mo.

RESULTS

All ABCs except one (96%) showed healing or stable disease after a median of 4 (range 1-8) injections. Complete clinical and radiographic healing was observed in 16 cysts (70%), while partial radiographic healing with resolution of pain was seen in 6 cases (26%) and considered as stable disease. The cyst that failed to heal had

previously undergone curettage twice with recurrence. One patient with a large pelvic ABC experienced, right after two injections, a sudden drop in blood pressure, which could quickly be reversed. One patient with a juxtaphyseal ABC in the femoral neck showed a minor limb length discrepancy because of deformity. Beyond that, no complications were observed.

CONCLUSION

Percutaneous sclerotherapy with polidocanol appears to be a safe alternative for treatment of aneurysmal bone cysts. In our series of both primary and recurrent cysts, it showed the ability to achieve healing or stable disease in 22 of 23 cases (96%). Further studies are needed to decide if this provides a long-lasting effect.

Key Words: Aneurysmal bone cyst; Bone tumor; Sclerotherapy; Polidocanol; Healing rate; Complications

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Core Tip: This retrospective study presents the first outcomes after implementation of sclerotherapy for aneurysmal bone cysts (ABC) at our department. Compared to other series, 48% of our cohort consisted of patients with recurrent ABC after previous treatment or failed surgery. Sclerotherapy showed a high potency to achieve healing or stable disease and a low rate of adverse events in both treatment groups. We can recommend it as standard treatment both for primary and recurrent ABC, keeping in mind that randomized multicenter studies would be needed to provide evidence for the superiority of one treatment method.

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INTRODUCTION

Aneurysmal bone cysts (ABC) are rare benign bone tumors, usually affecting children and adolescents[1]. Patients mostly present with pain, with or without swelling, and sometimes with a pathological fracture.

Radiologically, these lesions are expansile and osteolytic and can be locally aggressive (Figure 1). On magnetic resonance imaging (MRI), fluid-fluid levels are diagnostic, and soft tissue expansion can be seen. It is the gold standard to verify the diagnosis with biopsy.

The traditional treatment, curettage and bone grafting, has shown high rates of morbidity and recurrence[1-4]. As a result of that, several other treatment options have been explored: embolization, radiotherapy, wide excision and sclerotherapy with different agents and more[5-9]. In recent years, percutaneous sclerotherapy, especially with polidocanol, alcohol or doxycycline, has shown promising results with similar recurrence rates and low morbidity compared to open surgery[10-17]. There are several series published with polidocanol as primary treatment, but to our knowledge, there are no larger reported series on polidocanol as a salvage procedure. In our series, 48% of the cysts were treated with polidocanol for failed surgery or recurrence after previous treatment.

In this study, we present our experience with percutaneous polidocanol treatment for primary and recurrent ABC with focus on healing rate, recurrence and complications.

MATERIALS AND METHODS

In this single-center retrospective study design, all patients treated for ABC with percutaneous sclerotherapy from 2016-2021 were included. In 2016, sclerotherapy was introduced as standard therapy for primary and recurrent ABCs at our institution. Through review of the electronic medical records, the following data was identified: healing and recurrence rate, number of treatments, gender, age, comorbidity, location of the tumor, side effects and complications, as well as any previous surgery for ABC. Twenty-two patients with a combined number of 23 ABCs were identified. The various characteristics are shown in Table 1. Imaging at first presentation included conventional radiographs and MRI in all patients. Furthermore, a histological sample was available in all patients, either from previous surgery or collected with open biopsy. In five patients, open biopsy was performed simultaneously with the first sclerosant injection (Figure 2).

Sclerotherapy was performed under general anesthesia. The cyst was punctured percutaneously with a 1.0 or 1.2 mm trocar needle under fluoroscopic guidance. In classic ABC, bloody fluid from the cyst can be aspirated at the beginning of treatment. The cyst was injected with 4 mg Polidocanol (Aethoxysklerol®) per kilogram bodyweight, as described by Brosjö *et al*[10], mixed with contrast agent Iohexol (Omnipaque®). Before injection, the needle with trocar was directed in all cystic areas to break down possible septae. During injection, contrast agent was used to ensure that all parts of the cyst

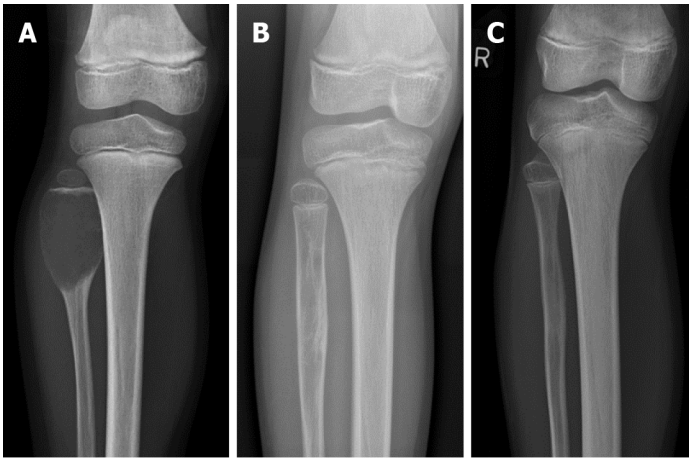
Table 1 Demographic data and treatment details

Patient-ID	Age at presentation	Gender	Location	No. of injections	Ossification	Previous treatment	Follow-up (mo)	Histologic result
1	13	M	Pubic bone	5	Complete	Curettage + bone graft	13	Classic ABC
1	13	M	Sacrum	3	Partial	None	13	Consistent with ABC
2	13	F	Distal fibula	5	Absent	Two curettages + bone graft	37	Classic ABC
3	10	M	Ischium	6	Partial	None	29	Classic ABC
4	6	M	Scapula	7	Partial	None	24	Classic ABC
5	25	F	Proximal femur	3	Partial	Two curettages + bone graft	8	Classic ABC
6	14	M	Ileum	6	Partial	None	16	Consistent with ABC
7	4	M	Distal fibula	3	Complete	None	4	Consistent with ABC
8	12	F	Distal tibia	1	Complete	Curettage + bone substitute	31	Classic ABC
9	16	M	Proximal tibia	4	Complete	Curettage + bone graft	33	Classic ABC
10	6	M	Distal tibia	8	Complete	Triamcinolone injection	47	Consistent with ABC
11	5	F	Proximal fibula	3	Complete	Curettage + bone substitute	38	Classic ABC
12	15	M	Ischium	2	Partial	None	4	Consistent with ABC
13	14	M	Distal fibula	4	Complete	Curettage + bone graft	23	Classic ABC
14	25	M	Acetabulum	1	Complete	Two curettages + bone graft	35	Classic ABC
15	10	F	3. metatarsal	4	Complete	Curettage + bone substitute	19	Classic ABC
16	10	M	Proximal femur	3	Complete	None	26	Classic ABC
17	27	M	Proximal radius	1	Complete	None	11	Classic ABC
18	16	M	Proximal fibula	5	Complete	None	6	Classic ABC
19	18	M	Proximal femur	2	Complete	Three curettages + bone graft	20	Consistent with ABC
20	9	M	Ischium	4	Complete	None	16	Classic ABC
21	7	F	Distal tibia	6	Complete	None	5	Classic ABC
22	1	F	Proximal femur	6	Complete	None	9	Classic ABC

ABC: Aneurysmal bone cysts.

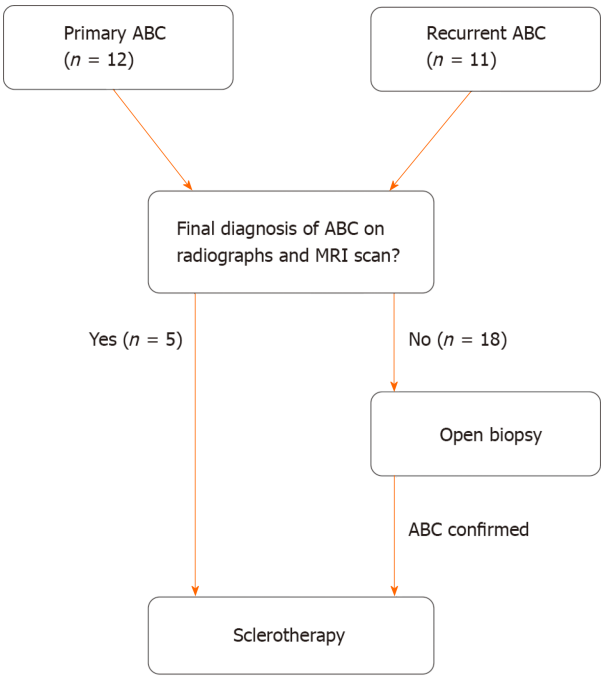
were treated (Figure 3). After injection, the needle was flushed with saline or previously aspirated blood, and after needle removal, pressure was applied at the site for at least two minutes to prevent extravasation.

The procedure was repeated every 4-6 wk, following the example of Brosjö *et al*[10], until satisfactory radiographical and clinical healing of the cyst was seen. Healing was defined as resolution of pain on clinical examination in addition to complete ossification on radiographs (Figures 1 and 4). Partial ossification or stable disease was determined as resolution of pain on clinical examination in addition to thickening of cortex and partial ossification without increase in cyst size on radiographs (Figure 5). The median radiographic follow-up was 19.5 mo (range: 4-47 mo).



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Figure 1 Radiographs of an aneurysmal bone cyst in the proximal fibula of a 5-year-old girl. A: At presentation; B: After three injections of polidocanol; C: At 38 mo follow-up



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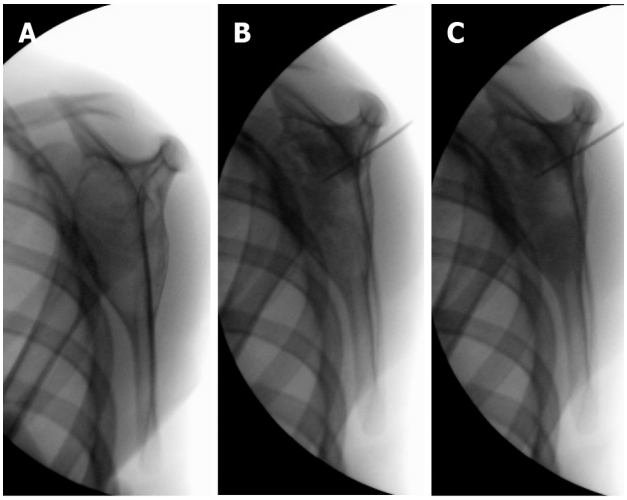
Figure 2 Flowchart of the algorithm from initial diagnosis to final management. ABC: Aneurysmal bone cysts; MRI: Magnetic resonance imaging.

RESULTS

The summary of the patient characteristics and treatment results is shown in Table 1. The median age at beginning of treatment was 12.5 years (range: 1-27), and males accounted for 68% of patients. Of the 23 cysts, eleven had undergone previous surgical intervention (48%) with subsequent recurrence, wherein ten cysts had been treated with curettage and bone grafting/bone substitute and one with glucocorticoid injection (for details see Table 1). Histopathologically, the diagnosis was confirmed in 17 cases, and in the remaining six cases, the sample was consistent with aneurysmal bone cyst. There were no tumors with an ABC-like area (previously called secondary ABC) or malignancies.

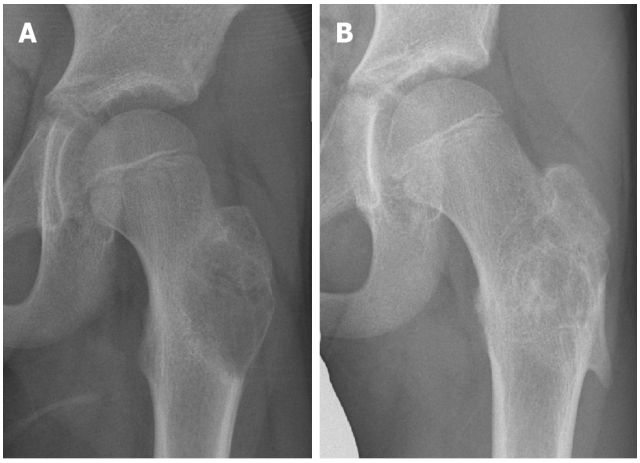
All cysts except one (96%) showed healing or stable disease after a median of four (range: 1-8) injections. Complete ossification was observed in 16 cysts (70%), while partial ossification with complete resolution of pain were seen in six cases (26%), which were considered as stable disease. There were no recurrences in the follow-up period.

The cyst in the distal fibula that failed to heal had previously undergone curettage twice with recurrence. During the course of five polidocanol injections, it showed recurring radiolucency in different parts of the cyst, and the patient displayed persistent pain. Finally, extended curettage with high-speed burring and bone grafting with polidocanol as adjuvant was performed, and the cyst healed without recurrence.



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Figure 3 Intraoperative fluoroscopy images showing sclerotherapy of an aneurysmal bone cyst in the scapula. A: Before injection; B: During injection with polidocanol and contrast agent; C: After injection



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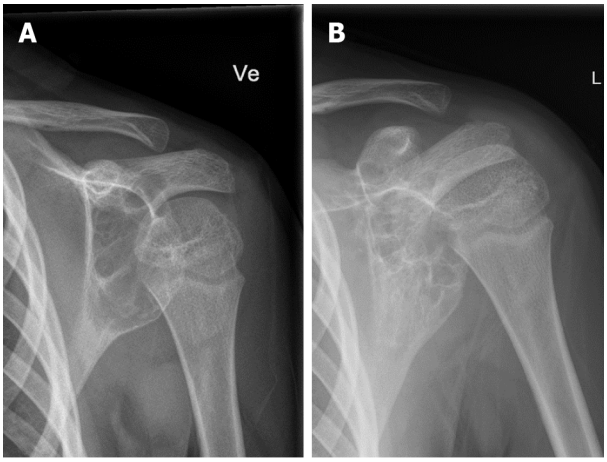
Figure 4 Radiographs of an aneurysmal bone cyst in the proximal femur showing complete ossification. A: At presentation; B: At 26 mo follow-up after sclerotherapy.

Due to a possible allergic reaction, one patient with a large cyst in the ischium showed a sudden drop in blood pressure to 60 mmHg systolic right after injection of polidocanol/iohexol in two settings, which could quickly be reversed after a bolus of ephedrine and fluid.

One patient with a juxtaphyseal ABC in the femoral neck, who was only 18 mo old at the beginning of treatment, developed a minor limb shortening because of deformity in the trochanteric area at 9 mo follow-up, possibly requiring further orthopedic treatment in the future. Beyond that, no complications, such as skin necrosis or infections, were observed.

DISCUSSION

In this study, we present our experience with percutaneous sclerotherapy of ABC with polidocanol. In our series, 96% of all cysts showed satisfactory treatment response with complete resolution of pain, with 70% showing complete ossification and 26% showing partial ossification without increase in cyst size. There were no recurrences in the follow-up period, but one cyst failed to heal, and treatment was converted to extended curettage and bone grafting with polidocanol as adjuvant. The healing rate of 96% in this study is comparable to the results published in recent literature, with healing rates ranging from 83%-100%[10-13,17-20], except for one study discussed further below. The studies comparing sclerotherapy with polidocanol with curettage found healing rates slightly in favor of sclerotherapy (93.3% *vs* 84.8% and 100% *vs* 82%, respectively) and showed lower morbidity in the sclerotherapy group[11,17].



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Figure 5 Radiographs of an aneurysmal bone cyst in the scapula showing partial ossification. A: At presentation; B: At 24 mo follow-up after sclerotherapy.

There is no agreement about the clear definition of successful treatment, or healing, in the literature. As applied in this study, most authors accept the following clinical and radiological signs as successful treatment: Resolution of pain, restoring of function, increasing sclerosis and cortical thickness without increase in cyst size[12,13,17,18].

One study showed less favorable results in both groups: Failure of sclerotherapy with polidocanol and need for further treatment in 34.5% of cases as well as a 38.5% recurrence rate with need for further treatment after intralesional curettage [21]. The authors find a possible explanation for these less satisfactory results in the more accurate cyst size measurement based on MRI scans and higher initial cyst volume in their study compared to similar studies[21]. Furthermore, MRI scans might be more sensitive to detect residual cyst activity (*i.e.*, fluid-fluid levels) than conventional biplanar radiographs, though the clinical importance of this finding remains unclear.

Apart from polidocanol, other sclerosing agents have been used for ABC with promising results. Publications on sclerotherapy with ethanol (in one study combined with Surgiflo®) and doxycycline showed success rates ranging from 68%-100% and 86%-100%, respectively, making them comparable to treatment with polidocanol[14,15,22-25]. At this stage, no sclerotherapy modality has been proven superior, and the treatment choice is usually dependent on regional preference and experience.

The general disadvantage of sclerotherapy is the need for repeated treatments in most cases, which, in this patient age group, usually requires general anesthesia.

Our cohort consisted of 12 primary ABCs and 11 cysts that had undergone previous surgical intervention with subsequent recurrence. To our knowledge, there are no larger reported series on polidocanol as a salvage procedure. In this series, 10 of the 11 recurrent ABCs (92%) showed satisfactory treatment response after sclerotherapy (Table 1).

One recurrent cyst, which had previously undergone curettage twice, failed to heal. Five injections of polidocanol were performed, but the patient showed persistent pain, and radiologically recurrent osteolytic areas were observed in different parts of the cyst. Finally, extended curettage with high-speed burring and bone grafting with polidocanol as adjuvant was performed, and the cyst healed without recurrence. We argue that it can be difficult to address all areas of a recurrent cyst, which in some cases consists of many subcavities. Especially if there are bony septae, it can be challenging to reach a certain subpart of the cyst percutaneously.

There are other described methods for ABC as salvage treatment or in patients where sclerotherapy or open surgery are contraindicated or not feasible. Selective arterial embolization has shown good results and is primarily used in the spine and other anatomically difficult locations, as well as a preoperative adjuvant to surgery. However, it is a technically demanding, operator-dependent procedure with potentially serious side effects due to ischemia, and it requires that a feeding vessel to the cyst can be identified[26,27].

Furthermore, there are pharmacological treatments available as rescue therapy for ABC. In several studies, denosumab, a monoclonal antibody inhibiting osteoclast formation and activity, has been shown to achieve re-ossification of ABC[6, 28-30]. However, serious side effects have been described. Some patients demonstrated severe hypo- or hypercalcemia under or after denosumab treatment[30,31]. Moreover, knowledge regarding the long-term consequences of denosumab on the growing skeleton is lacking so far. A related medical therapy is the use of bisphosphonates, such as zoledronic acid, which also inhibits osteoclast activity. They are widely used to successfully treat and manage various unresectable or metastatic bone tumors. Two smaller studies, with five and eight patients, respectively, have shown positive clinical and radiological effects of bisphosphonates in ABC without adverse events[32,33]. The authors even suggest bisphosphonates as treatment of choice in spinal ABC without neurological deficit or instability[32].

Based on the results of the present study, sclerotherapy with polidocanol might be another alternative salvage procedure to stabilize refractory or recurrent ABC. It can be considered before advancing to salvage treatments with a spectrum of more serious adverse events, as described above. However, further studies with more patients and longer follow-ups are needed to decide whether this is of lasting effect.

There was one adverse event observed in our cohort: A ten-year-old boy with a large cyst in the ischium showed a sudden drop in blood pressure to 60 mmHg systolic right after injection of polidocanol/iohexol in two settings. The reaction could quickly be reversed after a bolus of ephedrine and fluid. This phenomenon has also been described by other authors[18,34]. Like in the present study, it is usually harmless and quickly reversible, but in two cases, severe reactions have been described: One patient developed hypovolemic shock and cardiac arrest needing resuscitation, and the other one presented ventricular tachycardia with a sharp drop in blood pressure[18,34]. Both patients are reported to have recovered completely, but these observations necessitate this procedure only to be performed in a controlled setting with monitoring of vital signs.

Other authors reported minor complications to sclerotherapy, *e.g.*, skin induration, hypopigmentation, minor inflammatory reactions, ulceration or temporary pain[10,12,13,17,19,20]. On the other hand, the studies comparing sclerotherapy to curettage and/or resection found a higher rate of clinically pertinent complications and poorer functional outcomes in the surgery group[11,17,21].

One important limitation of this study is the short radiological follow-up in some patients. The retrospective study design meant that the follow-up was planned individually by the treating surgeon, not following a standard plan. Some patients showing signs of healing and resolution of pain in the first year after treatment were discharged and informed to contact our department again should pain or other symptoms recur. For these patients, our department is the responsible center for treating ABCs. The electronic medical journal showed no contacts to our or other hospitals in the region concerning their previous ABC in the following months and years. Furthermore, it was ensured that the place of residence was still in our region. The authors therefore argue that recurrence with clinical signs most likely would have been detected in these patients.

The other limitations of this study consist primarily of the number of patients, the retrospective study design and the lack of a control group. Randomized multicenter studies would be needed to provide evidence for the superiority of one treatment method for aneurysmal bone cysts.

CONCLUSION

This study supports evidence in the current literature that percutaneous sclerotherapy with polidocanol is an efficient and safe alternative to conventional surgery for the treatment of aneurysmal bone cysts. It can especially be recommended for cysts in difficult anatomic locations where open surgery would cause significant morbidity. Based on the present study, it may also be considered as a salvage procedure for failed surgery or multiple recurrences. Further studies are needed to decide if this provides a long-lasting effect and which of the discussed treatment methods is superior for primary or recurring aneurysmal bone cysts.

ARTICLE HIGHLIGHTS

Research background

As an alternative to the traditional treatment of aneurysmal bone cysts (ABC), which consists of curettage with bone grafting, alternative treatment methods with promising results have been described. At our department, we have been using percutaneous sclerotherapy with polidocanol for primary and recurrent ABC. To our knowledge, this is the first larger series reporting on polidocanol as a salvage procedure.

Research motivation

The main challenge with aneurysmal bone cysts is their locally aggressive nature and a high risk of recurrence. Therefore, there is a need to find evidence for the best available treatment, which optimally shows high efficacy and at the same time low morbidity and low rates of recurrence.

Research objectives

The main objective was to identify the efficacy and safety of sclerotherapy with polidocanol in primary and recurrent ABC. The outcomes of this study, especially regarding recurrent ABC, propose sclerotherapy as a relevant treatment method to be considered.

Research methods

This is a single-center retrospective study, where all patients treated for ABC with percutaneous sclerotherapy from 2016-2021 were included. The data was collected through review of the electronic medical records.

Research results

In our series, sclerotherapy with polidocanol showed the ability to achieve healing or stable disease in 96% of cases (100% in primary ABC and 92% in recurrent ABC). These results support the positive experience with sclerotherapy for primary ABC in the recent literature and open the debate about sclerotherapy as a possible salvage treatment. The median length of radiographic follow-up was 19.5 mo. Further studies with longer follow-up are needed to decide if this provides a long-lasting effect.

Research conclusions

Based on the present study, sclerotherapy with polidocanol may also be considered as a salvage procedure for failed surgery or multiple recurrences. This can be a valuable alternative to other salvage treatment methods, which may have higher morbidity.

Research perspectives

Given the variety of possible treatment methods, future research should focus on randomized clinical trials to identify the gold standard treatment for primary and recurrent ABC.

FOOTNOTES

Author contributions: Weber KS designed and performed the research and wrote the paper. Jensen CL and Petersen MM designed the research, contributed to the analysis and supervised the report.

Institutional review board statement: The study was approved by the Danish Patient Safety Authority and the Data Protection Agency of the Capital Region of Copenhagen.

Informed consent statement: According to the Danish medical law and the institutional review board statement, this retrospective study did not require informed consent from the patients.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Clinical Trials Study

Use of orthotics with orthotic sandals versus the sole use of orthotics for plantar fasciitis: Randomised controlled trial

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Abstract

BACKGROUND

Plantar fasciitis (PF) affects around 10% of the population. Prefabricated orthotics with arch support has been shown to provide symptom relief in PF by decreasing the repetitive stress sustained by the plantar fascia. However, prefabricated orthotics are only effective when shoes are worn, meaning the foot may be left unsupported when it is impractical to wear shoes. Using orthotic sandals in conjunction with prefabricated orthotics may increase PF symptom relief, as they can be worn inside the home, extending the period in which the foot is supported.

AIM

To compare the combined use of prefabricated orthotics and orthotic sandals *vs* the sole use of prefabricated orthotics in the treatment of PF.

METHODS

98 participants with PF were randomised into two groups. The intervention group received the Aetrex L420 Compete orthotics and the Aetrex L3000 Maui Flips (orthotic sandals), whilst the control group received the Aetrex L420 Compete orthotics only. Foot pain was assessed both by the numerical rating scale (NRS) and the pain sub-scale of the foot health status questionnaire (FHSQ). Foot functionality was measured using the function sub-scale of the FHSQ. Symptom change was measured using the global rating of change scale (GROC).

RESULTS

Foot pain scores measured both by NRS and FHSQ pain sub-scale showed statistically significant reductions in foot pain in both groups ($P < 0.05$) at six months. Both groups also reported statistically significant improvements ($P < 0.05$) in function as measured by the FHSQ function subscale and improvement of symptoms as measured by the GROC scale. Between-group analysis showed that the intervention group with the combined use of orthotics and orthotic sandals scored better on all four outcome measures as compared to the control group with the sole use of orthotics. However, the between-group analysis only reached statistical significance on the NRS pain score ($P < 0.05$).

CONCLUSION

Combined use of prefabricated orthotics and orthotic sandals provides a greater decrease in foot pain and improvement in foot function in PF compared to using prefabricated orthotics alone.

Key Words: Plantar fasciitis; Foot diseases; Musculoskeletal pain; Foot orthoses

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Core Tip: Plantar fasciitis (PF) is a common cause of heel pain and affects 10% of the population. Prefabricated orthotics provides relief of symptoms by supporting the arch but can only be used with shoes. Using both prefabricated orthotics and orthotic sandals can extend the period of support. This study finds that the combined use of Aetrex L420 orthotics and Aetrex L3000 orthotic sandals and the sole use of Aetrex L420 orthotics provide statistically significant decreases in foot pain and improved foot function in PF. The effect was greater when both the orthotic and orthotic sandals were used in combination.

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INTRODUCTION

Plantar fasciitis (PF) is the most common cause of heel pain, affecting 10% of the population[1]. Despite the name "fasciitis", which suggests inflammatory causes, the condition is indicated to result from degeneration of the plantar fascia. Histological findings typically reveal degenerative changes such as localised fibrosis, matrix calcification, collagen necrosis and angiofibroblastic hyperplasia. Hence, the term plantar fasciopathy may be preferred[2]. PF is most commonly found in individuals between 40 and 70 years old and is more frequent in women than in men[1,3]. Both physically active and sedentary populations can develop the condition, and risk factors consist of, among others, a recent increase in running, prolonged standing activities, tightness of the gastrocnemius, obesity, pes cavus or pes planus foot types, and the use of footwear that is either unsupportive or that alters foot kinematics[1]. Although the exact aetiology of the condition remains unclear, mechanical overload is thought to contribute to its development[4]. Studies have shown that excessive tensile forces on the fascia cause microscopic changes[5]. Disparity in leg length and tightness of the gastrocnemius contribute to increased tensile loading of the fascia, which heightens the pressure on the longitudinal arch [6]. This may result in microscopic tears and degeneration in the fascia. Symptoms include sharp pain following palpation of the medial plantar calcaneal region and heel pain during the first steps of the day or following extended periods of inactivity[4]. The resulting pain from PF can cause activity limitation and considerable disability, negatively impacting overall quality of life[7].

PF is a self-limiting condition, with most cases resolving within 6 to 18 mo[8]. However, some reports suggest that up to 49% of PF patients are symptomatic for 1.5 to 5 years following the onset of symptoms, and an estimated 2 million people worldwide will receive treatment for the condition annually[9,10]. However, there is currently no standardised treatment method for the condition, with very few studies providing high-quality analysis across different treatment modalities[11]. Furthermore, many studies use treatment methods in combination, making it difficult to determine which is the most beneficial as a stand-alone modality.

Gastrocnemius contracture is an evident contributor to PF[12], and so stretching techniques such as calf-stretching and plantar-fascia-specific-stretching are frequently prescribed. However, a systematic review of the literature found only very low-quality evidence to support their use over sham stretching[13]. Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used in the treatment of PF. Long-term use of NSAIDs, defined as consumption of three or more times a week for more than three months[14], is not without risk of complications, including gastrointestinal bleeding, nephrotoxicity, and dependency[15]. A 2015 systematic review evaluated the literature investigating the efficacy of various taping techniques, including calcaneal and low dye taping, in the treatment of PF. The review found that taping, in general, is beneficial in treating the condition. However, all studies included in the review only assessed short-term

effects, so no evidence was available regarding long-term outcomes[16]. Probe *et al*[17] assessed the effects of the combined use of Achilles stretching exercises, shoe recommendations and anti-inflammatory medications, with and without the addition of night splints, on PF symptoms. They found that the addition of night splints provided no statistical difference in improvements.

Orthotics have been found to decrease foot pain and increase function in PF patients compared to other non-interventional methods[18]. Such benefits from orthotics result from evened weight distribution across the plantar area and arch, shock absorption, and enhanced proprioception[19,20]. The arches of the foot are maintained not just by bony contours but also by the soft tissues that surround the structure. During weight bearing, the arches are depressed and lengthened. The repetitive lengthening whilst weight bearing has been implicated as one of the causative mechanisms of PF[21]. A contoured orthotic which provides mechanical support to the foot prevents repetitive deformation whilst weight bearing and thereby can provide symptom relief and prevent relapse of PF[21]. However, a recent systematic review and meta-analyses of orthotics for plantar heel pain have reported low-quality evidence due to the high risk of bias in studies[22]. Another systematic review and meta-analyses suggest that conclusions have been drawn from low-quality trials and future high-quality trials are required[23].

Like orthotic insoles, orthotic sandals may offer improved arch support and even weight distribution. Research has shown that the use of orthotic sandals and flip-flops with moulded footbeds can have significant effects on the symptoms of PF, including foot pain, function, and foot health[24,25]. The combined use of orthotics and orthotic sandals may be appropriate, as they are both non-invasive and complement each other. Although PF is self-limiting, it is painful and disabling during periods of activity, and hence symptom relief is essential. Unfortunately, orthotics can only be used when donning shoes. Utilising orthotic sandals in conjunction with prefabricated orthotics may enhance symptom relief in PF, as orthotic sandals can be used when donning shoes may not be practical, as whilst at home and indoors. The pain and symptoms from PF is also most severe early in the morning on waking. It may be more feasible to get into orthotic sandals rather than into shoes and orthotics as one takes the first step in the morning. To our knowledge, no research has been conducted into the effects of the combined use of prefabricated orthotics and orthotic sandals in the treatment of PF.

Hence the aim of this study is to identify if the combined use of prefabricated orthotics and orthotic sandals is superior to the use of orthotics only in the treatment of PF. The clinical significance for health providers and patients is that though PF is a self-limiting disorder, symptom relief is required during the active phase of the disease. As most cases of PF only require symptomatic treatment, it is needless to burden the overstretched healthcare system to treat this disorder. This trial hopes to identify a method by which patients can safely and reliably choose a non-invasive treatment modality to address plantar heel pain.

MATERIALS AND METHODS

This study is a non-blinded randomised control trial (RCT) and was conducted over a period of 17 mo between July 2021 and November 2022 through an independent musculoskeletal clinic. The participants were volunteers who responded to social media advertisements about the study. The primary objective is to investigate whether the combined use of prefabricated orthotics and orthotic sandals *vs* the sole use of prefabricated orthotics is more beneficial in decreasing foot pain and increasing foot functionality in PF. The Wales Research Ethics Committee (REC) 5 provided ethical approval on April 14, 2021 by REC reference: 21/WA/0099 and IRAS project ID: 297181. Reporting of the study conforms to the CONSORT statement (CONSORT 2010 statement)[26].

Sample size calculation

A sample size calculation was performed using a target of a one-point change in the numerical rating scale (NRS) pain score (SD 1.6) (the primary outcome), with 80% power and a significance level of 5%. A 20% drop-out rate was allowed. This led to a required sample size of 52 per group, resulting in a total sample size of 104 study participants.

Participants

Participants were recruited from mainland United Kingdom including England, Scotland, Wales and Northern Ireland on a voluntary basis through social media advertisements. Potential participants were provided with a participant information sheet by post or email.

PF whose ICD-10-CM diagnosis code is M72.2[27], is diagnosed both from history and examination findings. The study was designed during the coronavirus pandemic when non-urgent and non-acute cases were diverted to telephone or online consultations. In telephone and online consultations, a physical clinical examination is not possible. To accommodate the restrictions of the lockdown and social distancing the study was designed to diagnose PF only from history and without the advantage of physical examination. To be included in the study, participants had to state that their pain was in the medial-inner aspect of the heel and that the pain was most severe in the morning upon waking. If a potential participant stated otherwise, they were disqualified from participating in the trial. Participants then had a telephone consultation with the lead investigator, a consultant orthopaedic surgeon who has 20 + years of experience post certificate of completion of speciality training.

Inclusion criteria required participants to be aged between 18-75 years old and to have experienced symptoms of PF for at least two months. Participants were excluded if they had received any treatment other than analgesia within the last 12 mo, had any history of foot surgery, and had any congenital or acquired foot abnormalities that would prevent the use of normal footwear. Participants were informed that they could withdraw from the study at any time without needing to give a reason. Participants were then given the opportunity to raise any questions they had about the study. Subse-

quently, participants agreeing to enrol in the trial were asked to provide informed written consent, either online *via* legalesign.com, or by post.

Randomisation

Following recruitment, participants were randomised into one of two groups using an allocation ratio of 1: 1, the intervention group, or the control group. Randomisation was achieved by opening sealed, opaque envelopes, which either contained labels stating, "O and F", denoting orthotics and flips (sandals) and corresponding to the intervention group or "O Only", denoting orthotics only and corresponding to the control group. An individual independent of the research team then randomly selected an envelope, the contents of which assigned the participant to their group. Blinding of participants or researchers was not possible due to the nature of the study.

Intervention

Participants in the intervention group received both the Aetrex L420 Compete orthotics (Figure 1) and the Aetrex L3000 Maui Flips (Figure 2) by post according to their shoe size. Participants in the control group received the Aetrex L420 Compete orthotics only. Participants were instructed to use the devices where possible for a period of 6 mo.

Data collection

Basic demographic information and baseline data were collected upon recruitment. The outcome measures used in this study were foot pain by NRS and foot health status questionnaire (FHSQ), foot functionality (by FHSQ) and change in PF symptoms [by global rating of change scale (GROC)]. Data for all outcomes were collected *via* questionnaires upon initial recruitment, then at three weeks, six weeks, three months, and six months. Participants completed this questionnaire online at smartsurvey.co.uk or as a paper copy provided *via* post, depending on their preference.

Primary outcome measure

The primary outcome measure was to measure the change of foot pain between baseline and 6 mo follow-up using an 11-point NRS, which ranged from zero, denoting "no pain", and ten, denoting "extremely severe pain". The minimal clinically important difference (MCID) on the NRS scale is a 1.7 score change of the median[28].

Secondary outcome measures

Foot pain was also scored along with foot functionality using the "foot pain" and "foot functionality" sub-scales of the FHSQ. For these sub-scales, 5-point likert scales ranging from "no problems, pain or limitations" to "severe problems, pain or limitations" were provided. A dedicated FHSQ programme (https://www.fhsq.org/) was then utilised to calculate an overall score between 0 and 100, depending on the participants' answers, with 0 representing "the worst foot health" and 100 representing "the best foot health". The MCID for the FHSQ pain subscale is 13 points and for the FHSQ function subscale is 7 points[29]. Change in symptoms was assessed using the GROC, an 11-point scale from -5 to + 5, with "-5" representing "very much worse", "0" representing "no change" and "+5" representing "completely recovered".

A data monitoring committee consisting of patients, an independent doctor not part of the research team, and a medical statistician was implemented during the study to ensure that the data collected was legitimate and reliable and to observe for any significant adverse outcomes.

Statistical analysis

NRS for pain: Wilcoxon signed-rank test was used to assess the within-group statistical significance of changes from baseline to 6-mo follow-up of the NRS pain scale. The Mann-Whitney U test was used to assess the between-group statistical differences for the two groups from baseline to six months.

FHSQ pain and function sub-scales: The paired T-test was used to assess the within-group statistical significance of changes from baseline to 6-mo follow-up of the FHSQ pain and function sub-scale. The independent sample t-test was used to compare the between-group differences.

GROC: Wilcoxon signed-rank test was used to assess the within-group statistical significance of changes from 3 wk to 6-mo follow-up on the GROC scale. The Mann-Whitney U test was used to assess the between-group statistical differences for the two groups from 3 wk to six months. The statistical methods of this study were reviewed by an independent statistician from the department of data health sciences, University of Liverpool.

RESULTS

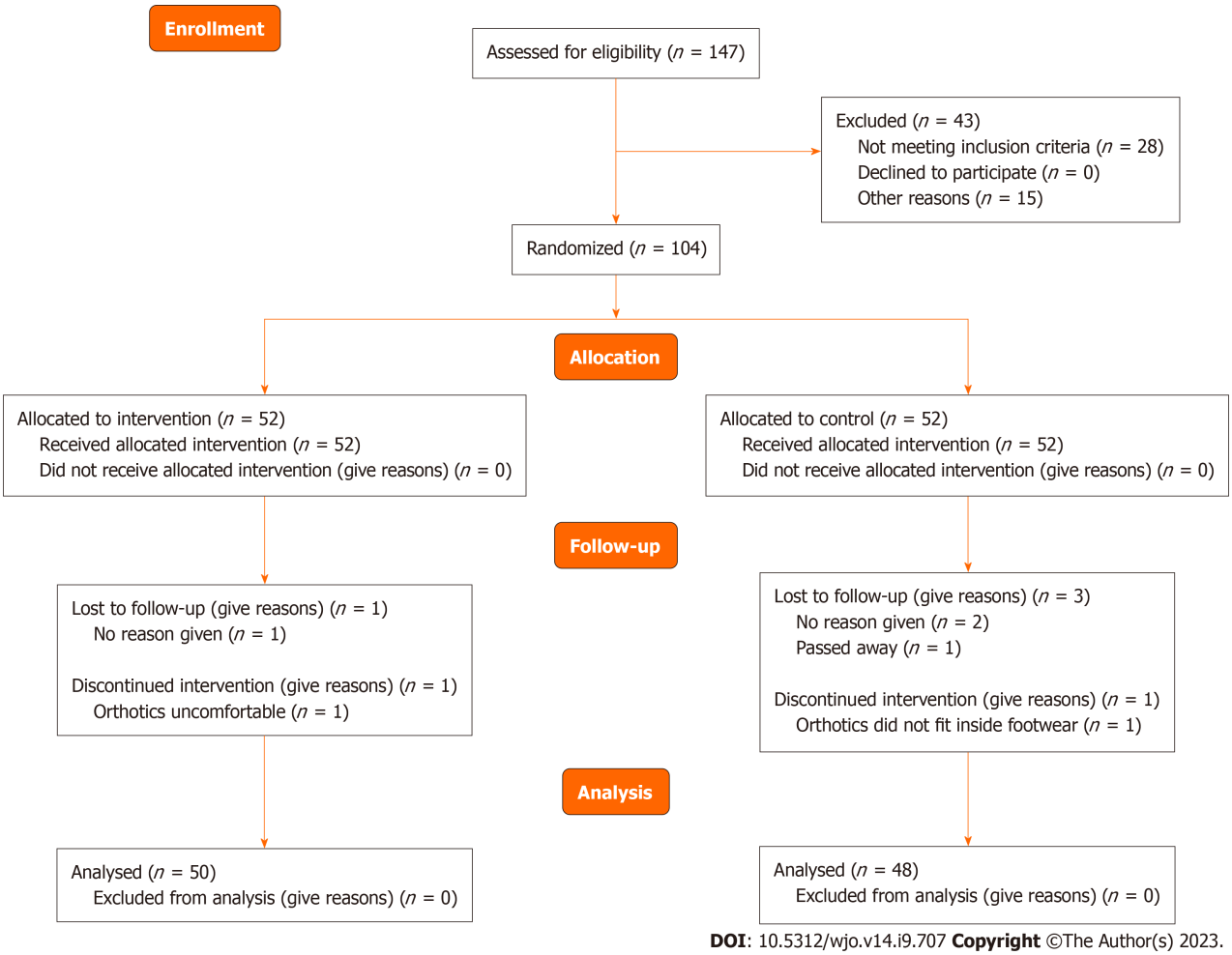
One hundred and four participants were recruited for this RCT. Of these 104 participants, six were not included in the final analysis (drop-out rate = 5.7%), leaving a total of 98 participants to be included in the analysis. In the intervention group (orthotics and orthotic sandals) 1 participant failed to respond and 1 discontinued as the orthotic was uncomfortable. In the control group 2 participants failed to respond, 1 passed away due to unrelated reasons and 1 discontinued as the orthotic did not fit in the shoe. Ninety-eight of the 104 complied with the treatment giving a compliance rate of 94.2%. Details of participant flow through the study, including the number of withdrawals and reasons, are provided in Figure 3. Fifty of the 98 participants included in the analysis were randomly allocated to the intervention group and 48 to the control group. Data collection began in July 2021 and ended in November 2022.



Figure 1 Aetrex L420 Compete orthotics. This orthotic was provided to participants in both the intervention and control group. Copyright ©Aetrex, Inc.



Figure 2 Aetrex L3000 maui orthotic sandals. This orthotic sandal was provided only to participants in the intervention group. Copyright ©Aetrex, Inc.



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Figure 3 CONSORT flow diagram.

The baseline demographics of the participants in the intervention and control groups are shown in Table 1. The participants' ages ranged from 29 to 71 years old (mean age = 48.81). Participants in the intervention group with the combined use of orthotics and the orthotic sandals were, on average, slightly younger (mean age = 48.44) than participants in the control group with the sole use of orthotics (mean age = 49.19). Participants in both the intervention group (94%) and the control group (91.6%) were predominantly female. Results for all outcome measures are provided in Table 2. All outcomes were collected at baseline, 3 wk, 6 wk, 3 mo and 6 mo, aside from the GROC, which was collected at all time points except baseline.

At 6 mo, there was a statistically significant improvement in foot pain by the NRS in both groups. Median change of pain was 6 [interquartile range (IQR) 3.25, $P < 0.001$] in the interventional group with the combined use of orthotics and orthotic sandals and 4 (IQR 4.75, $P < 0.001$) in the control group with the sole use of orthotics. Between-group analysis with the Mann-Whitney U test showed statistically significant improvement ($P = 0.003$) in the interventional group with the combined use of orthotics and orthotic sandals as compared to the sole use of orthotics.

Mean pain scores on the FSHQ subscale improved significantly during the six-month period in the interventional group by 51.49 points [95% confidence interval (CI): 44.52 to 58.46, $P < 0.001$] and in the control group by 42.07 points (95% CI: 35.20 to 48.94, $P < 0.001$). Between-group analysis showed that though the mean pain score improved more in the intervention group with the combined use of orthotics and orthotic sandals as compared to the control group with the sole use of orthotics, it did not reach statistical significance ($P = 0.07$).

Foot functionality, measured using the function sub-scale of the FHSQ, improved during the six-month period in the interventional group by 41.50 (95% CI: 34.44 to 48.56, $P < 0.001$) and in the control group by 37.64 (95% CI: 30.19 to 45.09, $P = 0.001$). Between-group analysis showed that there was again greater improvement of function in the intervention group with the combined use of orthotics and orthotic sandals as compared to the control group with the sole use of orthotics, the improvement was not significant ($P = 0.46$).

The findings for the GROC scale demonstrated statistically significant improvement in symptoms over time for both groups (Median improvement in intervention group 2 ($P < 0.05$) *vs* Median improvement in control group 2 ($P < 0.05$). Between-group analysis showed that there was again greater improvement of symptoms in the intervention group with the combined use of orthotics and orthotic sandals as compared to the control group with the sole use of orthotics, but the improvement was not significant ($P = 0.093$).

Figures 4-7 show how the study outcomes varied for each group over time. Figures 4, 5 and 6 show that, for both the intervention group with the combined use of the orthotics and orthotic sandals and the control group with the sole use of orthotics, the greatest improvements in foot pain reported *via* NRS and FHSQ pain sub-scale and foot functionality reported *via* the FHSQ function sub-scale, were between baseline and 3 wk. Following the 3-wk period, there was a slower but sustained improvement in both groups. Additionally, for these three outcomes, the rate of initial improvement between baseline and week 3 was greater for the intervention group with the combined use of the orthotics and orthotic sandals than the control group with the sole use of orthotics. Figure 7 shows the median change in GROC scale scores for each group over time. At each time point that data were collected, a greater improvement in symptoms was reported by the intervention group with the combined use of the orthotics and orthotic sandals than by the control group with the sole use of orthotics.

DISCUSSION

This article presents the results from a RCT. The study investigated whether the combined use of prefabricated orthotics and orthotic sandals provided enhanced symptom relief from PF in comparison to the sole use of orthotics.

The main findings show that both the intervention group with the combined use of orthotics and orthotic sandals and the control group with the sole use of orthotics experienced significant decreases in foot pain at 6 mo as assessed *via* both the NRS and FHSQ pain sub-scale. Decreases in foot pain on both measures were significantly greater in the intervention group with the combined use of orthotics and orthotic sandals, as compared to the control group with the sole use of orthotics. However, between-group differences in pain scores reached statistical significance only on the NRS pain score ($P < 0.05$). Foot function, as assessed by the FHSQ function sub-scale, also showed statistically significant improvement in both the intervention and control groups at 6 mo. Similarly, there was greater improvement in foot function in the intervention group with the combined use of orthotics and orthotic sandals compared to the control group with the sole use of orthotics but it did not reach statistical significance. At 6 mo, the GROC showed a statistically significant improvement in each of the two groups but between-group analysis did not reach statistical significance.

Baldassin *et al*[30] evaluated the effectiveness of both prefabricated and customised insoles on PF in 142 symptomatic adults. The study employed the visual analogue score (VAS) and the foot function index (FFI) to compare pain and function at baseline, 4 wk, and 8 wk. Results showed that both the use of prefabricated and customised orthotics significantly reduced pain and improved function at 8 wk. However, no significant difference was found between the two groups, suggesting that the costlier customised orthotics were not superior to prefabricated orthotics.

Conversely, other studies have had mixed results. Landorf *et al*[7] conducted an RCT containing 136 participants who were randomised into one of three groups to receive either prefabricated foot orthotics, custom foot orthotics or sham orthotics (placebo). Like the current study, this employed the FHSQ to evaluate pain and function. Findings revealed that, at 3 mo, both prefabricated and custom orthotics significantly improved function. However, no continued significant effects were observable at 12 mo for any outcome in either group. This lack of continued significant improvement at 12 mo may have been caused by the self-limiting nature of PF, in which spontaneous resolution of symptoms may occur with the passage of time. Nevertheless, the findings did show that prefabricated orthotics are effective in the period when

Table 1 Table of participant demographics

	Intervention group orthotics and orthotic sandals (%)	Control group orthotics only (%)	Both groups (%)
Sex			
Male	3 (6.0%)	4 (8.3%)	7 (7.1%)
Female	47 (94.0%)	44 (91.7%)	91 (92.9%)
Age (year)			
20-29	1 (2.0%)	0 (0.0%)	1 (1.0%)
30-39	4 (8.0%)	10 (20.8%)	14 (14.3%)
40-49	21 (42.0%)	13 (27.1%)	34 (34.7%)
50-59	20 (40.0%)	18 (37.5%)	38 (38.8%)
60-69	4 (8.0%)	6 (12.5%)	10 (10.2%)
70-79	0 (0.0%)	1 (2.1%)	1 (1.0%)
Mean age	48.44	49.19	48.81
Total	50	48	98

the symptoms of PF are potentially most severe. Furthermore, results indicate that more cost-effective prefabricated orthotics obtain similar results to the costlier custom orthotics.

Wrobel *et al*[18] conducted a RCT to compare the use of custom foot orthoses (CFO), prefabricated foot orthoses (PFO) and sham insoles for the treatment of PF. Outcomes measured were first-step pain, end-of-day pain, Revised FFI short form (FFI-R), and a short form health survey. Following 3 mo of orthoses/sham insole use, the results showed that both the CFO and PFO groups demonstrated significant improvements in morning and evening pain. All groups, including the sham orthotics group, also reported significant improvements in FFI-R pain and short form health survey at 3 mo.

Costa *et al*[31] evaluated the efficacy of flip-flop sandals, adapted with insoles, on pain and function in PF patients. Sixty-six participants were randomised to receive either a pair of adapted flip-flop sandals with custom insoles or a pair of un-adapted plain sandals. Participants were instructed to use the flip-flops for at least 4 h a day for 12 wk. Data regarding first-step pain, as assessed by VAS, and function, as assessed by the FFI, were collected at baseline and 12 wk. Results showed that the group with the adapted flip-flop sandals with custom insoles had significant improvements with first-step pain and function compared to the un-adapted plain sandals group.

In addition, Chuter *et al*[25] investigated the effects of sandals with a moulded footbed on pain and function in PF. Results showed that, after 12 wk of intervention, there were significant improvements in the primary outcome of foot pain, also measured using FHSQ. In further agreement with our study findings, secondary outcomes of function and pain measured using VAS also improved significantly.

Vicenzino *et al*[24] compared the effects of a contoured sandal, a flat flip-flop and contoured in-shoe orthotics for plantar heel pain. The study contained 50 participants who had experienced plantar heel pain for at least 4 wk. Like our study, this used a GROC scale to determine change in symptoms. The lower extremity function scale (LEFS) was also used to assess function. Findings showed that participants who had been provided with the contoured sandals were 68% more likely to experience symptom improvement using the GROC compared to those who used the flat flip-flop. The contoured sandal group was also 61% more likely to report improvements on the LEFS. No significant differences were observed between the effects of the contoured sandals and the contoured in-shoe orthotics. The findings of these investigations, along with the findings of our study, suggest that the use of orthotic sandals is effective in the treatment of PF.

In our study, the intervention group with the combined use of orthotics and orthotic sandals reported greater improvements on all measures than the control group with the sole use of orthotics. However statistical significance in between-group differences was only reached on the NRS pain scale. We hypothesise that these enhanced benefits were due to the extended periods of support to the feet, and consequent symptomatic relief, provided by the orthotic sandals. Prior to this study, the combined use of prefabricated orthotics and prefabricated orthotic sandals for PF had not been investigated. Nevertheless, studies have assessed the effects of sandals whose weight-bearing surface is contoured like an orthotic on PF as an independent intervention.

The current study investigated the long-term benefits of the intervention, with final data collection at 6 mo. In comparison, other studies only investigated short-term symptom relief, such as 8 wk[25], and 12 wk[26]. The natural history of PF is that most cases resolve spontaneously within 6 to 18 mo[8], and hence symptom relief is required during the active or symptomatic phase of the study. This study demonstrates that both the combined use of orthotics and orthotic sandals or the sole use of orthotics alone can be beneficial for relieving symptoms of PF when it is most symptomatic. In addition, both orthotics and orthotic sandals are drug-free and non-invasive modality to treat PF. Hence it has a lower cost burden and decreased long-term risk profile than other treatment strategies. The combined use of orthotics and orthotic sandals were better on all outcome measures as compared to the sole use of orthotics but between group differences only reached statistical significance on the NRS pains scales.

Table 2 Table of analysis for all outcomes

	Intervention group (orthotics and orthotic sandals)							Control group (orthotics only)							Between-group sig.[test]
	Baseline	3 wk	6 wk	3 mo	6 mo	Change	Sig.[test]	Baseline	3 wk	6 wk	3 mo	6 mo	Change	Sig.[test]	
Foot pain NRS (IQR)	7 (2)	5 (4)	4 (2)	2 (3)	1.5 (3)	-6 (3.25)	$P < 0.001$[a]	8 (3)	5 (3)	4 (3)	4 (4)	3 (3)	-4 (4.75)	$P < 0.001$[a]	$P = 0.003$[b]
Foot pain FHSQ (SD)	28.48 (16.32)	56.50 (20.83)	66.83 (17.23)	74.98 (18.51)	79.98 (15.80)	51.49 (25.15)	$P < 0.001$[c]	29.17 (19.70)	49.57 (19.34)	57.93 (20.23)	62.79 (21.96)	71.24 (18.98)	42.07 (24.79)	$P = 0.001$[c]	$P = 0.07$[d]
Foot function FHSQ (SD)	46.13 (21.47)	71.5 (22.13)	79.25 (17.83)	82.63 (16.72)	87.63 (14.86)	41.50 (24.94)	$P < 0.001$[c]	43.10 (23.68)	65.48 (21.82)	71.74 (23.31)	75.56 (22.80)	80.73 (21.95)	37.64 (26.34)	$P = 0.001$[3]	$P = 0.46$[d]
Symptom change GROC (IQR)		1 (2)	2 (2)	3 (2)	4 (2)	2(2)	$P < 0.001$[a]		1 (2)	1.5 (3)	2 (2)	3 (3)	2 (3)	$P < 0.001$[a]	$P = 0.93$[b]

[a]Wilcoxon Signed Rank Test.
[b]Mann-Whitney U Test.
[c]Paired T-test.
[d]Independent sample T-test.
NRS: Numerical rating scale; FHSQ: Foot health status questionnaire; GROC: Global rating of change score; IQR: Interquartile range.

The findings of this study contribute to existing literature surrounding the use of orthotics and orthotic sandals in the treatment of PF. By combining the use of prefabricated orthotics and prefabricated orthotic sandals, this study has taken a novel approach. To our knowledge, no study has previously been conducted into the combined effects of prefabricated orthotics and orthotic sandals. We wish to propose that the combined use of orthotics and orthotics sandals resulted in greater improvement due to the increased time that the foot is supported.

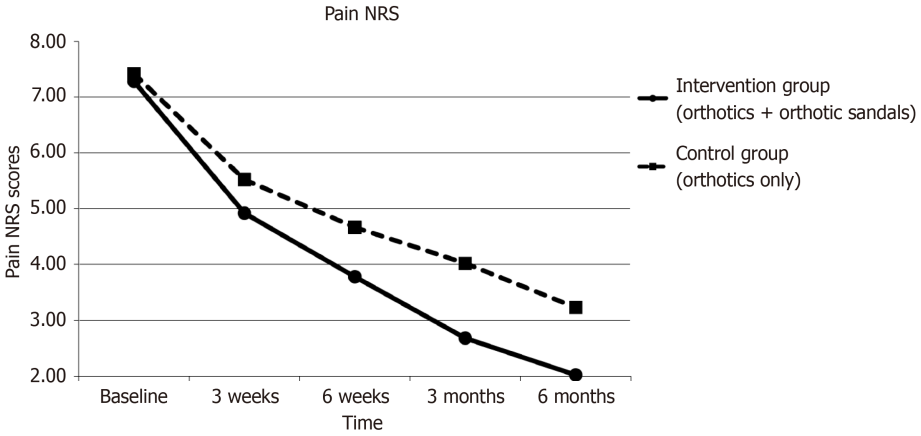
Strengths and limitations

A strength of this study is the inclusion of participants with a wide age range of 18-75 years old. This increases the generalisability of our findings to the wider population of patients with PF. The cohort recruited for this trial is similar to other studies in terms of mean age and female predominance[30,31], and reflects global prevalence[3,32].

However, as participants were recruited voluntarily through social media adverts, the sample may not be representative of the general population. This might have limited our participants to individuals who use the computer, internet and social media whilst excluding a large segment of the population that do not use digital media.

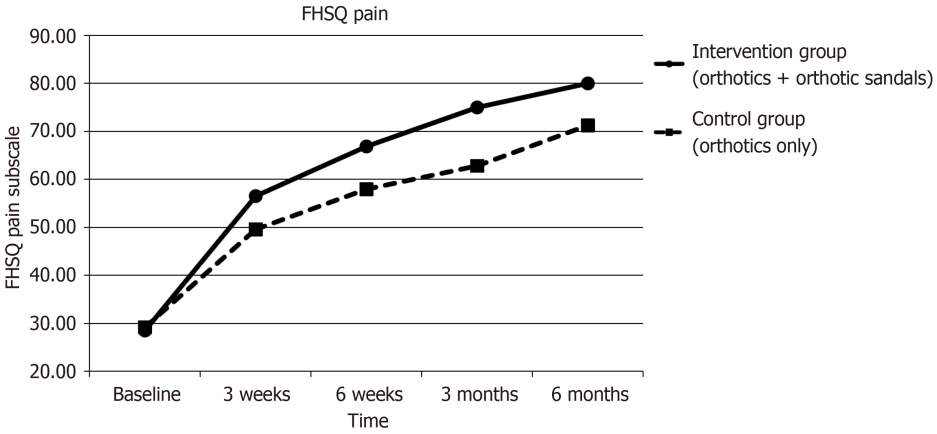
In addition, the study design was drafted in the periods of national lockdowns due to the coronavirus pandemic. It was not known for how long the national lockdowns would last and therefore the protocol and the study design were created to accommodate social distancing by introducing telephone/virtual consultation with the lead author on inclusion into the study. The telephone/virtual consultation and the lack of a physical examination could have led to both over and under-diagnosis of PF in the study population.

In this study, both groups showed significant improvements in foot pain, foot function and symptoms. Significant improvements in control groups may be associated with factors such as regression to the mean and Hawthorne effects [31]. Due to the nature of this study, blinding participants to group allocation was not possible. Therefore, participants in



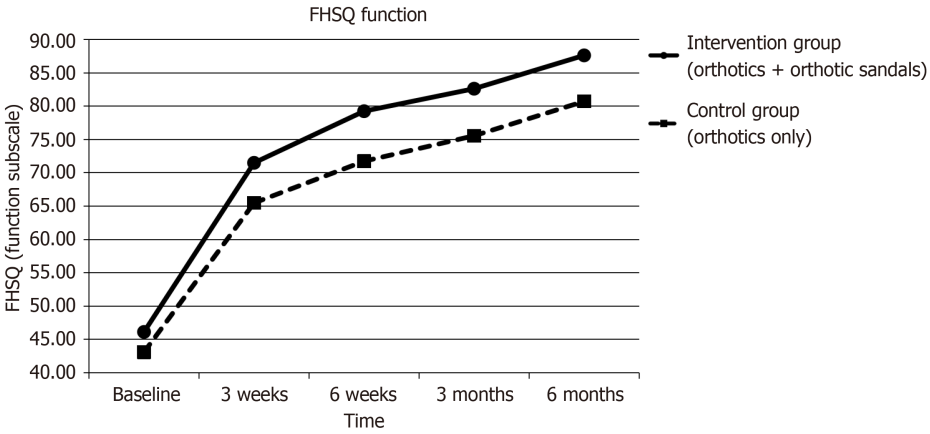
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Figure 4 Foot pain over the last week, measured by numerical rating scale, across time from baseline to 6 mo. NRS: Numerical rating scale.



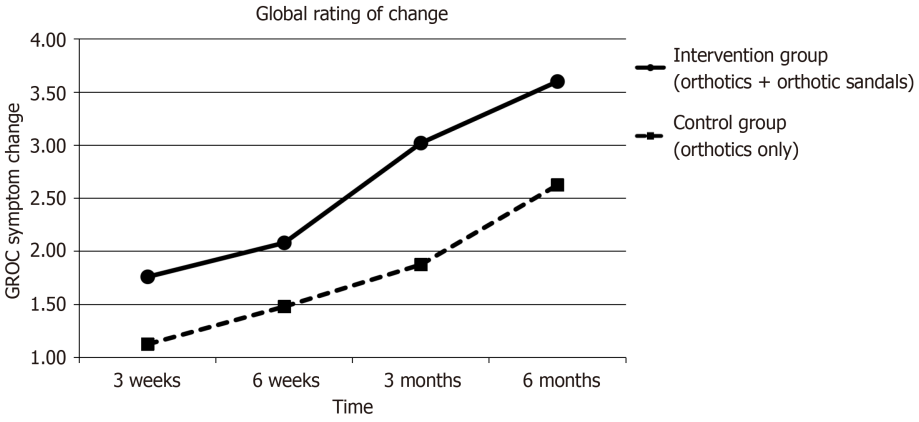
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Figure 5 Foot pain, as assessed by the foot health status questionnaire, across time from baseline to 6 mo. FHSQ: Foot health status questionnaire.



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Figure 6 Foot function, as assessed by the foot health status questionnaire, across time from baseline to 6 mo. FHSQ: Foot health status questionnaire.



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Figure 7 Symptom change from week 3 to month 6, as assessed by the global rating of change score scale. GROC: Global rating of change score.

the intervention group may have expectations that the combined use of orthotics and orthotic sandals would improve pain and functionality. In future studies, the use of a sham orthotic placebo may be beneficial in reducing bias. However, a sham intervention should provide as little an effect as possible whilst being perceived as equally credible compared to the real intervention[33]. Hence, a sham orthotic should not provide the same mechanical benefits as the real orthotics, and yet participants should expect both to provide similar effects. This may be difficult when attempting to blind participants, as they may detect the sham as a fake, causing their results to be influenced by the nocebo effect. Mitigating this would depend greatly on the design of the sham orthotic to convince the participants that the sham they receive is credible. However, inconsistencies have been found in the construction, blinding and biomechanical validation of sham orthotics in research. Therefore, the quality and reliability of the findings from studies which utilised sham orthotics have been questioned[34]. NRS was selected as the outcome measure to score pain, and though this has been shown to be valid, reliable and appropriate when used for the assessment of pain[35], it is still subjective and therefore has the potential for bias.

In future studies, it would be valuable to collect data on how long each participant has been experiencing plantar heel pain before the study commenced. PF is a self-limiting condition that spontaneously resolves within 12 mo in 75% of cases[36]. Therefore, a natural improvement would be expected regardless of intervention. Hence, data on the duration of participants' pre-study PF would have allowed for this to be factored into the analysis. In addition, monitoring of how often each participant wore orthotic devices would be advised in future studies to determine study compliance and reveal the effect on outcomes. This study was not designed to collect information on risk factors for PF, such as structural foot abnormalities, activity levels, high body mass index *etc.* Future studies may find a correlation between the prevalence of these risk factors and their influence on PF symptom control when using orthotics and orthotic sandals. The current study also did not collect data on concurrent or past treatments like physiotherapy and exercises. This could also be considered in future studies.

However, the main purpose of the study was to empower patients to choose a non-invasive and over-the-counter treatment to address PF or plantar heel pain without the need to seek professional help and thereby reduce the burden on the health care system.

CONCLUSION

The within-group results of this study indicate that both the combined use of prefabricated orthotics and orthotic sandals, as well as the sole use of prefabricated orthotics, significantly improved pain and function in PF in all the four outcome measures utilised in this study. Between-group analysis showed that the combined use of orthotics and orthotic sandals provided better benefits than the sole use of orthotics in all four outcome measures, but the improvement was statistically significant only for foot pain on the NRS scale.

ARTICLE HIGHLIGHTS

Research background

Prefabricated orthotics with arch support provides symptom relief in plantar fasciitis (PF) but are only effective when shoes are worn. Hence, the foot may be left unsupported when it is impractical to wear shoes, such as in the morning or evening at home. Utilising orthotic sandals in conjunction with prefabricated orthotics may enhance symptom relief for PF patients, as they can be worn inside the home, thereby extending the period in which the foot is supported. Prefabricated orthotics and orthotic sandals have been investigated as treatment methods for PF independently, but not in

combination.

Research motivation

PF affects around 10% of the population. The resulting pain can cause activity avoidance, disability, and reduced quality of life. However, the natural history of PF is that it resolves naturally with time. Unfortunately, it remains symptomatic during the active phase and requires intervention for pain relief and symptom improvement. As most cases of PF spontaneously resolve with the passage of time, it is needless to burden the already overburdened healthcare system to address this disorder. This trial sought to identify the superiority between two drug-free and non-invasive treatment modalities to address plantar heel pain which can be used as a self-help measure by patients.

Research objectives

To compare the combined use of orthotics and orthotic sandals *vs* the sole use of orthotics in the treatment of PF.

Research methods

104 participants were randomly assigned to the intervention group, who received both prefabricated orthotics and orthotics sandals, or the control group, who received prefabricated orthotics only. Participants were instructed to use the devices as much as possible. Data were collected at baseline, three weeks, six weeks, three months, and six months. Foot pain was assessed using an 11-point numerical rating scale (NRS). Foot pain and functionality were assessed using the foot pain and foot functionality sub-scales of the foot health status questionnaire (FHSQ). The global rating of change score (GROC) was provided at three weeks, six weeks, three months and six months to assess PF symptom change. A series of Wilcoxon signed-rank tests, Mann-Whitney U tests, Paired T-tests and independent sample t-tests were performed for analysis.

Research results

Foot pain scores significantly improved in both groups, as assessed and measured by the NRS and FHSQ pain sub-scale. Significant improvements in function by the FHSQ function subscale and changes in the level of symptoms by the GROC scale were also observed in both groups. The combined use of orthotics and orthotic sandals showed superior outcomes on all four measures but only reached statistical significance on the NRS pain scales.

Research conclusions

This study provides evidence that both the combined use of orthotics and orthotic sandals and the sole use of orthotics alone, improve pain and function significantly in PF patients. Between-group differences show that the combined use does provide a greater decrease in foot pain compared to using orthotics alone.

Research perspectives

Though this study provides evidence that the combined use of prefabricated orthotics and orthotic sandals improves foot pain in PF patients more than the use of prefabricated orthotics alone, it was not without limitation. Hence, future research should aim to address these limitations, including collecting data on participants' duration of PF symptoms on enrolment, and risk factors for the condition.

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FOOTNOTES

Author contributions: Ampat G supervises the research team and acquired the funding; Ampat G and Sims JMG conceptualised the study and were involved in protocol development and gaining ethical approval; Ampat G and Sims JMG were involved in participant recruitment and data acquisition; Amoako-Tawiah P, Love H, Chacko Madathilethu J, LaCourse J, Fortune AE, and Sims JMG wrote the manuscript; All authors reviewed and edited the manuscript and approved the final draft.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: George Ampat and Jonathan M G Sims are employees of Talita Cumi Ltd, which has a commercial relationship with Aetrex Worldwide, Inc. 414 Alfred Avenue Teaneck, NJ 07666, United States. All other authors have no conflict of interest to declare.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Observational Study

Relationships among body weight, lipids and bone mass in elderly individuals with fractures: A case-control study

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Abstract

BACKGROUND

The prevalence of osteoporosis and low bone mass is steadily rising each year. Low body weight is commonly linked to diminished bone mass and serves as a robust predictor of osteoporosis. Nonetheless, the connection between body mass index (BMI), bone mineral density, and lipid profiles among the elderly remains elusive.

AIM

To examine the association between BMI and bone mass, explore the correlation between lipid profiles and bone mass, and delve into the interplay between lipid metabolism and bone health.

METHODS

The study included 520 patients aged ≥ 65 years (178 men and 342 women). Age, sex, weight, and height were recorded. Femoral neck bone mineral density and T scores were determined using a dual-energy X-ray absorptiometry scanner. Blood calcium (Ca), phosphorus (P), albumin (ALB), alkaline phosphatase (ALP), aspartate aminotransferase, alanine aminotransferase, triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were measured. Patients were classified by sex (male and female), age (65-79 years and ≥ 80 years), and T score (normal bone mineral density, osteopenia and osteoporosis).

RESULTS

Age, sex, BMI, and ALP and TG levels were independent risk factors for osteoporosis. For the 65-79- and ≥ 80-year-old groups, females presented lower T scores than males. Ca, P, ALB, ALP, TC, HDL and LDL levels were significantly different between men and women in the 65-79-year-old group. In addition, BMI and TG levels were significantly decreased in osteoporotic patients compared with patients with normal bone mass. TC levels declined in 65- to 79-year-old male and female osteoporosis patients. In the group of women aged ≥ 80 years, osteoporotic patients showed significantly increased ALP levels. Furthermore, we found positive correlations between BMI and TG levels in the male and female patient groups. However, we found no significant differences in ALB, Ca, P, HDL and LDL levels in osteoporotic patients compared to patients with normal bone mass.

CONCLUSION

Osteoporotic patients showed significantly decreased BMI and TG levels compared with those with normal bone mass. BMI showed positive correlations with TG levels in male and female patients. These results indicate correlations between BMI and bone mass and between lipid profiles and bone mass.

Key Words: Osteoporosis; Weight loss; Elderly patients; Body mass index; Lipid profiles

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Core Tip: Older age, female gender, low body mass index (BMI), and low triglycerides (TG) were identified as overall independent factors for osteoporosis. Furthermore, low total cholesterol represented a gender-unspecific risk factor for osteoporosis in elderly patients aged 65-79 years, and high alkaline phosphatase represented a specific risk factor for osteoporosis in elderly male patients aged 80+ years. In addition, positive correlations were found between BMI and serum TG levels, suggesting an interaction between bone and fat metabolism that may have an impact on the development of osteoporosis and would provide a new strategy for the treatment of osteoporosis.

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INTRODUCTION

The incidence of osteoporosis and low bone mass is progressively rising on an annual basis. Osteoporosis affects over 33% of individuals aged 50 years or older in China[1]. Osteoporosis is marked by diminished bone mineral density (BMD) and compromised bone microarchitecture, resulting in reduced bone mass and heightened bone fragility, thereby elevating the susceptibility to fractures[2]. Numerous factors contribute to osteoporosis, encompassing age, sex, lifestyle, and various medical conditions[3]. Alongside the T score, dual-energy X-ray absorptiometry (DXA) is deemed a pivotal and extensively employed technique for osteoporosis diagnosis[4]. Typically, osteoporosis is classified based on the T score, following the World Health Organization (WHO) guidelines: Normal bone density (≥ -1.0), osteopenia (-1.0 to -2.5), and osteoporosis (≤ -2.5)[5,6].

Recently, numerous studies have examined osteoporosis risk factors, including body mass index (BMI), serum lipid profiles, serum calcium (Ca) and phosphorus (P), serum albumin (ALB), alkaline phosphatase (ALP), and serum alanine transaminase (ALT) and aspartate aminotransferase (AST)[7-11].

Previous research has reported a link between obesity and osteoporosis, suggesting that obesity might act as a protective factor against osteoporosis[12,13]. Obese individuals subject their bones to greater mechanical loads, which can be advantageous for bone mass[14,15]. Furthermore, weight loss detrimentally impacts musculoskeletal health[16], and it has been linked to bone loss and identified as a potent predictor of osteoporosis[17]. Elderly women who experienced weight loss demonstrated heightened bone loss in the hip region[18]. Another investigation noted a relationship between weight loss and hip-bone loss among elderly men and women[17]. These findings imply that elderly individuals with lower body weight face greater risks of both osteoporosis and fractures than their counterparts with higher body weight. Additionally, plasma lipid profiles have been demonstrated to undergo alterations in response to weight changes[19]. Assessing BMI provides a straightforward approach to categorizing an individual's weight status and is linked to the proportion of body fat[20].

Nevertheless, the relationship among BMI, bone mass, and lipid profiles remains unexplored in populations with osteoporosis and fragility fractures. Fragility fractures frequently occur in elderly patients with severe osteoporosis, exacerbating the prognosis[21]. The impact of weight gain on enhancing the lipid profile and subsequently mitigating the prevalence of osteoporosis and fragility fractures remains uncertain. This study aimed to examine the interaction between BMI and bone mass, explore the correlation between lipid profiles and bone mass, and further analyze the interrelationship between lipid metabolism and bone health in individuals experiencing fragility fractures.

MATERIALS AND METHODS

Study participants

This retrospective study was conducted at a singular orthopaedic trauma centre during the time span of January 2017 to December 2020. The study meticulously applied specific inclusion and exclusion criteria as delineated below:

Inclusion criteria were as follows: (1) Age exceeding 65 years at the moment of injury; (2) confirmed diagnosis of fractures in the hip, vertebral region, distal radius, or proximal humerus; and (3) hospitalization at our centre.

Exclusion criteria were as follows: (1) Patients afflicted with cancer, thyroid disorders, hypopituitarism, rheumatoid arthritis, chronic renal failure, or renal insufficiency; (2) patients undergoing lipid-lowering, synthetic thyroid, or hormone replacement therapies; or (3) presence of incomplete data.

Our study managed to acquire comprehensive clinical data suitable for analysis. Participants were categorized based on gender (male and female), age groups (65-79 years and ≥ 80 years), BMI ranges (< 18.5, 18.5-24, > 24 kg/m^2), and T scores [normal BMD (≥ -1.0), osteopenia (-1.0 to -2.5), and osteoporosis (≤ -2.5)]. All laboratory data used in this study were obtained from blood samples collected during the initial admission.

Data collection

Age, sex, height, and weight were recorded from patient documents. BMI was calculated using weight and height (kg/m^2). Femoral neck BMD and T scores were determined using a DXA scanner (Hologic Discovery Wi with software version 13.2). According to the WHO classification, the T score was used to define the BMD categories. Serum samples were collected immediately after the patients were admitted, and serum Ca, P, ALB, AST, ALT, ALP, triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were analyzed.

Statistical analysis

Data are presented as the mean ± standard deviation (SD). IBM SPSS statistics software (version 26.0, SPSS Inc., Chicago, United States) and GraphPad Prism software (version 8.4.0, GraphPad Software, Boston, United States) were used to analyze the data. After analysing the normality using the Shapiro-Wilk test, data between two groups were evaluated by the *t* test and nonparametric test. For three groups, data were evaluated by one-way ANOVA. Multivariate analysis was performed by multiple linear regression. The Pearson correlation test was used to analyse the association between BMI and TG levels. $^aP < 0.05$, $^bP < 0.01$, $^cP < 0.001$ and $^dP < 0.0001$ indicated significant differences.

RESULTS

In total, 520 patients aged ≥ 65 years were included in our study. A total of 178 male patients were enrolled, including 48 normal, 81 osteopenic and 49 osteoporotic patients. A total of 342 female patients were included in our study, including 37 normal, 103 osteopenic, and 202 osteoporotic patients (Table 1). Age, sex, BMI and ALP and TG concentrations were significantly different among the groups of normal, osteopenic and osteoporotic patients. Moreover, age, sex, BMI and ALP and TG concentrations were independent risk factors for osteoporosis (Table 1).

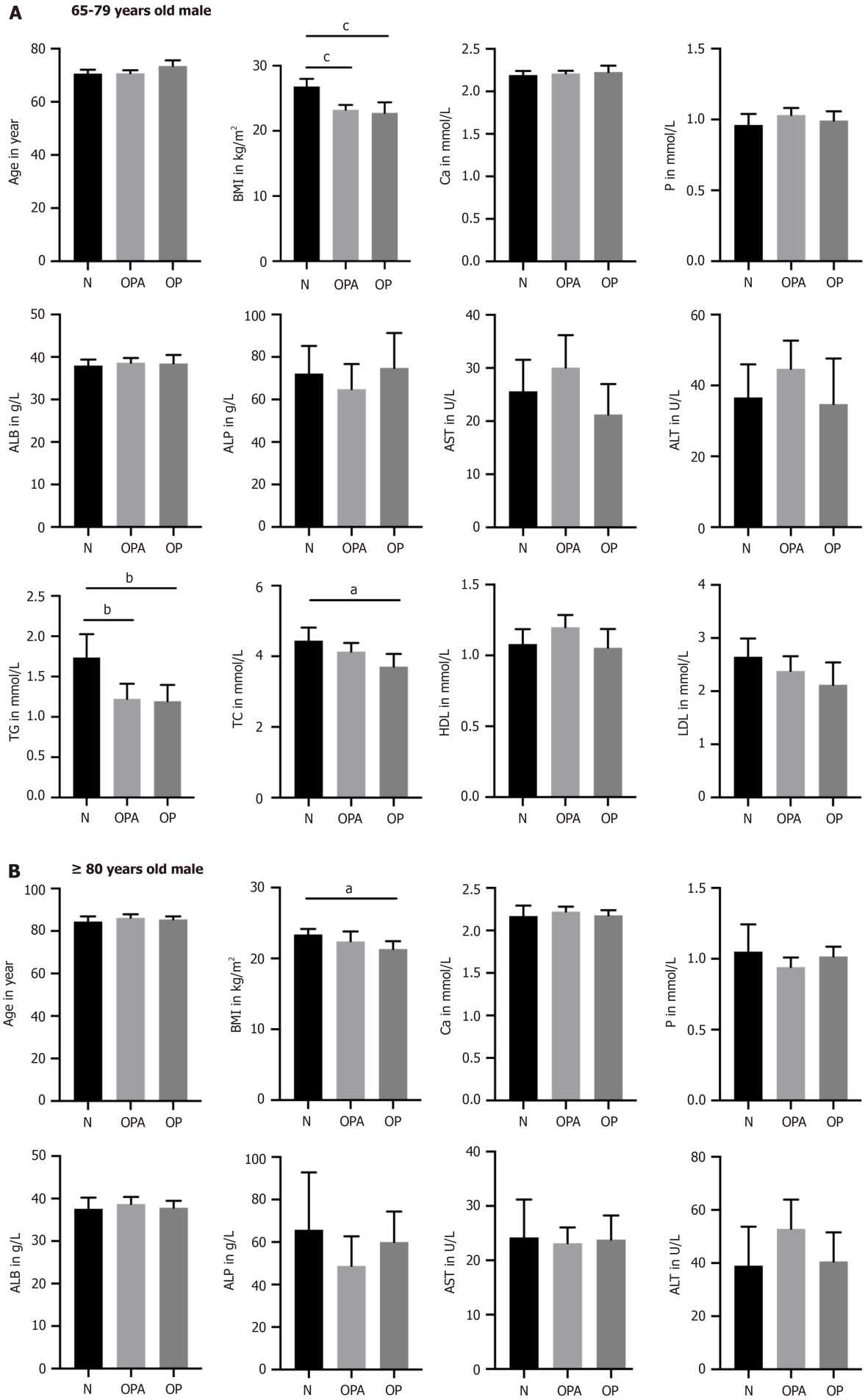
Patients were divided into two groups according to age (65-79 years and ≥ 80 years). To analyze sex differences, a total of 106 men and 188 women were included in the 65- to 79-year age group (Table 2). As shown in Table 2, there were significant differences in the T score and Ca, P, ALB, ALP, TC, HDL and LDL concentrations between male and female patients. However, male patients showed no difference in age, BMI, or AST, ALT and TG concentrations in comparison with female patients.

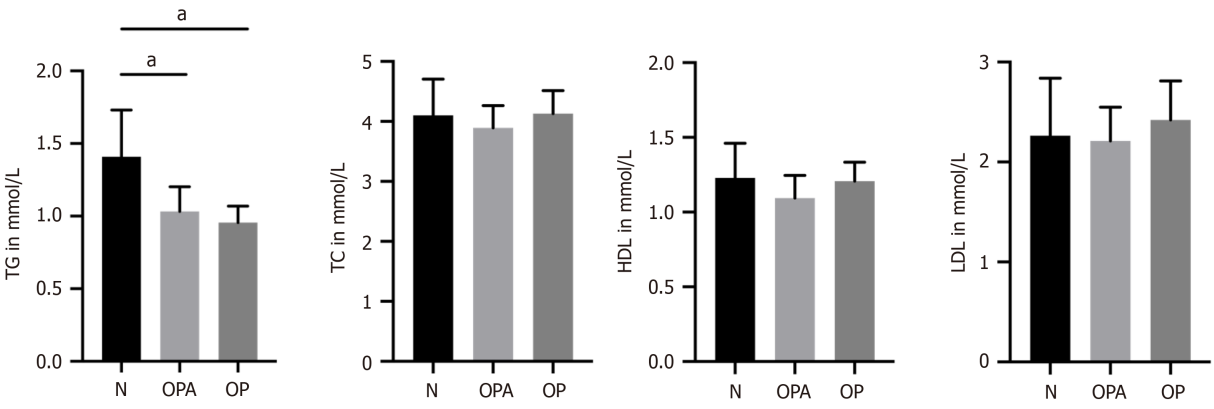
A total of 72 men and 154 women aged ≥ 80 years were examined in our study. The T score was significantly different in male patients compared to female patients. There were no significant differences in BMI or Ca, P, ALB, ALP, AST, ALT, TG, TC, HDL and LDL concentrations between male and female patients (Table 3).

In the group of 65- to 79-year-old male patients, BMI was lower in osteoporotic patients than in patients with normal bone mass. Furthermore, we found a positive correlation between BMI and T-value in the groups of male patients (Supplementary Figure 1). Moreover, TG and TC levels were also lower in patients with osteoporosis compared to those with normal bone mass. Osteoporotic patients showed no significant differences in Ca, P, ALB, ALP, AST, ALT, HDL and LDL levels compared to patients with normal bone mass. In men aged ≥ 80 years, BMI was significantly lower in osteoporotic patients than in patients with normal bone mass. We also observed decreased TG levels in osteoporotic patients compared to those in patients with normal bone mass. Ca, P, ALB, ALP, AST, ALT, TC, HDL and LDL levels were not significantly different between patients with and without osteoporosis (Figure 1).

In the group of 65- to 79-year-old females, BMI and TG and TC levels were significantly lower in osteoporotic patients than patients with normal bone mass. We also found a positive correlation between BMI and T-value in the groups of female patients (Supplementary Figure 1). Osteoporotic patients also showed no significant differences in Ca, P, ALB, ALP, AST, ALT, HDL and LDL levels compared to patients with normal bone mass. In the group of women aged ≥ 80 years, osteoporotic patients showed significantly decreased BMI and TG levels as well as increased ALP levels. We also did not find significant differences in the Ca, P, ALB, AST, ALT, TC, HDL and LDL levels in osteoporotic patients compared with patients with normal bone mass (Figure 2).

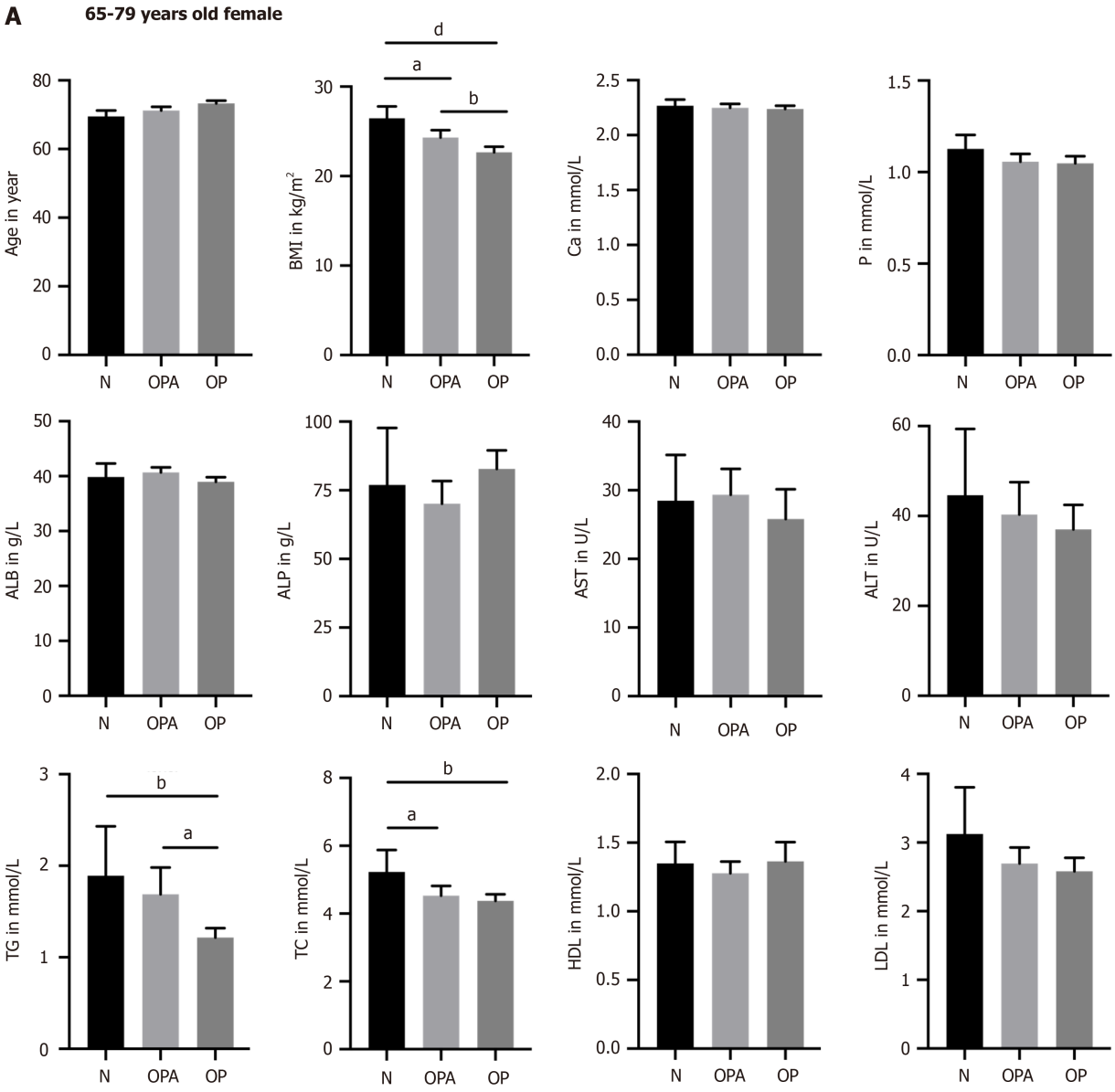
Furthermore, we found a positive correlation between BMI and TG levels in the groups of male patients aged 65-79 and ≥ 80 years. A positive correlation was also found between BMI and TG levels in the groups of 65-79- and ≥ 80-year-old

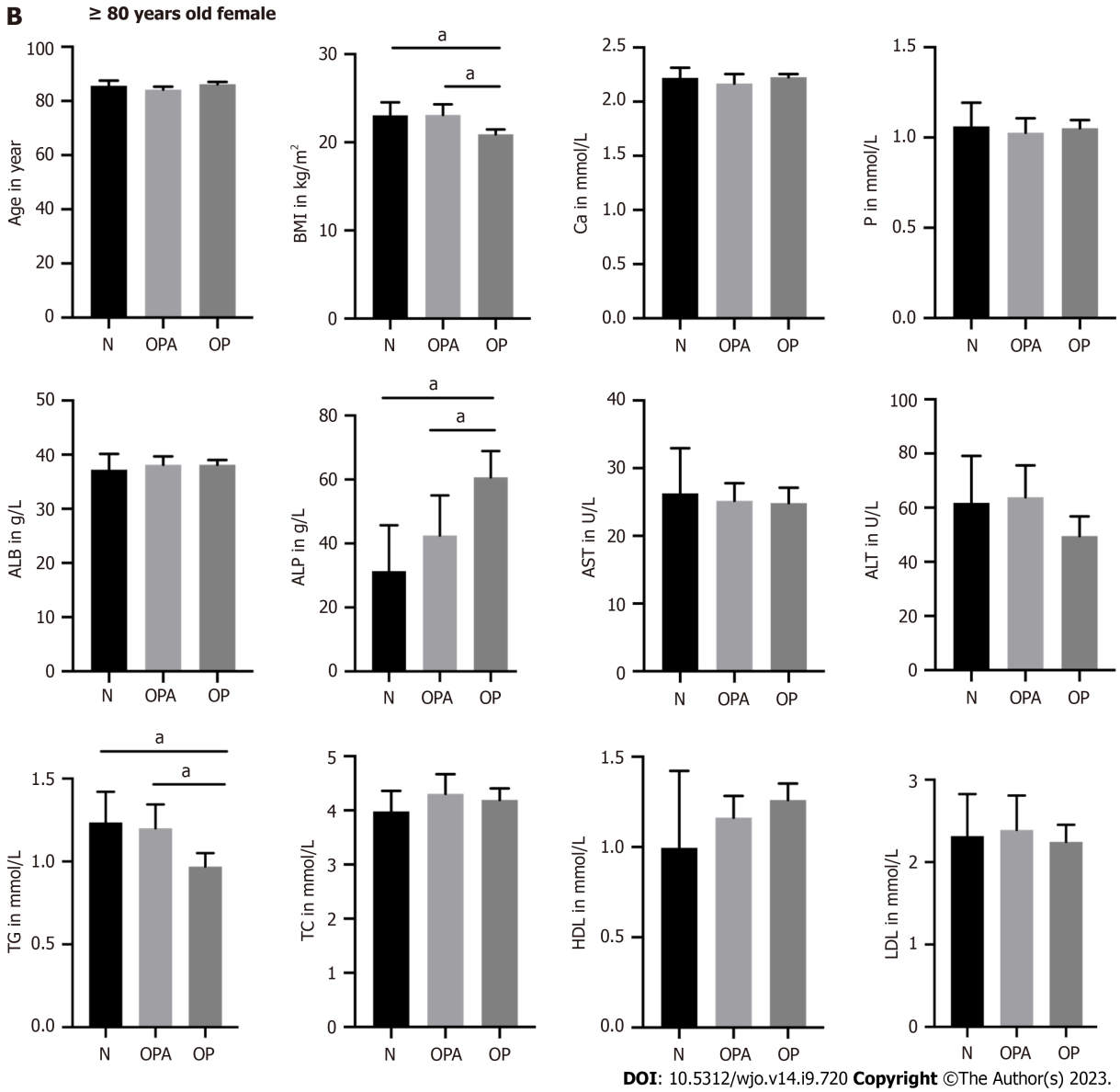

A
65-79 years old male
Age in year
BMI in kg/m2
Ca in mmol/L
P in mmol/L
ALB in g/L
ALP in g/L
AST in U/L
ALT in U/L
TG in mmol/L
TC in mmol/L
HDL in mmol/L
LDL in mmol/L
N
OPA
OP
B
≥ 80 years old male



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Figure 1 The differences of age, body mass index, calcium, phosphorus, albumin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein in male patients. A: Presented the group of 65-79 years old man; N(N) = 35, N(OPA) = 50, N(OP) = 21; B: Presented the group of ≥ 80 years old man; N(N) = 13, N(OPA) = 31, N(OP) = 28. $^{a}P < 0.05$, $^{b}P < 0.01$ and $^{c}P < 0.001$ as different significance levels. BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; N: Normal bone mass; OPA: Osteopenia; OP: Osteoporosis.





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Figure 2 The differences of age, body mass index, calcium, phosphorus, albumin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein in female patients. A: Presented the group of 65-79 years old female; N(N) = 19, N(OPA) = 65, N(OP) = 104; B: Presented the group of ≥ 80 years old female; N(N) = 17, N(OPA) = 38, N(OP) = 99. [a]*P* < 0.05, [b]*P* < 0.01 and [d]*P* < 0.0001 as different significance levels. BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; N: Normal bone mass; OPA: Osteopenia; OP: Osteoporosis.

female patients (Figure 3).

DISCUSSION

In our study, we analyzed the clinical data of 520 patients aged ≥ 65 years. We found that osteoporotic patients showed significantly decreased BMI and TG levels in comparison with patients with normal bone mass. The number of patients diagnosed with osteoporosis is increasing annually, and previous studies have shown that many factors contribute to osteoporosis, including age, sex, BMI, and Ca, P, ALB, ALP, AST, ALT, TG, TC, HDL and LDL levels.

Previous studies have reported that many factors contribute to osteoporosis[3,22]. In our study, we found that age, sex, BMI, and ALP and TG levels were independent risk factors for osteoporosis. With increasing age, a series of factors are altered, such as a lack of sex steroids, declining levels of growth factors and changes in food intake, exercise and mechanical loading, leading to bone loss. Based on this, we classified the groups according to age. Regarding the relationship between sex and bone mass, previous studies have demonstrated that men tend to have a higher BMD at a later age and a lower rate of bone mass loss than women[23,24], suggesting that bone mass loss differs by sex. In our study, female patients in the 65-79- and ≥ 80-year-old groups presented lower T scores than male patients. The reason for

Table 1 Univariate and multivariate analysis of related factors for osteoporosis

	Univariate analysis				Multivariate analysis		
	Normal (*n* = 85)	Osteopenia (*n* = 184)	Oeteoporosis (*n* = 251)	*P* value	OR	95%CI	*P* value
Age (year old)	75.54 ± 8.22	76.31 ± 8.00	79.72 ± 7.62	< 0.001	-0.04	0.016-0.064	0.001
Gender (*n*)				< 0.001	1.34	0.968-1.720	< 0.001
Male	48	81	49				
Female	37	103	202				
BMI (kg/m^2)	25.46 ± 3.32	23.43 ± 3.32	21.83 ± 3.10	< 0.001	-0.018	-0.373	< 0.001
≤ 18.5 (*n*)	1 (1.18)	9 (4.89)	38 (15.14)	< 0.001			
18.5-24 (*n*)	27 (31.76)	92 (50.00)	148 (58.96)				
≥ 24 (*n*)	57 (67.06)	83 (45.11)	65 (25.90)				
Ca (mmol/L)	2.21 ± 0.16	2.20 ± 0.15	2.22 ± 0.15	0.69			
P (mmol/L)	1.05 ± 0.29	1.02 ± 0.19	1.04 ± 0.20	0.56			
ALB (g/L)	38.21 ± 4.72	39.27 ± 4.26	38.49 ± 4.36	0.09			
ALP (U/L)	64.02 ± 41.37	59.40 ± 38.83	70.89 ± 39.63	0.01	0.01	0.006-0.015	< 0.001
AST (U/L)	26.19 ± 14.73	27.64 ± 15.36	24.83 ± 16.01	0.19			
ALT (U/L)	43.89 ± 30.07	48.50 ± 31.54	42.16 ± 31.87	0.11			
TG (mmol/L)	1.62 ± 0.83	1.35 ± 0.87	1.09 ± 0.47	< 0.001	-0.56	-1.132	< 0.001
TC (mmol/L)	4.48 ± 1.15	4.27 ± 1.06	4.22 ± 1.01	0.16			
HDL (mmol/L)	1.16 ± 0.31	1.21 ± 0.28	1.28 ± 0.44	0.1			
LDL (mmol/L)	2.67 ± 0.93	2.48 ± 0.84	2.40 ± 0.80	0.12			
CHD (*n*)	7	14	27	0.52			

BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CHD: Coronary heart diseases.

the differences in bone mass between sexes might be that hormones differ in males and females[23]. Moreover, significant differences were observed in the Ca, P, ALB, ALP, TC, HDL and LDL levels between men and women in the 65- to 79-year-old group. These results indicate that men and women present differences in many factors for osteoporosis. Cui *et al* [7] supported our results in their analysis of 1035 men and 3953 women, where they also showed significant differences in BMI and T scores, as well as in TG, TC, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels, between men and women. According to their and our results, we classified the groups by sex and age (65-79 and ≥ 80 years old).

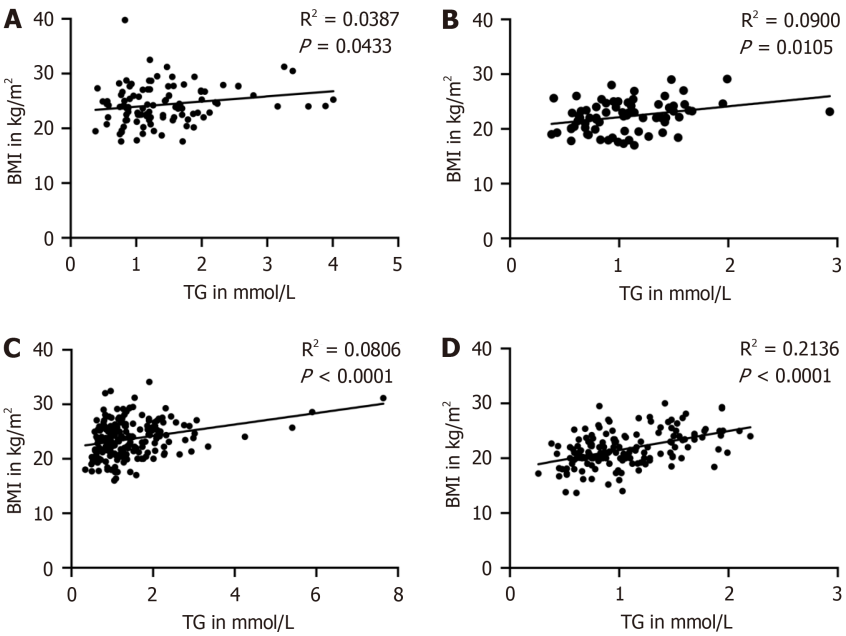
Previous studies have revealed the correlation among lipid profiles, BMI, and BMD[7,25,26]. In our study, we found that male and female osteoporotic patients showed significantly decreased BMI in the groups aged 65-79 and ≥ 80 years. Supporting our findings, many studies have reported an association between BMI and BMD. Alay *et al*[27] investigated 452 postmenopausal women in an outpatient clinic between 2012 and 2015 and observed that a decreased BMI was related to a lower BMD. In addition, Fawzy *et al*[28] analyzed 101 men and women and found that a decline in BMI was associated with a lower BMD. The possible mechanisms for the association between BMI and BMD might be that weight gain places greater static mechanical loads on the bones and increases various hormone levels, which are beneficial for bone mass and bone remodelling[26,29-31].

Moreover, our study demonstrated that male and female osteoporotic patients presented obviously decreased TG levels in the groups aged 65-79 years and ≥ 80 years. In addition, male and female osteoporotic patients also showed obviously decreased TC levels in the group aged 65-79 years. However, we did not find any significant differences in the HDL and LDL levels between the two groups in our study. Although previous studies have reported the association between serum lipid profiles and BMD, the literature is conflicting. Our study findings were in agreement with those of Cui *et al*[7], who showed that BMI and TG levels were significantly lower in patients with osteoporosis than in those with normal BMD. However, there was no significant difference in TC levels. In a meta-analysis, Chen *et al*[32] selected ten publications and investigated the relationship between lipid profiles (HDL, LDL, TG, and TC levels) and osteoporosis in postmenopausal women, finding significantly higher HDL and TC levels in the postmenopausal osteoporosis group than in the normal BMD group. Although the difference was not significant, postmenopausal osteoporosis patients presented with a lower TG level. Alfahal *et al*[33] also reported a lower TG level in postmenopausal individuals with osteoporosis

Table 2 Male and female patients aged between 65 to 79 years old in related factors for osteoporosis

	Male (*n* = 106)	Female (*n* = 188)	*P* value
Age (year)	71.25 ± 4.39	72.18 ± 4.52	0.095
T-value	-1.51 ± 0.94	-2.5 ± 1.03	< 0.0001
BMI (kg/m^2)	24.33 ± 3.52	23.63 ± 3.37	0.134
≤ 18.5 (*n*)	3 (2.83)	13 (6.91)	0.316
18.5-24(*n*)	48 (45.28)	85 (45.21)	
≥ 24 (*n*)	55 (51.89)	90 (47.88)	
Ca (mmol/L)	2.21 ± 0.13	2.25 ± 0.14	0.027
P (mmol/L)	1.00 ± 0.19	1.06 ± 0.14	0.01
ALB (g/L)	38.40 ± 4.11	39.67 ± 4.21	0.013
ALP (U/L)	69.29 ± 39.15	77.79 ± 35.53	0.032
AST (U/L)	26.86 ± 18.85	27.30 ± 19.34	0.258
ALT (U/L)	40.06 ± 27.97	38.94 ± 28.56	0.953
TG (mmol/L)	1.39 ± 0.73	1.45 ± 0.91	0.727
TC (mmol/L)	4.15 ± 0.95	4.52 ± 1.11	0.005
HDL (mmol/L)	1.13 ± 0.26	1.33 ± 0.45	< 0.001
LDL (mmol/L)	2.42 ± 0.83	2.68 ± 0.86	0.048

BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.



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Figure 3 The correlation between body mass index and triglyceride in male and female patients. A: Presented the group of 65-79 years old male patients; *n* = 106; B: Presented the group of ≥ 80 years old male patients; *n* = 72; C: Presented the group of 65-79 years old female patients; *n* = 188; D: Presented the group of ≥ 80 years old female patients; *n* = 154. *P* < 0.05 as a different significance level. BMI: Body mass index; TG: Triglyceride.

Table 3 Male and female patients aged ≥ 80 years old in related factors for osteoporosis

	Male (*n* = 72)	Female (*n* = 154)	*P* value
Age (year)	85.60 ± 4.08	85.65 ± 33.89	0.839
T-value	-2.06 ± 1.21	-2.94 ± 1.29	< 0.0001
BMI (kg/m^2)	22.34 ± 3.26	21.68 ± 3.12	0.15
≤ 18.5 (*n*)	10 (13.89)	22 (14.29)	0.829
18.5-24 (*n*)	41 (56.94)	93 (60.39)	
≥ 24 (*n*)	21 (29.17)	39 (25.32)	
Ca (mmol/L)	2.20 ± 0.17	2.21 ± 0.19	0.234
P (mmol/L)	1.01 ± 0.28	1.09 ± 0.58	0.092
ALB (g/L)	38.19 ± 4.34	38.04 ± 4.68	0.823
ALP (U/L)	56.21 ± 38.95	52.95 ± 40.44	0.455
AST (U/L)	23.61 ± 9.93	25.08 ± 10.77	0.238
ALT (U/L)	45.61 ± 28.78	54.45 ± 36.12	0.06
TG (mmol/L)	1.07 ± 0.44	1.08 ± 0.49	0.857
TC (mmol/L)	4.03 ± 0.99	4.20 ± 1.03	0.171
HDL (mmol/L)	1.17 ± 0.30	1.21 ± 0.32	0.425
LDL (mmol/L)	2.31 ± 0.78	2.29 ± 0.78	0.926

BMI: Body mass index; Ca: Calcium; P: Phosphorus; ALB: Albumin; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine transaminase; TG: Triglyceride; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

compared with individuals with normal bone mass individuals. However, Bijelic *et al*[34] evaluated lipid profiles and BMI in 100 postmenopausal osteoporotic patients and patients with normal BMD. They proved that in postmenopausal patients, osteoporosis was associated with LDL, TC, and TG levels. Contrary to our results, they showed increased TG levels in osteoporotic patients compared with those with a normal BMD. The reason might be that, in their study, there were 72 overweight patients in the osteoporosis group and 54 overweight patients in the normal BMD group. However, Alay *et al*[27] did not observe significant differences in HDL, LDL, TG, and TC levels between groups with normal bone mass and osteoporosis. BMI and TG levels were independent risk factors for osteoporosis in our study. Moreover, we also observed a positive correlation between BMI and TG levels in the groups of male and female patients aged 65-79 and ≥ 80 years. These results suggest a positive relationship among BMI, TG levels and BMD.

It has been reported that lipids may be a predisposing factor for osteoporosis and are associated with bone fragility [11], and TG metabolism is considered to be correlated with bone metabolism. Dragojevič *et al*[35] performed a gene expression study by analysing bone tissue from 50 patients with osteoporosis and 62 controls. They reported that osteoporosis patients had decreased osteoblastogenesis, increased osteoclastogenesis, and lower TG metabolism than controls. TGs are considered an important form for the storage of fatty acids. Fatty acids are essential components of all lipids and are involved in producing energy in all vertebrates; fatty acid metabolism plays essential roles in osteoblast and osteoclast function and activities as well as in bone remodelling[36-38]. This could be one explanation for the relationship between serum TG levels and bone remodelling. However, the underlying mechanism between TG metabolism and bone metabolism remains unclear, and more studies should be performed in the future.

In addition, we did not observe significant differences in other factors for osteoporosis, such as Ca, P, AST, ALT and ALB levels, between the osteoporosis and control groups in our study. Regarding the association between serum Ca and P levels and osteoporosis, many studies have shown different results. Our study reported that serum Ca and P levels were normal in postmenopausal women with or without osteoporosis. This may be because the levels of Ca and P in serum may not reflect their storage in bones. Serum Ca and P levels are regulated, and homeostasis is maintained in serum[39,40]. In previous studies, nutrition was reported to be related to osteoporosis, and serum ALB levels were lower in patients with osteoporosis[41,42]. By analysing the serum ALB levels of 15539 individuals, hypoalbuminemia (serum ALB less than 3.5 g/dL) was found to be associated with osteoporosis[42]. However, the mean serum ALB levels were more than 35 g/L in patients with normal bone mass and osteoporotic patients and did not show differences between groups in our study. This might be the reason why serum ALB was not a factor for diagnosing osteoporosis in our study. AST and ALT are liver enzymes, and they were also reported to be associated with osteoporosis. In agreement with our study, Do *et al*[9] selected 7160 subjects to analyse the association between liver enzymes and BMD in Koreans. They also did not show differences in the association of AST and ALT with femur BMD. We discovered that ALP was an independent factor for osteoporosis, and osteoporotic female patients aged ≥ 80 years showed significantly increased ALP levels. Supporting our results, increased serum ALP levels in postmenopausal women indicate high bone turnover and

are helpful for diagnosing osteoporosis[43-45].

This study investigated the interplay between BMI, lipid profile, and bone mass within a population vulnerable to brittle fractures. Our research has several strengths. Firstly, our study utilized blood samples collected from fragility fracture patients upon admission to assess pertinent lipid metabolism markers. Secondly, individuals with fragility fractures frequently experience bone loss or osteoporosis. Our findings introduce a novel perspective for future endeavours in osteoporosis and fragility fracture prevention. Furthermore, our hierarchical analysis provides preliminary results, enhancing the generalizability of our research outcomes.

Nonetheless, our research bears certain limitations. Firstly, being a single-centre study, not all patients had lipid metabolism indicator data available for analysis due to admission discrepancies among fragility fracture patients, which resulted in a significant reduction in sample size. Among patients undergoing DXA assessments, the T-value of the proximal femur was the only site measurement employed for standardization, with lumbar and radius measurements being omitted. Furthermore, follow-up data for the study cohort is absent, impeding outcome comparison. Moving forward, we aspire to extend this discourse through a multicentre, large-sample study. Additionally, we intend to investigate the nexus between BMI, lipid profile, and bone mass *via* prospective studies involving nutritional interventions in patients.

CONCLUSION

In conclusion, osteoporotic patients showed significantly decreased BMI and TG levels in comparison with patients with normal bone mass in our study. These results indicate an association between TG metabolism and bone metabolism and provide a new method for the treatment of osteoporosis.

ARTICLE HIGHLIGHTS

Research background

The increasing incidence of osteoporosis and low bone mass, affecting a significant portion of individuals aged 50 years or older in China, underscores the urgent need to address this public health concern. While obesity's potential protective role and the complex interplay between body mass index (BMI), lipid profiles, and bone health are subjects of recent investigation, their specific impact on populations with osteoporosis and fragility fractures remains relatively unexplored.

Research motivation

The relationship between BMI, bone mass, and lipid profiles in populations with osteoporosis and fragility fractures remains understudied.

Research objectives

This study aims to shed light on the potential impact of weight gain and lipid profiles on bone health in individuals with fragility fractures which may provide a new method for the treatment of osteoporosis.

Research methods

This retrospective study conducted at a single orthopaedic trauma center between January 2017 and December 2020 included participants aged 65 years and above with diagnosed fractures in specific region. Participants' comprehensive clinical data, including gender, age groups, BMI ranges, DXA scores, and laboratory measurements, were collected and analyzed using statistical software. Data were analyzed using IBM SPSS and GraphPad Prism software, employing t-tests, nonparametric tests, one-way ANOVA, multiple linear regression, and Pearson correlation tests ($^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$, $^{d}P < 0.0001$ denoting significance) after assessing normality with the Shapiro-Wilk test.

Research results

In this study involving 520 participants aged ≥ 65 years, distinct gender and age-related disparities were observed in osteoporosis prevalence and associated factors. While a significant divergence in age, sex, BMI, alkaline phosphatase (ALP), and triglyceride (TG) concentrations was noted among normal, osteopenic, and osteoporotic groups, multivariate analysis revealed age, sex, BMI, ALP, and TG concentrations as independent risk factors for osteoporosis. Differential correlations between BMI and bone health parameters, along with lipid profiles, were elucidated across age and gender cohorts. Notably, these findings underscore the intricate interplay between metabolic and skeletal factors in the context of osteoporosis.

Research conclusions

In conclusion, osteoporotic patients showed significantly decreased BMI and TG levels in comparison with patients with normal bone mass in our study.

Research perspectives

These results indicate an association between TG metabolism and bone metabolism and provide a new method for the

treatment of osteoporosis.

FOOTNOTES

Author contributions: Chen XX and Tian CW contributed equally to this work; Chen XX and Tian CW designed the study, including the research questions and methodology; Bai LY, Zhao YK, Zhang C, Shi L, Zhang YW, Xie WJ, Zhu HY, Chen H asisted in study design, contributed to data collection and management; Tian CW performed data analysis, provided critical insights into data interpretation; Rui YF supervised the entire study, provided guidance on research design and took a lead in manuscript writing and revision; All authors have read and approve the final manuscript.

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MINIREVIEWS

Triggering, clicking, locking and crepitus of the finger: A comprehensive overview

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Abstract

Triggering, locking, clicking, and crepitus of the fingers are common symptoms patients present with. Even though crepitus and triggering can occur as part of the same underlying diagnosis, it is important to differentiate between them, as they usually indicate different possible diagnoses. The differential diagnoses that should be considered include trigger finger, metacarpophalangeal joint (MCPJ) arthritis, fractures or dislocations, extensor digitorum communis subluxation or dislocation, locked MCPJ, avascular necrosis of the metacarpal head, and Dupuytren's disease. A thorough clinical examination with appropriate special investigations can permit the clinician to make the correct diagnosis. Appropriate management of a confirmed diagnosis is successful in providing symptomatic improvement.

Key Words: Trigger finger; Locking; Crepitus; Metacarpophalangeal joint; Dislocation; Differential diagnosis

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Core Tip: Despite trigger fingers being one of the most common causes of hand pain and disability, there are other possible causes of triggering, locking, clicking, and crepitus of the fingers. Failure to recognize and diagnose these other causes can lead to treatment errors and inappropriate management of patients.

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INTRODUCTION

Trigger fingers are one of the most common causes of pain and disability of the adult hand[1,2]. Even though a trigger finger is commonly associated with locking of the finger in flexion and a painful snapping (clicking) during extension[3,4], a mild trigger finger (Green 1)[5] may present with only pain, swelling and stiffness in the morning[6,7], whereas a severe one (Green 4)[5], may have a locked digit[7], presenting like a flexion contracture[7] which has to be distinguished from a Dupuytren's contracture.

When associated with severe flexor synovitis, patients with trigger fingers may even have crepitus in the palm[7], but when crepitus is present, a clinician will tend to consider metacarpophalangeal joint (MCPJ) arthritis as a diagnosis. A well-known medical cliché is: "common things occur commonly." This is important to remember, but at the same time, as clinicians, we have to keep in mind that "not all that glitters is gold."

In this minireview, we provide a short summary of the broad differential diagnosis for triggering and crepitus of the finger and briefly discuss the clinical presentation, workup, and treatment of these different conditions.

PRESENTING SYMPTOMS

In this modern day and age, many patients, after extensive internet research, will present to their doctor with a diagnosis. The majority of patients will still present with troublesome symptoms, which include the following.

Pain is probably the most common symptom. It is important to differentiate between pain in the mornings (inflammatory) and pain with motion (mechanical). A trigger finger will often be more painful in the mornings or evenings and will also experience pain with extension when triggering. Arthritis will generally cause pain with all motion of the joint and less pain when resting, except in cases of inflammatory arthritis, which can also present with morning and evening pain.

Stiffness is often associated with many conditions affecting the hand. It is important to determine whether there is a fixed decreased range of motion or just temporary stiffness or uneven motion.

Triggering can be reported in some individuals. Most patients will describe it as clicking or locking, depending on the severity of the disease.

Crepitus is a symptom that patients tend not to complain about; however, patients commonly describe it as grinding or they say it feels as though they have sand or gravel around the tendon when they try and move. In the case of a fracture, they may even describe a feeling of cracking.

The history is important as acute onset following trauma would guide the diagnosis more towards a fracture or sagittal band injury.

DIFFERENTIAL DIAGNOSIS

Several conditions need to be considered in the differential diagnosis of these symptoms. The most common conditions are listed below and reported in Table 1.

Trigger finger

Trigger finger remains the most common diagnosis[1]. It is caused by a discrepancy in the size of the flexor tendon and the A1 pulley[8], but in 1% of cases, the triggering can occur at the A2 pulley[5]. There is a bimodal distribution with pediatric trigger fingers presenting before the age of 8 and adult cases presenting in the 5th and 6th decade[1,3]. It is more common in females[3] and tends to affect the ring and middle fingers more commonly[1]. Many conditions are associated with trigger fingers including diabetes, inflammatory conditions, carpal tunnel syndrome, hypothyroidism, gout, storage diseases, De Quervain's tenosynovitis, and Dupuytren's contracture[7,8].

MCPJ arthritis[9]

Arthritis causes pain, swelling, and a limited range of motion. Rheumatoid and other inflammatory arthritis used to be the most common causes of MCPJ arthritis. With improved medical control, this is seen less than it used to be. Osteoarthritis, posttraumatic arthritis, and crystalline deposition disorders should be included in the differential diagnosis.

Fractures and dislocations

This seems like an obvious diagnosis, but can be missed if not considered. There should be a clear trauma history with a

Table 1 Differential diagnosis of triggering, clicking, and locking of the finger

Differential diagnoses
Trigger finger
Metacarpophalangeal joint arthritis
Fractures and dislocations
Extensor digitorum communis subluxation/dislocation
Locked metacarpophalangeal joint
Avascular necrosis of the metacarpal head
Dupuytren's contracture

painful, swollen, and bruised finger and crepitus and pain with motion. Consider metacarpal head and neck fractures and fractures at the base of the proximal phalanx as well as MCPJ dislocations.

Extensor digitorum communis subluxation/dislocation

In acute traumatic injury, Boxer's Knuckle, there is a rupture of the sagittal band (most commonly the radial sagittal band), causing subluxation or dislocation of the extensor digitorum communis (EDC) tendon[10,11]. It can also occur due to attrition as seen in Rheumatoid Arthritis patients or occasionally in osteoarthritis[10]. The middle finger is most affected in a Boxer's Knuckle[10-12]. The MCPJ is swollen and tender[11] and patients can complain of clicking with crepitus found during examination, which is called pseudo triggering[10]. In mild cases (Rayan and Murray grade 1)[13] the MCPJ is just swollen and tender, but in cases of complete EDC dislocation (Rayan and Murray grade 3)[13] active extension may not be possible[10,11] and can create the impression of a locked MCPJ or even an extensor tendon rupture.

Locked MCPJ

A patient can present with a loss of active and passive MCPJ extension, without affecting interphalangeal joint motion and while maintaining full flexion[14,15]. This is caused by entrapment of the collateral ligament (usually the radial collateral ligament)[15] behind an osteophyte of the metacarpal head in flexion, which prevents extension. In certain cases, the ligament does not get stuck but just causes snapping as it passes over the osteophyte[16]. It can be caused by any condition that causes an abnormal shape of the metacarpal head, such as acromegaly or achondroplasia[15]. Impingement of a torn palmar plate can cause locking of the MCPJ[15,16], but in these cases, flexion can often be limited rather than extension[15].

Avascular necrosis of the metacarpal head (Dietrich's/Mauclaire's disease)

Avascular necrosis (AVN) of the metacarpal head is very rare. It occurs more commonly in young men and more commonly in the middle finger[17,18]. Patients can present with pain and crepitus, very similar to arthritis, and it is associated with anatomical variations in blood flow, trauma, steroid use, systemic lupus erythematosus (SLE), hypercoagulability, alcoholism or it can be idiopathic[17,18].

Dupuytren's disease

Dupuytren's disease is an idiopathic fibrosis of the palmar aponeurosis leading to contractures of the fingers[19]. It can be associated with trigger fingers, but should also be considered as a differential diagnosis for a locked finger. Even though the diagnosis may seem obvious, some patients can have subtle cords, making it less obvious. It should also be remembered that Dupuytren's can be associated with trigger fingers and both diagnoses can co-exist on the same finger.

DIAGNOSIS

Clinical

In many cases, the diagnosis can be made through history and clinical examination. In the case of a trigger finger, the patient will present with a typical history of temporary locking of the finger in flexion and painful snapping during extension[4]. Triggering may not be elicited in all cases, but there is generally mild swelling of the finger and tenderness over the A1 pulley[1,3].

In MCPJ arthritis, the patient will complain of pain with motion and a decreased range of motion. On examination, the joint will be swollen and tender, with a decreased range of active and passive motion[9] and a positive grind test. Crepitus may be felt.

Fractures and dislocations around the MCPJ should present with a typical trauma history with a painful swollen and bruised finger and hand. There can be a deformity and any motion will be extremely painful and may even produce crepitus. With a dislocation, the joint may seem locked in a certain position.



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Figure 1 X-ray of a hand with crepitus. Osteoarthritis of the middle finger metacarpophalangeal joint.

EDC subluxation may present with a trauma history[20] in cases of sagittal band rupture, but may also have a spontaneous onset[20] in cases of sagittal band attrition[10]. The MCPJ will generally be swollen and tender dorsally with clicking (pseudo triggering)[10] noted during motion[11]. In Rayan and Murray[13] grade 3 cases, there may be an extensive deficit during active motion, with normal passive extension. During full active MCPJ flexion, the EDC can be observed to sublux/dislocate out of its central position over the MCPJ.

A patient who presents with a locked MCPJ may suggest a trivial traumatic event as a cause of their condition. There may be signs of osteoarthritis of the other small joints in the hand and the MCPJ is often not swollen and non-tender. There will be decreased active and passive extension with normal interphalangeal joint motion and full active flexion of the finger[14,15].

AVN of the metacarpal head is a rare condition[17,18] and a diagnosis of exclusion[18]. There will be pain and possibly crepitus[17,18] and a decreased range of motion in a patient who is younger than would be normally expected to be seen in an arthritic joint. Conditions associated with AVN such as steroid use, alcoholism, SLE, and hypercoagulability[17,18] may be present.

In a patient with Dupuytren's contracture, there will be a fixed contracture limiting full extension and there should be a visible and palpable cord and possible family history. A careful examination is mandatory as some patients can have very subtle cords and be aware that there may be a co-existing grade 1 trigger finger with a tender A1 pulley.

X-ray

Where the diagnosis is not obvious on clinical examination, radiographs should be the first special investigation and will assist with the diagnosis of a fracture, dislocation, and arthritis (Figure 1). In sagittal band attrition, there may be signs of underlying arthritis and in a locked MCPJ an osteophyte may be visible (Figure 2). X-rays may be normal in early cases of AVN, but in more advanced cases collapse will be present.

Ultrasound

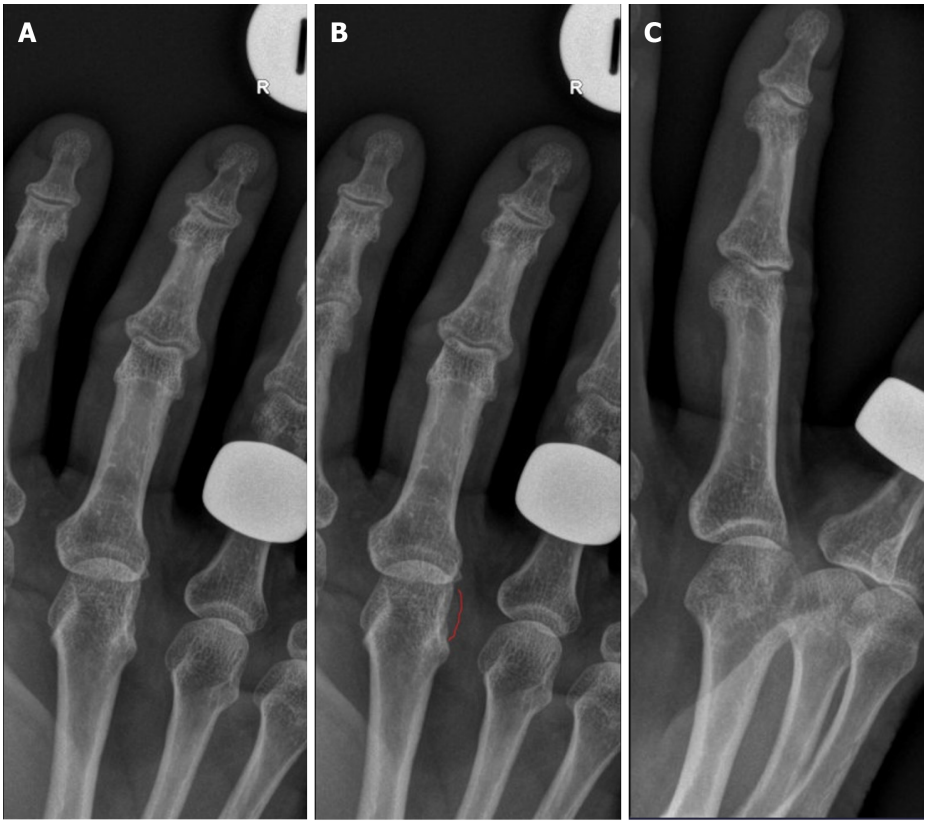
Ultrasound can be used to confirm the diagnosis of a trigger finger if there is any doubt, and it will show a thickening of the A1 pulley and possibly the flexor tendon with or without signs of flexor synovitis. Dynamic scanning is possible for cases of suspected EDC subluxation/dislocation to assist with the diagnosis. Ultrasound can also be used in cases of a locked MCPJ to diagnose an entrapped collateral ligament or torn palmar plate. Even Dupuytren's nodules and cords can be confirmed with ultrasound[21].

Laboratory investigations

Blood tests will not help to differentiate between the diagnosis discussed here, but where a possible inflammatory or crystalline arthropathy is suspected or in cases of AVN it may be useful to determine the underlying cause.

Magnetic resonance imaging

The main purpose of magnetic resonance imaging (MRI) is in the detection of early AVN[17] (Figure 3) where the x-ray is still normal and other diagnoses have been excluded and it can assist in the diagnosis of a locked MCPJ[15]. Even though MRI will pick up trigger fingers, arthritis, sagittal band attrition/rupture, fractures, and Dupuytren's cords/nodules, it is not recommended as first-line investigation for any of these conditions.



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Figure 2 X-ray of a hand with locking. A: X-rays of locked metacarpophalangeal joint (MCPJ); B: X-rays with ulnar osteophyte marked; C: Oblique view of locked MCPJ.

TREATMENT

An in-depth discussion of the treatment of all these conditions is outside the scope of this article, but we will discuss some general treatment principles and in brief discuss specific treatments for each condition.

General measures

Lifestyle modification and diet change is the simplest early treatment. As long as lifestyle modification does not affect quality of life, it can be very effective. Therapy with or without the use of splints is the next line of non-invasive therapy. A Prospective, Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial showed that avocado/soybean unsaponifiables are more effective than placebo in providing symptomatic relief in hip and knee osteoarthritis[22]. Other medications such as non-steroidal anti-inflammatory medication can also be very effective in providing symptomatic relief. Cortisone injections, which in some cases only provide temporary symptomatic relief, can potentially be curable in for instance trigger fingers. Surgery is generally the last line of treatment, but in most cases is the most reliable solution for providing long-term relief.

Trigger fingers

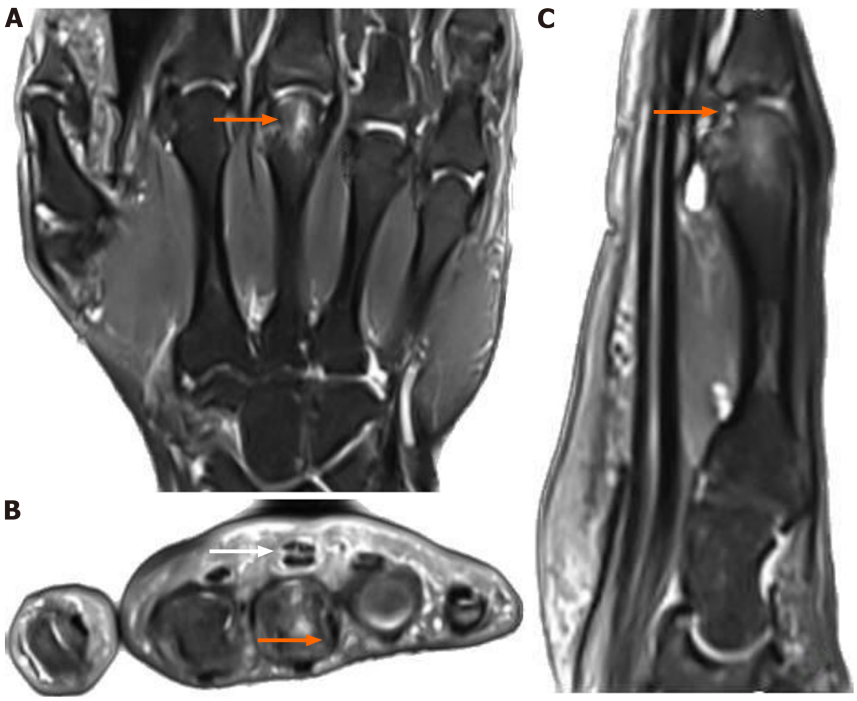
It is important to remember that 52% of trigger fingers will resolve spontaneously without any intervention within 8 mo of the onset of symptoms[23]. Splints can be effective in up to 55% of cases in 1 year, but it is uncertain how many of these would have resolved spontaneously[1]. A single cortisone injection can be curative in 45%-80% of cases with repeat injections being effective in 30%-40% of cases[1]. There seems to be no difference between an injection into the flexor sheath *vs* an injection outside the flexor sheath[24]. Surgery can be performed as either open or percutaneous[7] and provides the best chance of a long-term symptom-free result.

MCPJ arthritis

When conservative management fails (see under general measures), arthroplasty is usually the surgical option of choice [9]. In cases of inflammatory or crystalline arthropathy, it is important to refer the patient to a Rheumatologist to adequately manage the underlying cause. It is worth remembering that hemochromatosis can cause arthritis of the index and middle finger MCPJs[25] and the patient should be worked up for this and referred for treatment if indicated.

Fractures and dislocations

Fractures should be managed according to the fracture type, displacement, angulation, rotation, and shortening. Most



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Figure 3 Magnetic resonance imaging of a hand with pain and symptoms. A: Edema in the third metacarpal head (orange arrow) shown on magnetic resonance imaging (MRI) coronal view T2; B: Edema in the third metacarpal head (orange arrow) and flexor tendons with minimal effusion (white arrow) shown on magnetic resonance imaging transverse view; C: Edema in the third metacarpal head with effusion and joint surface involvement (orange arrow) shown on MRI sagittal view T2.

fractures can be managed conservatively in a splint, but if the position is not acceptable, may require a closed reduction with or without k-wires or an open reduction and internal fixation. Dislocations require reduction and this can mostly be achieved by closed means. In case of failed closed reduction or incongruent reduction, open surgery must be performed.

Extensor tendon subluxation/dislocation

The majority of cases can be managed in a splint[10,12], especially within 3 wk of the injury[11,20]. Surgery is reserved for the professional athlete, chronic cases, or those who failed conservative treatment and can be either a direct repair or sagittal band reconstruction[10,11].

Locked MCPJ

Closed reduction can be attempted by injecting local anesthetic into the joint and then applying gentle traction and rotation, but this does carry the risk of a potential fracture. Most cases are managed surgically by open reduction and excision of the osteophyte[14,15].

AVN of the metacarpal head

The first line of treatment should be rest and medication, but if this fails, then the surgical options are curettage and bone graft, osteotomy, osteochondral grafts, denervation, arthrodesis, or arthroplasty[17].

Dupuytren's contracture

Once there is the progression of the contracture and it becomes functionally debilitating, surgery, either percutaneous needle aponeurotomy or fasciectomy (partial or segmental), becomes the treatment of choice[19].

PROGNOSIS

The success of cortisone injections in trigger fingers has already been discussed. Surgery, whether open or percutaneous can have success rates of 90%-100%[1]. Arthroplasty for MCPJ arthritis is successful in improving pain and function and has patient satisfaction rates of up to 90% in certain studies, especially in osteoarthritis[9]. Conservative and surgical management, when indicated, is very effective in the treatment of EDC subluxation/dislocation in terms of symptom improvement[10]. In a case series of locked MCPJs, 13 of 14 patients (1 was lost to follow-up) had an excellent outcome with no pain and a normal range of motion[15]. AVN of the metacarpal head is rare and therefore little is known about the long-term prognosis[17]. Fractures, dislocations, and Dupuytren's contractures have so many treatment options and are such vast topics in themselves, that the discussion of treatment specifics and prognosis falls outside the scope of this

article.

SUMMARY

With regards to what we currently know about this condition, triggering, clicking, locking, and crepitus of the finger are symptoms typically associated with a condition known as "trigger finger" or stenosing tenosynovitis. This condition primarily affects the flexor tendons of the fingers and is characterized by certain signs and symptoms. Triggering is a sensation where the finger gets stuck in a bent position and then suddenly releases with a "click" or "pop." Clicking can be defined as an audible or palpable clicks or snaps during finger movement. Locking occurs when the finger becomes locked in a flexed position, requiring manual assistance to extend it. Crepitus can be described as the sensation or sound of grinding, popping, or crackling within the affected finger during movement.

Current knowledge suggests that these symptoms arise due to inflammation or thickening of the tendon sheath, obstructing the smooth gliding of the flexor tendon. The exact causes of the trigger finger are multifactorial, with risk factors including repetitive gripping activities, underlying medical conditions, and genetic predisposition.

The current theories that drive the clinical applications in the management include the inflammation within the tendon sheath plays a key role in trigger finger symptoms. Treatments often involve anti-inflammatory medications, corticosteroid injections, or physical therapy. The Structural Theory is thought that structural changes in the tendon, such as nodules or thickening, are responsible for the condition. Surgical interventions, such as tenosynovectomy or release, aim to address these structural issues. The Biomechanical Theory includes mechanical factors, like repetitive strain or improper hand ergonomics, which are thought to contribute to the development of trigger fingers. Occupational therapy and ergonomic modifications are employed to alleviate symptoms.

Further research on the trigger finger is essential for several reasons. Trigger finger is a common hand condition, and its prevalence is increasing, possibly due to changes in lifestyles and work habits. Understanding it better can help address this growing health concern. The condition can significantly impact an individual's quality of life, affecting their ability to perform daily activities and work. Improved management strategies can enhance patients' well-being. Trigger finger is associated with healthcare costs, including treatments, lost workdays, and rehabilitation. Better management approaches could reduce the economic burden.

Advancements in treatment are fundamental. As our understanding of the condition deepens, more targeted and effective treatment options can be developed, potentially reducing the need for surgery and minimizing recurrence rates. Research should focus on the long-term outcomes of different treatment modalities, including surgery, corticosteroid injections, and conservative therapies, to determine which provides the best-sustained relief.

Understanding the underlying pathophysiological mechanisms of the trigger finger can lead to more precise diagnostic tools and therapeutic targets. Identifying additional risk factors beyond those currently recognized can help with early detection and preventive measures. The efficacy of non-surgical treatments, such as physical therapy, occupational therapy, and ergonomic modifications, needs more extensive study to establish their role in managing the trigger finger.

Studies investigating the long-term outcomes of various treatment approaches, elucidating the precise pathophysiological mechanisms, identifying novel risk factors, and assessing the effectiveness of non-surgical interventions, can provide a more comprehensive understanding of this condition. Clinicians must seek to improve patient care and quality of life by guiding the development of more effective and evidence-based management strategies for trigger finger.

CONCLUSION

Triggering (locking, clicking) and crepitus of the fingers are symptoms that commonly occur. It can co-exist as part of the same pathology, but more often occur separately and point towards different pathologies. Even though trigger fingers are the most common cause of pain and disability in the hand, it is important to consider the other possible diagnoses. A thorough history and clinical examination with appropriate special investigations will aid in making the correct diagnosis. Adequate treatment has a high success rate in terms of resolution of symptoms and good functional recovery.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Machine learning applications for the prediction of extended length of stay in geriatric hip fracture patients

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Abstract

BACKGROUND

Geriatric hip fractures are one of the most common fractures in elderly individuals, and prolonged hospital stays increase the risk of death and complications. Machine learning (ML) has become prevalent in clinical data processing and predictive models. This study aims to develop ML models for predicting extended length of stay (eLOS) among geriatric patients with hip fractures and to identify the associated risk factors.

AIM

To develop ML models for predicting the eLOS among geriatric patients with hip fractures, identify associated risk factors, and compare the performance of each model.

METHODS

A retrospective study was conducted at a single orthopaedic trauma centre, enrolling all patients who underwent hip fracture surgery between January 2018 and December 2022. The study collected various patient characteristics, encompassing demographic data, general health status, injury-related data, laboratory examinations, surgery-related data, and length of stay. Features that exhibited significant differences in univariate analysis were integrated into the ML model

establishment and subsequently cross-verified. The study compared the performance of the ML models and determined the risk factors for eLOS.

RESULTS

The study included 763 patients, with 380 experiencing eLOS. Among the models, the decision tree, random forest, and extreme Gradient Boosting models demonstrated the most robust performance. Notably, the artificial neural network model also exhibited impressive results. After cross-validation, the support vector machine and logistic regression models demonstrated superior performance. Predictors for eLOS included delayed surgery, D-dimer level, American Society of Anaesthesiologists (ASA) classification, type of surgery, and sex.

CONCLUSION

ML proved to be highly accurate in predicting the eLOS for geriatric patients with hip fractures. The identified key risk factors were delayed surgery, D-dimer level, ASA classification, type of surgery, and sex. This valuable information can aid clinicians in allocating resources more efficiently to meet patient demand effectively.

Key Words: Machine learning; Extended length of stay; Hip fracture; Enhanced recovery after surgery; Risk factors

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Core Tip: Traditional models have been built to identify risk factors for extended length of stay (eLOS), offering new insights for optimizing treatment for hip fracture patients under the enhanced recovery after surgery concept. However, these traditional statistical methods suffer from poor performance and lack of features. Machine learning (ML) is a scientific discipline focused on teaching computers to learn from data, showing superior predictive performance compared to traditional methods. This study aims to develop ML models for predicting eLOS among geriatric patients with hip fractures, identify associated risk factors, and compare the performance of each model.

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INTRODUCTION

Hip fractures have become more prevalent as the global geriatric population increases[1]. They are associated with higher incidence, mortality, and disability, significantly impacting the quality of life of affected individuals[2,3]. Prolonged length of stay (LOS) not only places a financial burden on patients but also elevates the risk of mortality and complications[4]. Enhanced recovery after surgery (ERAS) refers to the integration of perioperative concepts using evidence-based medicine tools to reduce surgical stress and complications, shorten hospital stays, lower financial costs, and hasten postoperative recovery[5-7]. Based on this concept, Andrew *et al*[8] developed a logistic regression (LR) model to identify risk factors for extended length of stay (eLOS), offering new insights for optimizing treatment for hip fracture patients. However, traditional statistical methods suffer from poor performance and lack of features.

Machine learning (ML) is a scientific discipline focused on teaching computers to learn from data[9]. In recent times, ML has shown superior predictive performance compared to traditional methods and has found extensive application in clinical data processing and predictive modelling[10,11]. Mijwil and Aggarwal[12] enhanced the ML based estimation method for detecting acute appendicitis in individuals, achieving high accuracy. In the context of hip fractures among geriatric individuals, Oosterhoff *et al*[13] and Shtar *et al*[14] established ML models to predict prognosis and mortality, enhancing clinician decision-making ability. With the establishment of a clinical database for elderly hip fracture patients and advancements in ML algorithms, predicting the eLOS for this patient group through ML has become feasible.

This study aims to develop ML models for predicting the eLOS among geriatric patients with hip fractures, identify associated risk factors, and compare the performance of each model.

MATERIALS AND METHODS

Study design, setting and population

A retrospective study was conducted at a single orthopaedic trauma centre between January 2018 and December 2022. The study employed specific inclusion and exclusion criteria as follows inclusion criteria: (1) Age older than 60 years at the time of injury; (2) confirmed diagnosis of hip fracture; and (3) hospitalization at our centre. The study employed specific inclusion and exclusion criteria as follows exclusion criteria: (1) Admission with multiple fractures, pathological

fractures, or fractures around the prosthesis; (2) receipt of conservative treatment due to severe comorbidities; and (3) presence of missing data.

The enrolled patients had a median hospital stay of 9.5 d. Based on this median LOS, the patients were retrospectively divided into two groups: None LOS (LOS ≤ 9.5 d, n = 383, 50.2%) and eLOS (LOS > 9.5 d, n = 380, 49.8%).

Perioperative treatment and surgical procedure

All patients underwent comprehensive perioperative assessments to ensure standardized diagnosis and treatment. Our centre boasts a multidisciplinary team comprising geriatricians, anaesthetists, and intensive care unit (ICU) doctors who collaborate to review the perioperative care of patients with comorbidities[15]. Upon admission, a rapid preoperative risk assessment is performed, considering the patient's physical condition and specific needs. Subsequently, an individualized treatment plan is promptly devised. For patients requiring surgical intervention, a consistent surgical team oversees all procedures. Patients with femoral neck fractures receive surgical treatments such as total hip arthroplasty (THA), hemiarthroplasty of the hip, or internal fixation. Those with intertrochanteric fractures undergo surgical treatment, such as internal fixation. Throughout the surgery, the patient's temperature, blood volume, and haemodynamics are meticulously managed with the collaborative efforts of anaesthesia and surgical nurses.

Data collection

Data for the study were retrospectively gathered from electronic patient records at the institution. Demographic data encompassed sex, age, body mass index, general health status categorized by the American Society of Anaesthesiologists (ASA) classification, history of smoking, oral anticoagulant use, and comorbidities[16]. Injury-related data included fracture type, time from injury to admission, and the day of admission. Surgery-related data consisted of the type of surgery, anaesthesia used, ICU transfer, time to surgery, duration of surgery, intraoperative blood loss, and transfusion. Laboratory examinations conducted at admission and after surgery were also collected. Age was stratified into 60-85 and > 85 age groups; ASA classification was grouped as I-II and III-IV; admission day was grouped into Monday to Thursday and Friday to Sunday; injury time was stratified into ≤ 24 and > 24 h; and delayed surgery was defined as an operation performed more than 48 h after admission. Laboratory examinations were stratified according to normal values.

ML and statistical analysis

In the study, normally distributed data are presented as the means and standard deviations. Nonnormally distributed variables were expressed as medians along with their interquartile ranges. Categorical variables are represented as counts and percentages. To analyse the overall data, continuous variables were subjected to Student's t test or the Mann–Whitney U test, depending on their distribution. Categorical variables were analysed using the chi-square test, as appropriate. Variables showing significant differences in the univariate analysis were selected and included in the establishment of the ML model.

The predictive eLOS ML model was established according to the selected features, including basic algorithms for LR, decision tree (DT), random forest (RF), support vector machine (SVM), naïve Bayes, K-nearest neighbour, eXtreme Gradient Boosting (XGBoost) and artificial neural network (ANN) models. Next, we used a Shapley Additive Interpretation (SHAP) summary plot to determine the relationship between the eLOS and its main predictors in each model. Each ML model was integrated to ascertain feature importance. Then, the original data were split into a training set and a test set (training: test = 7:3), and 10-fold cross-validation was carried out. The accuracy score, precision score, recall score, F1 score, receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to evaluate the performance of the ML model of the original data and cross-validation. All statistical analyses were conducted using Python (version 3.8.2, Python Software Foundation, https://www.python.org) and the sklearn package (version 0.24.1). A 2-sided P value < 0.05 was considered significant. The flow diagram of the research process is shown in Figure 1.

RESULTS

Population and patient characteristics

Overall, 763 patients were enrolled in the final analysis; patients were divided into none LOS (n = 383) and eLOS (n = 380) groups based on LOS. The characteristics of the two groups are compared in Table 1. Univariate analysis showed that there were significant differences in sex, fracture type, ASA classification, admission day, injury to admission time, hypertension, diabetes, cerebral infarction, deep venous thrombosis (DVT), delayed surgery, THA, reduction and fixation, aspartate aminotransferase and D-dimer levels and aortic velocity at admission between the two groups (P < 0.05).

Establishment and evaluation of the ML model in the original data

We used 8 ML models to evaluate the predictors of LOS in the original data. Figure 2 shows the ROC curve, and Table 2 shows the performance indicators of each model. The tree models, including the DT (accuracy = 0.924, AUC = 0.988), RF (accuracy = 0.924, AUC = 0.985) and XGBoost (accuracy = 0.912, AUC = 0.976) models, showed stronger performance among the models. In addition, the performance of the ANN (accuracy = 0.886, AUC = 0.963) model was impressive.

Table 1 Baseline data comparison. Counts (%) unless otherwise specified

Features	Non-eLOS (*n* = 383)	eLOS (*n* = 380)	Statistic (t/χ^2)	*P* value
Sex			5.418	0.020
Male	107 (27.9)	136 (35.8)		
Female	276 (72.1)	244 (64.2)		
Age (yr)			0.096	0.757
60-85	255 (66.6)	257 (67.6)		
> 85	128 (33.4)	123 (32.4)		
BMI (kg/m^2)			2.578	0.461
< 18.5	48 (12.5)	44 (11.6)		
18.5-24.9	220 (57.4)	239 (62.9)		
25.0-29.9	99 (25.8)	82 (21.6)		
> 30.0	16 (4.2)	15 (3.9)		
Fracture type			20.516	*P* < 0.001
Femoral neck fracture	165 (43.1)	226 (59.5)		
Intertrochanteric fracture	218 (56.9)	154 (40.5)		
ASA classification			20.313	*P* < 0.001
I-II	197 (51.4)	134 (35.3)		
III-IV	186 (48.6)	246 (64.7)		
Admission time			5.340	0.021
Monday to Thursday	248 (64.8)	215 (56.6)		
Friday to Sunday	135 (35.2)	165 (43.2)		
Time from injury to admission			5.513	0.019
≤ 24 h	322 (84.1)	294 (77.4)		
> 24 h	61 (15.9)	86 (22.6)		
Comorbidities	3.99 2.22	4.19 2.25	1.221	0.223
Hypertension	207 (54.0)	245 (64.5)	8.588	0.003
Diabetes	85 (22.2)	112 (29.5)	5.279	0.022
ACS	59 (15.4)	66 (17.4)	0.537	0.464
Cerebral infarction	120 (31.3)	150 (39.5)	5.531	0.019
AKI	8 (2.1)	17 (4.5)	3.423	0.064
DVT	66 (17.2)	91 (23.9)	5.263	0.022
History of smoking	14 (3.4)	17 (4.5)	0.328	0.567
Oral anticoagulant use	71 (18.5)	71 (18.7)	0.003	0.959
History of fracture	77 (20.1)	83 (21.8)	0.348	0.556
Hip fracture	21 (5.5)	29 (7.6)	1.438	0.230
Lumbar fracture	25 (6.5)	24 (6.3)	0.014	0.905
Delayed surgery	153 (39.9)	267 (70.3)	70.842	*P* < 0.001
Type of surgery				
THA	52 (13.6)	95 (25.0)	16.002	*P* < 0.001
HHA	106 (27.7)	127 (33.4)	2.968	0.085
Reduction and fixation	225 (58.7)	158 (41.6)	22.488	*P* < 0.001
Duration of surgery	96.62 ± 27.83	118.43 ± 24.32	1.743	0.082

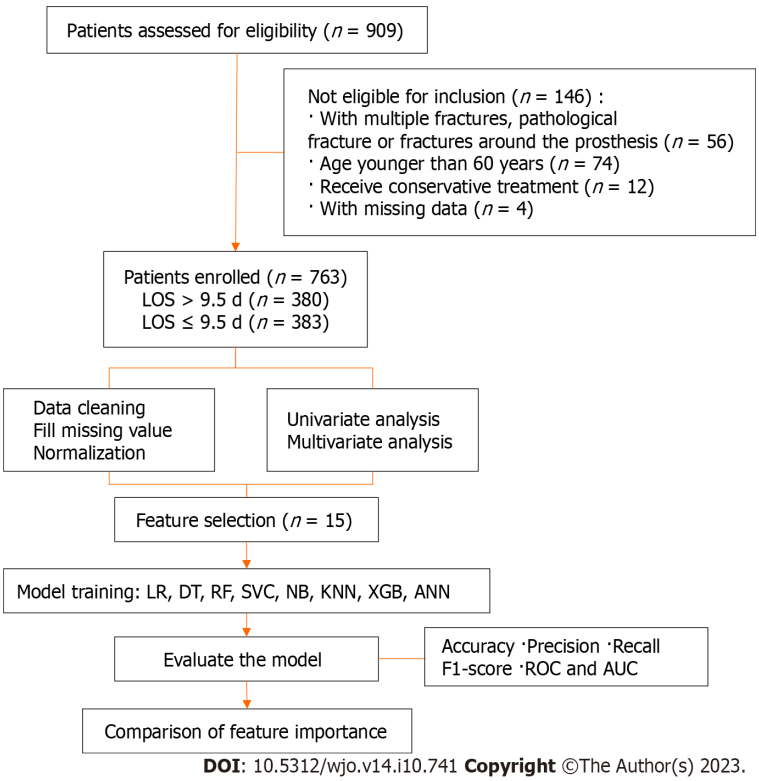
Intraoperative blood loss	164.54 ± 85.26	162.33 ± 104.20	-0.321	0.748
Blood transfusion	127 (33.2)	132 (34.7)	0.212	0.645
ICU transfer	103 (26.9)	111 (29.2)	0.508	0.476
Type of anaesthesia			0.769	0.380
General	336 (87.7)	341 (89.7)		
Regional	47 (12.3)	39 (10.3)		
Heart rate at admission (60-100)	339 (88.5)	331 (87.1)	0.353	0.553
Laboratory examination at admission				
RBC (≥ 4.3)	86 (22.5)	87 (22.9)	0.021	0.884
WBC (3.5-9.5)	208 (54.3)	217 (57.1)	0.605	0.437
Hb (≥ 110)	251 (65.5)	268 (70.5)	2.184	0.139
PLT (125-350)	321 (83.8)	306 (80.5)	1.406	0.236
N (40-75)	65 (17.0)	81 (21.3)	2.327	0.127
HCT (≥ 40)	82 (21.4)	65 (17.1)	2.272	0.132
K (3.5-5.1)	260 (67.9)	265 (69.7)	0.305	0.581
Ca (≥ 2.1)	257 (67.1)	260 (68.4)	0.152	0.697
Na (137-145)	248 (64.8)	229 (60.3)	1.640	0.200
ALB (30-40)	233 (60.8)	243 (63.9)	0.787	0.375
ALT (9-50)	347 (90.5)	342 (90.0)	0.079	0.779
AST (15-40)	338 (88.3)	316 (83.2)	4.040	0.044
LDH (120-246)	188 (49.1)	179 (47.1)	3.000	0.584
BUN (3.6-9.5)	304 (79.4)	302 (79.5)	0.001	0.973
Cr (58-110)	205 (53.5)	221 (58.2)	1.660	0.198
PT (9.4-12.5)	77 (20.1)	93 (24.5)	2.103	0.147
APTT (25.1-36.5)	326 (85.1)	331 (87.1)	0.630	0.427
INR (0.8-1.2)	311 (81.2)	304 (80.0)	0.176	0.675
FIB (2.38-4.98)	344 (89.8)	344 (90.5)	0.108	0.742
D-dimer (≤ 6500)	218 (56.9)	165 (43.4)	13.902	$P < 0.001$
Cardiac colour ultrasound at admission				
AV (≥ 1.0)	367 (95.8)	347 (91.3)	6.446	0.011
EF (≥ 70)	208 (54.3)	217 (57.1)	0.605	0.437
Laboratory examination after surgery				
Hb (≥ 110)	87 (22.7)	92 (24.2)	0.237	0.626
ALB (30-40)	310 (80.9)	303 (79.7)	0.175	0.676
Cr (58-110)	222 (58.0)	232 (61.1)	0.755	0.385

BMI: Body mass index; ASA: American society of anaesthesiologists; ACS: Acute coronary syndromes; AKI: Acute kidneyinjury; DVT: Deep venous thrombosis; THA: Total hip arthroplasty; HHA: Hip hemiarthroplasty; ICU: Intensive care unit; RBC: Red blood cell; WBC: White blood cell; Hb: Hemoglobin; PLT: Platelets; N: Neutrophile granulocyte; HCT: Hematocrit; K: Kalium; Ca: Calcium; Na: Natrium; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; Cr: Creatinine; PT: Prothrombin time; APTT: Activated partial thromboplastin time; INR: International normalized ratio; FIB: Fibrinogen; AV: Aortic velocity; EF: Ejection fraction.

Table 2 Evaluation of machine learning models in the original data

Model name	Accuracy	Precision	Recall	F1 score	AUC
LR	0.680	0.680	0.676	0.678	0.747
DT	0.924	0.994	0.853	0.918	0.988
RF	0.924	0.940	0.905	0.922	0.985
SVM	0.651	0.636	0.703	0.667	0.739
NB	0.657	0.676	0.598	0.634	0.709
KNN	0.747	0.748	0.742	0.745	0.828
XGB	0.912	0.941	0.879	0.901	0.976
ANN	0.886	0.899	0.868	0.883	0.963

AUC: Area under curve; LR: Logistic regression; DT: Decision tree; RF: Random forest; SVM: Support vector machine; NB: Naïve bayes; KNN: K-nearest Neighbour; XGB: eXtreme Gradient Boosting; ANN: Artificial neural network.



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Figure 1 The flow diagram of the research process. LOS: Length of stay; LR: Logistic regression; DT: Decision tree; RF: Random forest; SVC: Support vector classifier; NB: Naïve bayes; KNN: K-nearest neighbour; XGB: eXtreme Gradient Boosting; ANN: Artificial neural network; ROC: Receiver operating characteristic; AUC: area under the receiver operating characteristic curve.

Feature importance

Figure 3 shows the results of the SHAP analysis. We can intuitively understand the importance of features in each model and the direction of their association with the eLOS. Then, we summarized the importance of the features output by each model. Figure 4 shows the feature weights in descending order; delayed surgery was the most important feature in eLOS prediction. The other most important features that influenced the prediction of the eLOS were D-dimer level, ASA classification, type of surgery and sex.

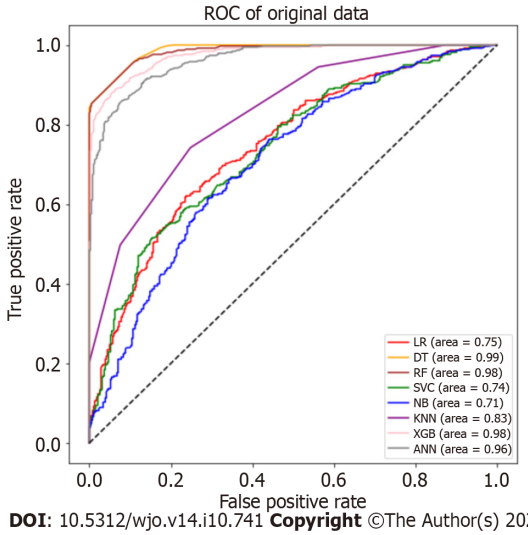
Evaluation of ML models after 10-fold cross-validation

We split the original data into training and test sets (training: test = 7:3) and carried out 10-fold cross-validation. Figure 5 shows the ROC curve, and Table 3 indicates the performance indicators of each model after cross-validation. We found that the performance of the model decreased after cross-validation compared to the original data. The best results were found by using the SVM (accuracy = 0.664, AUC = 0.712) model. Furthermore, the LR (accuracy = 0.650, AUC = 0.650)

Table 3 Evaluation of machine learning models after 10-fold cross-validation

Model name	Accuracy	Precision	Recall	F1 score	AUC
LR	0.650	0.643	0.668	0.655	0.650
DT	0.606	0.616	0.552	0.583	0.605
RF	0.619	0.618	0.613	0.616	0.619
SVM	0.664	0.656	0.659	0.658	0.712
NB	0.644	0.657	0.595	0.624	0.643
KNN	0.617	0.611	0.639	0.625	0.617
XGB	0.630	0.632	0.616	0.624	0.630
ANN	0.606	0.596	0.645	0.619	0.606

AUC: Area under curve; LR: Logistic regression; DT: Decision tree; RF: Random forest; SVM: Support vector machine; NB: Naïve bayes; KNN: K-nearest Neighbour; XGB: eXtreme Gradient Boosting; ANN: Artificial neural network.



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Figure 2 Receiver operating characteristic curve for machine learning models in the original data. ROC: Receiver operating characteristic; LR: Logistic regression; DT: Decision tree; RF: Random forest; SVC: Support vector classifier; NB: Naïve Bayes; KNN: K-nearest Neighbour; XGB: eXtreme Gradient Boosting; ANN: Artificial neural network.

model showed good performance after cross-validation.

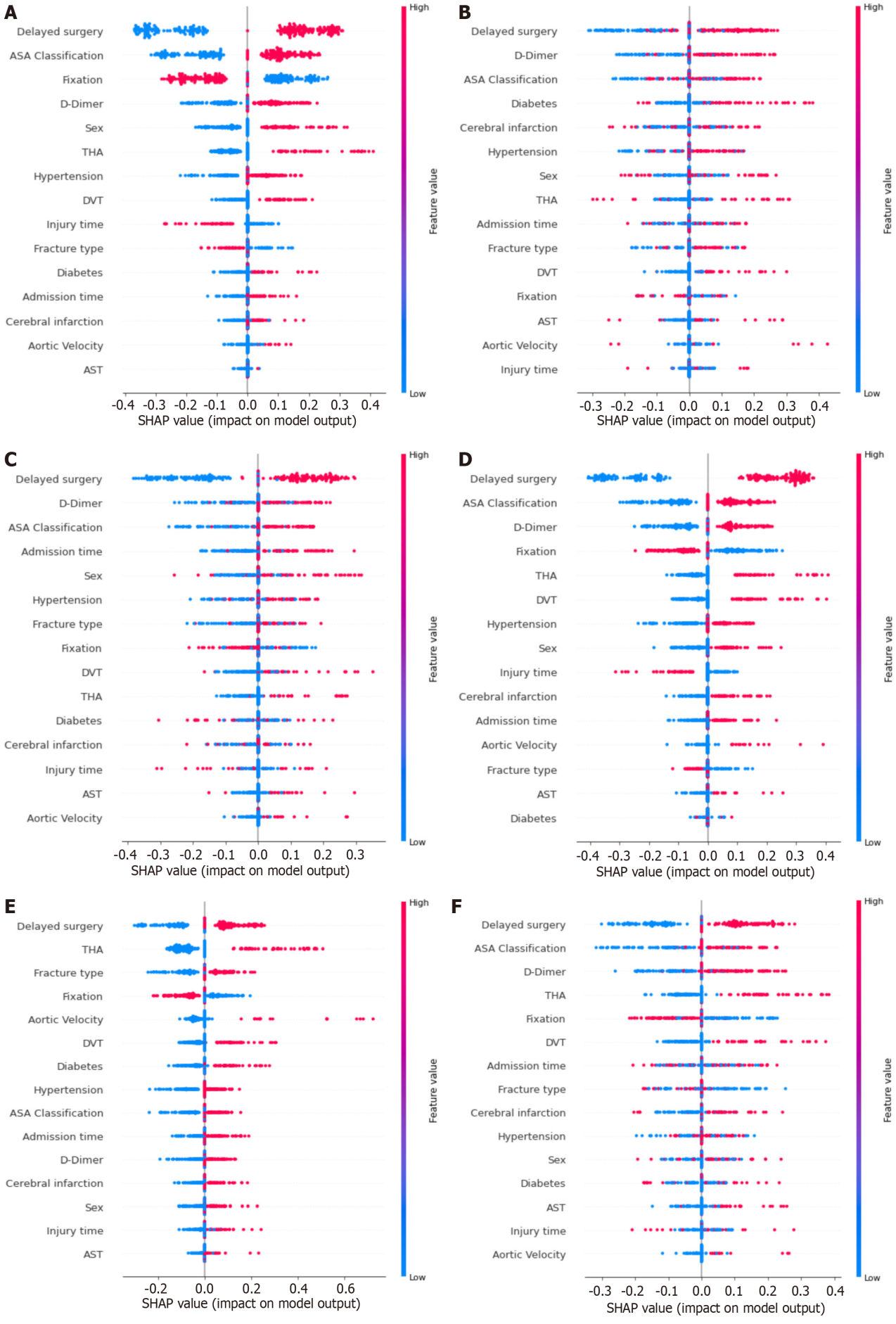
DISCUSSION

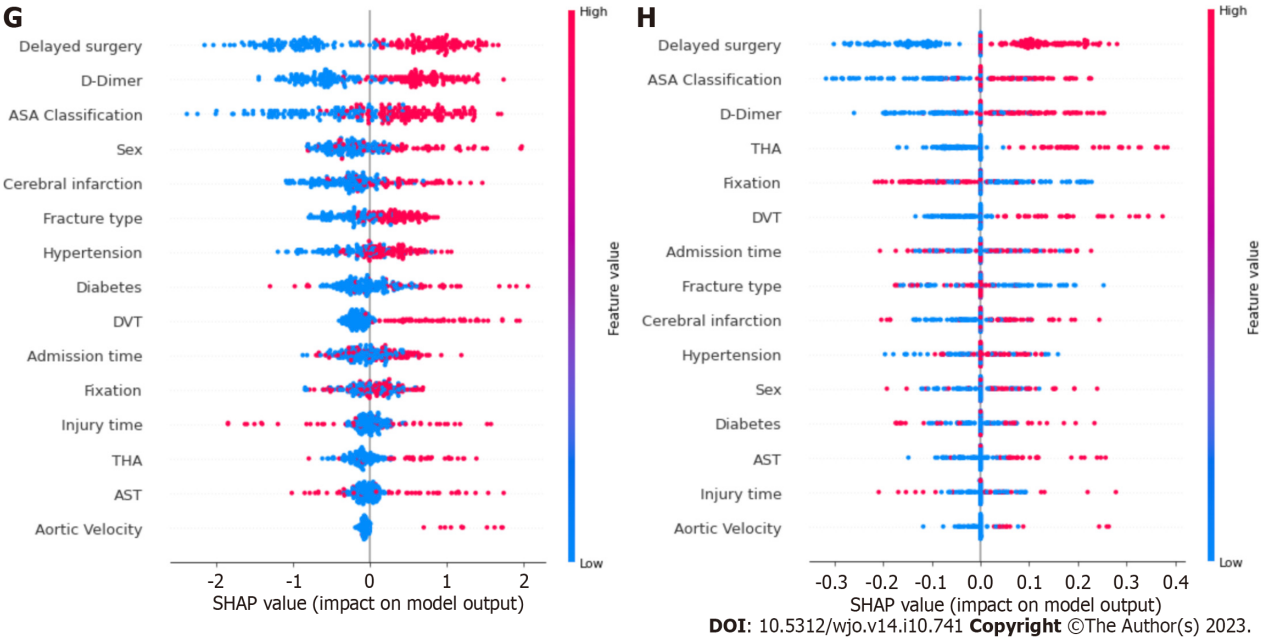
This study aimed to develop ML models for predicting eLOS in geriatric patients with hip fractures and to identify associated risk factors. Additionally, we assessed and compared the performance of each ML model. The DT and ANN models demonstrated the best performance with the original data. After cross-validation, the SVM and LR models also performed well.

Risk factors for eLOS among geriatric hip fracture patients

Although methods such as multidisciplinary management and ERAS have been shown to decrease LOS and lower inpatient hospitalization costs, geriatric hip fracture patients continue to be disproportionately large resource consumers [8,17,18]. Long-term LOS not only results in inefficient use of medical resources but also increases the risk of complications among hip fracture patients[19]. In addition, the length of hospital stay varies greatly among healthcare systems [17,18,20]. The identification of risk factors associated with the eLOS may be helpful in cost forecasting and patient management[21]. In our study, we used the median LOS to group the data.

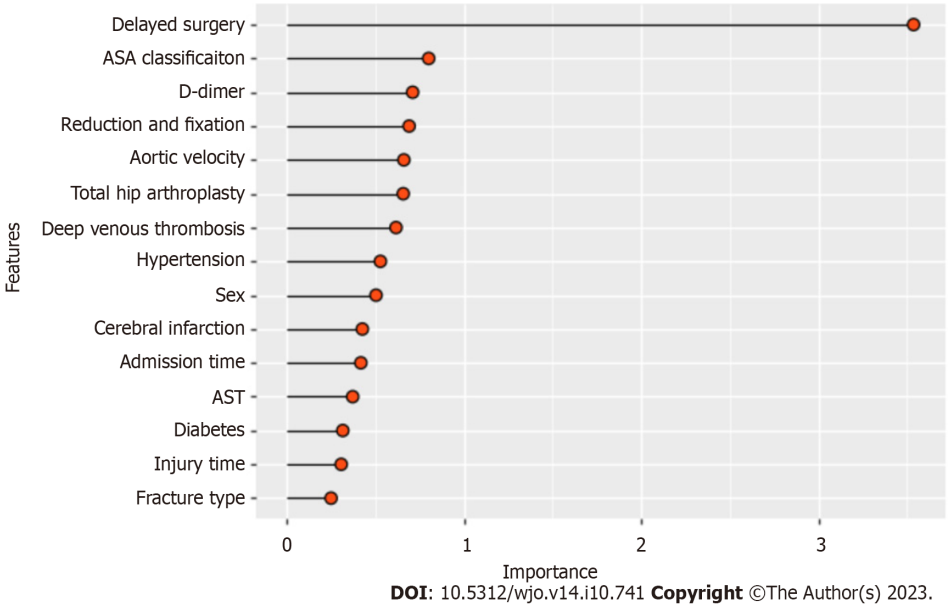
In previous studies, delayed surgery was considered the key factor that affected LOS. A retrospective study by Pincus *et al*[22] showed that patients who underwent surgery 1 day after admission had a longer postoperative stay. Hecht *et al* [23] developed a predictive model for LOS that showed that the prevention of reduced time to surgery was a significant


A
Delayed surgery
ASA Classification
Fixation
D-Dimer
Sex
THA
Hypertension
DVT
Injury time
Fracture type
Diabetes
Admission time
Cerebral infarction
Aortic Velocity
AST
-0.4 -0.3 -0.2 -0.1 0.0 0.1 0.2 0.3 0.4
SHAP value (impact on model output)
High
Feature value
Low
B
Delayed surgery
D-Dimer
ASA Classification
Diabetes
Cerebral infarction
Hypertension
Sex
THA
Admission time
Fracture type
DVT
Fixation
AST
Aortic Velocity
Injury time
-0.3 -0.2 -0.1 0.0 0.1 0.2 0.3 0.4
SHAP value (impact on model output)
High
Feature value
Low
C
Delayed surgery
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ASA Classification
Admission time
Sex
Hypertension
Fracture type
Fixation
DVT
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Diabetes
Cerebral infarction
Injury time
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Aortic Velocity
-0.4 -0.3 -0.2 -0.1 0.0 0.1 0.2 0.3
SHAP value (impact on model output)
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Delayed surgery
ASA Classification
D-Dimer
Fixation
THA
DVT
Hypertension
Sex
Injury time
Cerebral infarction
Admission time
Aortic Velocity
Fracture type
AST
Diabetes
-0.4 -0.3 -0.2 -0.1 0.0 0.1 0.2 0.3 0.4
SHAP value (impact on model output)
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Feature value
Low
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Delayed surgery
THA
Fracture type
Fixation
Aortic Velocity
DVT
Diabetes
Hypertension
ASA Classification
Admission time
D-Dimer
Cerebral infarction
Sex
Injury time
AST
-0.2 0.0 0.2 0.4 0.6
SHAP value (impact on model output)
High
Feature value
Low
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Delayed surgery
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DVT
Admission time
Fracture type
Cerebral infarction
Hypertension
Sex
Diabetes
AST
Injury time
Aortic Velocity
-0.3 -0.2 -0.1 0.0 0.1 0.2 0.3 0.4
SHAP value (impact on model output)
High
Feature value
Low



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Figure 3 Shapley additive explanations summary plots of each model. A: Logistic regression; B: Decision tree; C: Random forest; D: Support vector classifier; E: Naïve bayes; F: K-nearest neighbour; G: eXtreme Gradient Boosting; H: Artificial neural network. ASA: American society of anaesthesiologists; THA: Total hip arthroplasty; DVT: Deep venous thrombosis; AST: Aspartate aminotransferase.

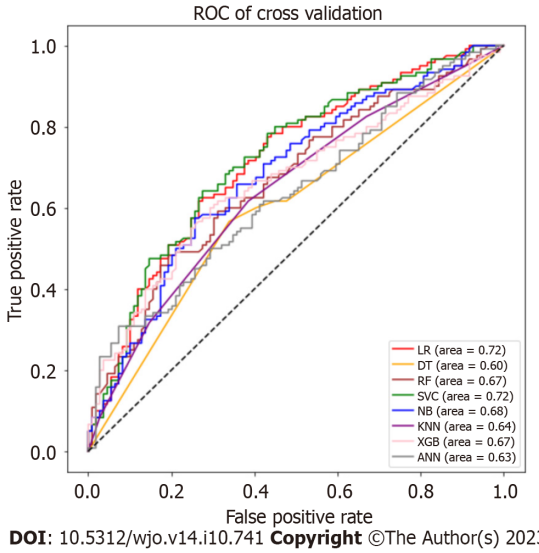


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Figure 4 Comprehensive importance of features. ASA: American society of anaesthesiologists; AST: Aspartate aminotransferase.

predictor of reduced LOS. In addition, the authors suggested that ASA classification was a stronger predictor of LOS than the Charlson comorbidity index. Similar findings were shown by Kristan *et al*[24], who found that the eLOS was associated with delayed surgery, ASA classification, anticoagulant therapy and surgery type. Furthermore, a higher D-dimer level, as a possible predictor of DVT, suggested that patients were at higher risk of thrombosis, which was also the cause of eLOS[25]. Our study achieved similar results to those described above. This result suggests that clinicians and multidisciplinary teams should continue to explore possible interventions to shorten LOS among hip fracture patients.

At the same time, our model identified male sex and fracture type as predictors of the eLOS. This is consistent with findings from the study by Garcia *et al*[26]. The results of their study showed that while the majority of hip fracture patients were female, male patients appeared to have a longer hospital stay. A meta-analysis by Haentjens *et al*[27] showed that male hip fracture patients had a higher risk of death, which appeared to be associated with more severe osteoporosis and a higher comorbidity burden among male patients with hip fractures[28]. In addition, patients with joint replacement surgery had higher functional requirements, which was why such patients took longer to stay and recover [29,30]. However, some studies mentioned the influence of age and comorbidities on the eLOS, but these factors were not



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Figure 5 Receiver operating characteristic curve for machine learning models after cross-validation. ROC: Receiver operating characteristic; LR: Logistic regression; DT: Decision tree; RF: Random forest; SVC: Support vector classifier; NB: Naïve bayes; KNN: K-nearest Neighbour; XGB: eXtreme Gradient Boosting; ANN: Artificial neural network.

identified by our model[24,27,30]. This might be due to changes in the management of hip fracture patients and the popularity of ERAS, which have allowed an increasing number of older patients with comorbidities to receive timely surgical treatment and rehabilitation guidance.

Predictive performance of ML models for eLOS

With the development of science and technology, ML is also being used in the field of medicine to improve patient outcomes and diagnostic accuracy[31]. Recently, ML has been widely used in the diagnosis, classification, identification and prognosis of hip fracture patients[32-34]. Promising results were obtained by Forssten *et al*[35], who used ML to predict 1-year mortality after hip fracture surgery, and by Galassi *et al*[36], who used ML to assess hip fracture risk. With the establishment of clinical databases, ML models will have better practical value in the future.

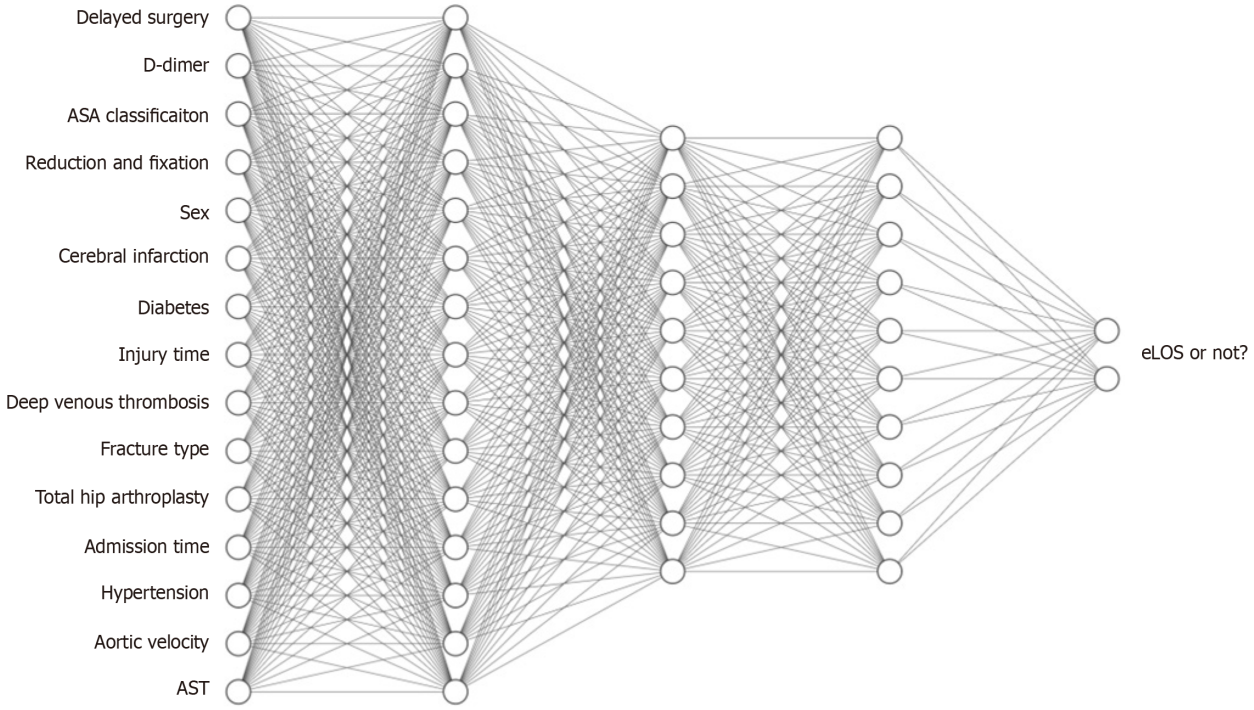
Most of the previous studies on the construction of prediction models were based on regression algorithms[9]. For binary clinical decision data, the tree model has a natural advantage[37]. The RF algorithm and the XGBoost integration algorithm also show similar results[38]. Based on gradient-boosted DTs, the XGBoost algorithm applied a second-order Taylor expansion to calculate the loss function and performed well in both computational speed and predictive precision [39]. Previous studies have also demonstrated this point. Hou *et al*[40] used XGBoost to predict 30-d mortality for the medical information mart for intensive care III patients with sepsis-3 and obtained high accuracy. Noh *et al*[41] similarly achieved good accuracy in identifying the optimal features of gait parameters to predict fall risk among older adults by XGBoost. In the original data set of our research, the performance of the tree model was far superior to that of other models, which might be the result of overfitting. Through cross-verification, we found that the performance evaluation index of the tree model declined the most. With the continuous expansion of the sample size, the performance of the tree model would also be improved. However, the performance of the traditional binary classification algorithm was stable. In our study, the SVM and LR models had the best performance after cross-validation.

Recently, ANNs have become a new hotspot in ML development. An ANN is a kind of ML algorithm inspired by biological neural networks[10]. Figure 6 shows the computational flow of the ANN in our study (hidden layer size = 15, 10, 10). The ANN contains nodes that communicate with other nodes *via* connections. Chen *et al*[42] showed that the ANN was more accurate than Cox regression in predicting mortality after hip fracture surgery. Using an ANN model can enable more appropriate and accurate processing of inputs that are incomplete or inputs that introduce noise[43,44]. Moreover, the results of Klemt *et al*[45] demonstrated its good application in binary data. In our research, the ANN model showed performance second only to that of the tree model in terms of original data and had considerable accuracy after cross-verification.

Strengths and limitations

This study conducted a novel experiment to develop and compare ML models for predicting eLOS among patients with hip fractures. Subsequently, risk factors for the eLOS were identified. The findings revealed that ML models outperformed traditional statistical methods in terms of accuracy. This provides clinicians with a valuable tool to efficiently identify populations at high risk of eLOS. By doing so, the diagnosis and treatment process can be optimized to reduce the LOS and allocate medical resources effectively, aligning with the ERAS concept.

However, there are several limitations to consider in our study. First, it was a single-centre study, and the length of hospital stay might vary significantly across different healthcare systems. Moreover, the high proportion of patients with ASA III-IV in our hospital indicates a higher prevalence of severe comorbidities and advanced disease compared to those treated in the community, leading to potential selection bias. Second, since this study aimed to establish ML models, the



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Figure 6 Schematic diagram of an artificial neural network. ASA: American society of anaesthesiologists; eLOS: Extended length of stay; AST: Aspartate aminotransferase.

sample size might be relatively small, resulting in some ML models being prone to overfitting. As a result, the findings of this study should be further validated and made applicable to a broader population through multicentre and large-sample studies.

CONCLUSION

In conclusion, we have effectively developed a highly accurate ML model for eLOS prediction in hip fracture patients. Notably, delayed surgery, elevated D-dimer levels, ASA classification, surgical type, and sex were significantly associated with the eLOS. By applying ML in clinical practice, we can optimize the diagnosis and treatment of elderly hip fracture patients, guide clinicians in decision-making, and allocate medical resources more efficiently.

ARTICLE HIGHLIGHTS

Research background

Geriatric hip fractures are a frequent occurrence and can lead to increased risks of complications and mortality during prolonged hospital stays. This study focuses on utilizing machine learning (ML) to create predictive models aimed at forecasting extended length of stay (eLOS) in elderly patients with hip fractures.

Research motivation

This research endeavor seeks to construct ML models to forecast eLOS in geriatric patients afflicted with hip fractures. Additionally, the study aims to discern the pertinent risk factors contributing to eLOS and conduct a comparative assessment of the performance of each developed model.

Research objectives

This research endeavors to construct ML models for the purpose of forecasting eLOS in geriatric patients who have suffered hip fractures. Furthermore, it seeks to discern the pertinent risk factors associated with this outcome and conduct a comparative analysis of the model performances. We have successfully formulated a highly precise ML model for the prediction of eLOS in patients with hip fractures. Significantly, factors such as delayed surgical intervention, elevated D-dimer levels, American Society of Anaesthesiologists (ASA) classification, surgical procedure type, and gender exhibited notable associations with eLOS. The integration of ML into clinical settings holds the potential to enhance the diagnostic

and therapeutic processes for elderly hip fracture patients, assist clinicians in informed decision-making, and optimize the allocation of healthcare resources.

Research methods

A retrospective investigation was carried out at a sole orthopaedic trauma center, encompassing all individuals who underwent surgery for hip fractures from January 2018 to December 2022. This study compiled a comprehensive array of patient characteristics, encompassing demographics, general health status, injury-related information, laboratory results, surgical data, and length of hospital stay. Features that demonstrated significant distinctions in univariate analysis were incorporated into the development of ML models, which were subsequently subjected to cross-validation. The research then undertook a comparative assessment of the ML models' performance and identified the risk factors associated with eLOS.

Research results

Incorporating a cohort of 763 patients, of which 380 experienced eLOS, the study evaluated the predictive performance of various ML models, with decision tree random forest, and eXtreme Gradient Boosting models emerging as the most robust. Additionally, the artificial neural network model demonstrated commendable results. Following cross-validation, the support vector machine and logistic regression models displayed superior predictive capabilities. Key predictors for eLOS encompassed delayed surgery, D-dimer levels, ASA classification, type of surgery, and gender.

Research conclusions

The application of ML yielded exceptional accuracy in forecasting eLOS among geriatric hip fracture patients. Notably, the study identified significant risk factors, including delayed surgery, D-dimer levels, ASA classification, surgical procedure type, and gender. This valuable insight has the potential to assist clinicians in optimizing resource allocation to meet patient demands more effectively.

Research perspectives

Future research in ML applications for predicting eLOS in geriatric hip fracture patients will likely focus on refining models, integrating them into clinical practice, ensuring interpretability, and addressing ethical and practical considerations to enhance the utility and impact of these predictive tools in healthcare.

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FOOTNOTES

Author contributions: Tian CW and Chen XX contributed equally to this work; Tian CW and Chen XX designed this study and wrote the manuscript; Zhu HY performed the experiments and analyzed the data; Tian CW and Zhu HY collected the clinical data; Shi L, Dai GC and Chen H provided technical support; Rui YF provided the idea and revised and proofread the paper; All the authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Catania flatfoot score: A diagnostic-therapeutic evaluation tool in children

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Abstract

BACKGROUND

Flexible flatfoot (FFF) is a very common condition in children, but no evidence-based guidelines or assessment tools exist. Yet, surgical indication is left to the surgeon's experience and preferences.

AIM

To develop a functional clinical score for FFF [Catania flatfoot (CTF) score] and a measure of internal consistency; to evaluate inter-observer and intra-observer reliability of the CTF Score; to provide a strong tool for proper FFF surgical indication.

METHODS

CTF is a medically compiled score of four main domains for a total of twelve items: Patient features, Pain, Clinical Parameters, and Functionality. Each item refers to a specific rate. Five experienced observers answered 10 case reports according to the CTF. To assess inter- and intra-observer reliability of the CTF score, the intra-class correlation coefficients' (ICCs) statistics test was performed, as well as to gauge the correlation between the CTF score and the surgical or conservative treatment indication. Values of 75% were chosen as the score cut-off for surgical indication. Sensitivity, specificity, positive likelihood ratio (PLHR), negative likelihood ratio (NLHR), positive predictive value (PPV), and negative predictive value (NPV).

RESULTS

Overall interobserver reliability ICC was 0.87 [95% confidence interval (CI): 0.846-0.892; $P < 0.001$]. Overall intra-observer reliability ICC was 0.883 (95%CI: 0.854-0.909; $P < 0.001$). A direct correlation between the CTF score and surgical treatment indication [Pearson correlation coefficient = 0.94 ($P < 0.001$)] was found.

According to the 75% cut-off, the sensitivity was 100% (95%CI: 83.43%-100%), specificity was 85.71% (95%CI: 75.29%-92.93%), PLHR was 7 (95%CI: 3.94-12.43), NLHR was 0 (95%CI: 0-0), PPV was 75% (95%CI: 62.83%-84.19%) and NPV was 100% (95%CI: 100%-100%).

CONCLUSION
CTF represents a useful tool for orthopedic surgeons in the FFF evaluation. The CTF score is a quality questionnaire to reproduce suitable clinical research, survey studies, and clinical practice. Moreover, the 75% cut-off is an important threshold for surgical indication and helps in the decision-making process.

Key Words: Pes planus; Score; Assessment; Clinic; Surgery; Outcome; Reparability

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Core Tip: There was no validated children's flexible flatfoot questionnaire in the literature. Catania flatfoot is a medical score of four main domains for a total of twelve items: Patient features, pain, clinical parameters, and functionality. The tool was easy to perform and reproduce in clinical research, survey studies, or clinical practice. The 75% cut-off is an important threshold for surgical indication and help in the decision-making process.

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INTRODUCTION

The flexible flatfoot (FFF), known as pes planus, is a very common condition in children characterized by loss of the medial arch and an increase in the support base along with valgus of the hindfoot, yet 40 different definitions were formulated[1]. FFF is associated with anatomical conditions, including valgus heel, subluxation of the subtalar joint with intra-rotation of the talus and flexion of plantar abduction of the mid-tarsal joint with naval dorsal subluxation[2]. Generally, FFF is an age-related physiological variant, not a disease, and its incidence decreases significantly in terms of increased age: In children 3-years-old, it is 54%, whereas in children 6-years-old, it is 24%[3]. A history should include pain, location, intensity, functional problems, while trauma or recurrent ankle sprains should be specifically questioned. FFF is typically an asymptomatic condition[4]. Lower limb pain[5] and lower limb function[6] were found as the main manifestations in symptomatic FFF. Until 2022, more than 300 scientific articles were published, without evidence-based guidelines. The challenge for health professionals is to identify when a child's foot is consistent with developmental expectations, particularly in relation to foot posture, and/or function to reassure, monitor or intervene accordingly[7-10]. Therefore, the measure to indicate where foot posture is outside of expected flatness in children (*i.e.*, the diagnoses of flat foot) must be valid, reliable, and appropriate for developing foot posture typically observed. Recently, a systematic review[1] highlighted there was no consistency used to determine pediatric FFF in the literature or the choice of foot posture measures, in relation to validity and reliability, which was rarely justified. A surgical indication was in effect for the surgeon's experience[11,12]. The purpose of the study was to develop new functional clinical scores for FFF to assess toddlers and adolescent patients' characteristic functionality [Catania flatfoot (CTF] Score) and measure of internal consistency; to evaluate inter- and intra-observer reliability of the CTF Score; and to provide a reliable tool for proper FFF surgical indication.

MATERIALS AND METHODS

CTF score development

The CTF Score development was composed of two parts, the CTF Score Conception and CTF Score Composition and Scoring.

CTF score conception: An orthopedic team was involved in developing the questionnaire. The CTF score was designed to be used in different clinical settings, including clinical research, survey studies, and clinical practice to assess FFF-affected patients and possibly assess changes with treatment. The development team was composed of two senior orthopedic and trauma surgeons (Vito Pavone and Gianluca Testa), and one pediatric orthopedic (fully-trained) resident (Andrea Vescio). At an early stage, an author (Andrea Vescio) search was done to analyze the functional foot and ankle score previously described and developed as the CTF score. Senior authors (Vito Pavone and Gianluca Testa) reviewed and validated the scores.

CTF score composition and scoring: The questionnaire is a medically-compiled score of four main domains for a total of twelve items: Patient features (2 items), pain (1 item), clinical parameters (5 items), and functionality (4 items). Each item refers to a specific rate as reported in Supplementary Table 1. The lowest achievable value is -80, while the highest is 170. Calculation of the CTF score is based on the following formula:

$$\left[\frac{(Sum\ of\ items\ score + 80)}{250}\right] \times 100$$

The value is expressed as a percentage: Higher percentages are associated with a lower clinical presentation.

CTF score patient features domain: Patient features are composed of two items aimed to assess the principal general parameters of the evaluated subject. The first item is related to age; the second is linked to laxity. Hypermobility can be assessed according to the passive dorsiflexion of the fifth hand finger and thumbs, elbow, and knee hyperextension.

CTF score pain domain: The pain domain was composed of one item to assess generalized pain of the foot or ankle, as well as in the plantar arch, heel, tibialis posterior tendon, and fascia.

CTF score clinical parameters domain: The clinical parameters domain is composed of five items to assess the callous present, valgus of hindfoot, longitudinal arch, forefoot abduction, and triceps contracture. For each item, three answers are admissible: "none", "mild", and "severe". The first item "callous" allows for two answers: "yes" and "no".

CTF score functionality domain: The functionality domain provides four items to evaluate the patient's capacities. Fatigue, inadequate physical and sport performance, and wear of orthosis is recorded. The first and last items of the section ("fatigue" and "orthosis") allow for two answers: "yes" and "no", while others provide "none", "mild", and "severe".

Evaluation materials

A review of all infants, toddlers, and adolescents admitted through the pediatric orthopedic ambulatory were carried out. For each patient the following demographic and clinical data captured: Gender, age, the involved side, and presence or absence of associated syndromes or deformities, past and recent medical history for foot and ankle discomfort or pain. Frontal, lateral, and posterior view photos were taken. The pictures were performed in the same positions to provide the more possible objectivity and recorded in an online database. The inclusion criteria were as follows: (1) Chronological age 17-years-old; (2) physical and podoscopic examination; (3) complete photographic history; and (4) positive Tip Toe and Jack test; all cases were examined by the same expected pediatric orthopedic team.

Evaluation contributors

Children in the study were independently examined and assessed by two orthopedic surgeons and three residents in pediatric orthopedics: All evaluators had previous experience of at least twenty-four months. Three assessors, two surgeons, and a resident completed a full program while treating over 50 FFF patients in the previous two years. All observers had 1 h of theoretical FFF clinical manifestation and score system training before patients' assessment. Each contributor was provided with a summary of the medical history and clinical examination of the frontal, lateral, and posterior view photos. As per the web-based score, observers were asked about conservative or surgical indication. Answers were submitted *via* a link hosted by https://www.google.com/ forms and recorded by an Excel spreadsheet (Microsoft, Redmond, WA, United States). The CTF score was submitted at two different points.

Primary outcome measurement

To assess the inter- and intra-observer reliability of the CTF score, the intra-class correlation coefficients (ICCs) statistics test was performed. For scale development, it is generally accepted there should be at least five times the number of respondents as questions, for at least 60 in total[11].

Secondary outcome measurement

To assess the correlation between the CTF score and surgical or conservative treatment, values of 75% were used as a score cut-off for surgery. Sensitivity, specificity, positive likelihood ratio (PLHR), negative likelihood ratio (NLHR), positive predictive value (PPV), and negative predictive value (NPV) were used.

Statistical analysis

Continuous data are presented as the mean and standard deviation when appropriate. The ICC (two-way random effects model, with single-measure reliability) was performed to evaluate intra- and interobservers' agreement. According to the Koo and Li guideline, agreement below 0.50 was considered "poor"; between 0.50 and 0.74 as "moderate"; between 0.75 and 0.89 as "good"; and above 0.90 as "excellent"[12]. The Pearson correlation coefficient (PCC) was utilized to assess the correlation between conservative or surgical treatment and the CTF score. PCC vales between -1 and 1, where values close to -1 indicated high negative correlation, with values close to 1 indicating a high positive correlation, and values close to 0 indicating no or a very week correlation.

A rule of thumb for interpreting the coefficient is provided by Colton *et al*[13]: (1) 0 to 0.25 (0 to -0.25) little or no relationship; (2) 0.25 to 0.50 (-0.25 to -0.50) fair degree of a relationship; (3) 0.50 to 0.75 (-0.50 to -0.75) moderate to good degree of a relationship; and (4) 0.75 to 1.00 (-0.75 to -1.00) very good to excellent relationship.

The Bland and Altman plot was produced to analyze differences between cohort measurements. The limits of agreement were calculated as the mean difference ± 1.96 SD[14]. A value of 75% was chosen as a score cut-off for surgical indication. Sensitivity, specificity, PLHR, NLHR, PPV, and NPV were recorded. *P* values of less than 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS, Version 24.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Five different experienced observers answered 10 case reports. For each patient, observers responded to 14 questions (12 items and 2 treatment indications) for a total of 140 responses. The web-based survey was submitted at two different times, while 280 observations were reported.

Inter- and intra-observer reliability

Overall interobserver reliability ICC was 0.87 [95% confidence interval (CI): 0.846-0.892; $P < 0.001$; "good"]. The ICC value for specialists was 0.809 (95%CI: 0.761-0.849; $P < 0.001$; "good"), but was 0.852 (95%CI: 0.821-0879; $P < 0.001$; "good") for residents (Table 1).

The overall intra-observer reliability ICC was 0.883 (95%CI: 0.854-0.909; $P < 0.001$) and considered "good" (Table 2 and Figure 1).

The ICC value for specialists was 0.869 (95%CI: 0.832-0.901; $P < 0.001$; "good"), but was 0.878 (95%CI: 0.846-0.907; $P < 0.001$; "good") for residents (Table 1).

CTF score treatment indication correlation

A fair inverse correlation occurred between the CTF score and conservative treatment indication (PCC = -0.483; $P < 0.001$) (Figure 2A).

The direct correlation between the CTF score and surgical treatment indication (PCC = 0.94; $P < 0.001$) was rated "from good to excellent" (Figure 2B).

CTF score for linear regression

According to the 75% cut-off, sensitivity was 100% (95%CI: 83.43%-100%), specificity was 85.71% (95%CI: 75.29%-92.93%), PLHR was 7 (95%CI: 3.94-12.43), NLHR was 0 (95%CI: 0-0), PPV was 75% (95%CI: 62.83%-84.19%), and NPV was 100% (95%CI: 100%-100%).

DISCUSSION

The CTF score was found to be a valid, effective tool in flatfoot assessment. The scale was seen as good or excellent for inter- and intra-observer reliability, done independently with experience levels. Higher score values were directly correlated with surgical treatment needs, while an increase in score reduced conservative management indication. In addition, the 75% CTF score values were discovered as reasonable cut-off points for surgical treatment, while high percentages of sensitivity and specificity guaranteed safe tool utilization.

In recent surveys, European[9] and Italian[10] pediatric orthopedics underlined the absence of a specific and universally-recognized clinical evaluation score for juvenile FFF. The CTF Score fills the literature void and, considering the good results, can be proposed as a helpful tool for clinical research, survey studies, and clinical practice to assess FFF-affected patients as well as changes with treatment.

Each domain scale was developed according to the weighted preferences of European and Italian pediatric orthopedics which ensure that each scale is internally consistent, *i.e.*, measures a single trait and that each item has different levels of difficulty or severity.

The final instrument comprises 12 questions divided into four domains which measure problems in domains titled *Patient features* (2 items), *pain* (1 item), *clinical parameters* (5 items), and *functionality* (4 items). Raw domain scores can be transformed into percentage scores to make them easier to interpret; higher scores indicate more severe disability. The item has strong face validity and is included as a categorical descriptive variable but not allied to any domain scale. The instrument is not suitable for those who are unable to walk, or who have a significant proximal component to their disability.

In 2005, the American Orthopedic Foot and Ankle Society (AOFAS) members identified the Foot Function Index, and the American Academy of Orthopaedic Surgeons Foot and Ankle module scores as the most frequently used in the literature[15]. Yet, AOFAS[16], Foot and Ankle Ability Measure[17], and the Rowan Foot Pain Assessment Questionnaire [18] were commonly utilized for foot and ankle disorder evaluation. On the other hand, previous scores were not specific for children or flatfoot, because they were developed for adult generalized foot and ankle disease or ankle osteoarthritis.

The Oxford Ankle Foot Questionnaire for Children (OxAFQ-C) is the only validated tool in the pediatric population to measure the subjective well-being of children from 5- to 16-years-old with foot and ankle conditions[19]. The major limit of the OxAFQ-C is its patient-reported nature, as several studies report a tendency in children to score themselves higher than their parents[20,21], while the physician CTF Score report an intra-observer reliability of 0.883, with the OxAFQ-C domain reliability rating at 0.6 and 0.83. In addition, the tool was useful for physicians with an intra- and interobserver reliability of 0.852 and 0.878, respectively.

Table 1 Intra-observer reliability intra-class correlation coefficients values

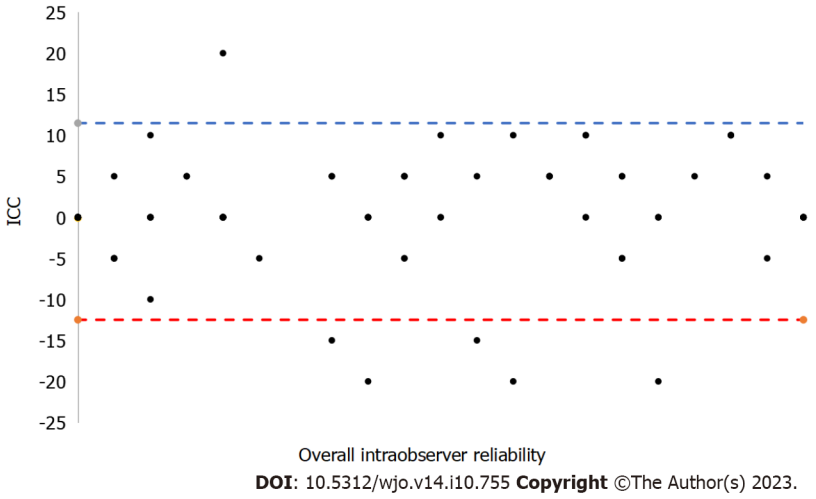
Sample	ICC	95% confidence interval		Value	*P* value
		Lower limit	Upper limit		
Overall	0.883	0.854	0.909	7.513	< 0.0001
Specialists	0.869	0.832	0.901	27.523	< 0.0001
Residents	0.878	0.846	0.907	44.351	< 0.0001

ICC: Intra-class correlation coefficients.

Table 2 Interobserver reliability intra-class correlation coefficients values

Sample	ICC	95% confidence winterval		Value	*P* value
		Lower limit	Upper limit		
Overall	0.870	0.846	0.892	34.479	< 0.0001
Specialists	0.809	0.761	0.849	9.475	< 0.0001
Residents	0.852	0.821	0.879	18.272	< 0.0001

ICC: Intra-class correlation coefficients.

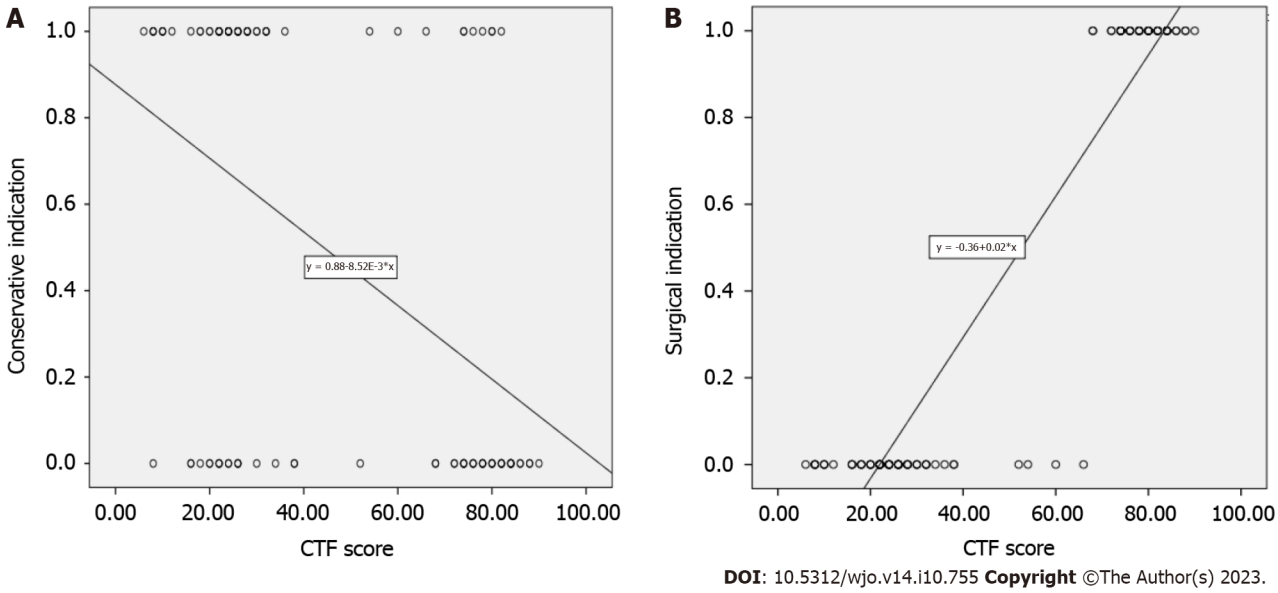


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Figure 1 Bland Altman plots according overall intra-observer reliability intra-class correlation coefficients. ICC: Intra-class correlation coefficients.

Since March 2020, the pandemic emergency raised questions about alternatives to normal clinical activity to avoid overcrowding in departments; for less risk of contagions, many checkups were procrastinated. This issue caused a possible loss of patient follow-up, which can reflect on the clinic and its outcomes. The necessity to develop management protocols highlights telemedicine as a valid alternative in particular conditions *vs* the face-to-face clinic, with safety margins and economic savings. The CTF score was administered with a web-based database, well-tolerated by observers; moreover, despite assessment of foot functionality, the CTF Score does not include a range of motion evaluation. The score was considered a good remote follow-up tool. The authors intend to promote the distribution of the score and face-to-face and remote validation.

Surgical treatment is still debated, as Bouchard and Mosca[22] suggested that surgical management be used only in Achilles' tendon retraction, while several authors highlighted issues of fatigue, inadequate physical performance, and pain as the main parameters for the decision-making process[23]. The 75% CTF score cut-off presented high sensitivity and specificity as reasonable cut-offs for surgical treatment. The tool does not replace the surgeon's experience, but represents a helpful orthopedic decision-making process. The CTF provides to general or pediatric physicians, podiatrist, physiotherapists, young or non-pediatric orthopedic trained orthopedic surgeons a common accepted and objective additional tool for the correct flatfoot grade and eventually surgical indication. The patient and family history, body posture assessment remain mandatory for the proper assessment. Future research into the development and validation of



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Figure 2 Scatter plot. A: The correlation between the Catania flatfoot (CTF) score and the conservative treatment indication; B: The correlation between the CTF score and the surgical treatment indication.

the questionnaire will assess whether the instrument is responsive to change. We will administer the questionnaire to general non-pediatric orthopedic surgeons, and reassess test-retest reliability while monitoring dimensionality and scaling of the instrument as more data become available.

The limits of the score are related to the domains compilation, in fact, the valgus of the hindfoot, longitudinal arch, forefoot abduction, and triceps contracture assessment are related to the physician or surgeon experience, and the fatigue, inadequate physical and sport performance items are related to the patient consciousness. In the future, the development of new and more objective criteria could make the CTF more usable.

CONCLUSION

In conclusion, the CTF Score is useful for orthopedic surgeons in the juvenile FFF evaluation. The CTF score is derived from a high-quality questionnaire for clinical research, survey studies, or clinical practice. The 75% cut-off point is a good threshold for surgical indication and decision-making. Given widespread use of telemedicine, the CTF score is also seen as an objective remote clinical examination.

ARTICLE HIGHLIGHTS

Research background

Flexible flatfoot (FFF) is a very common condition in children, but no evidence-based guidelines or assessment tools exist. Yet, surgical indication is left to the surgeon's experience and preferences.

Research motivation

The lack of common diagnostic criteria for FFF.

Research objectives

To develop a functional clinical score for FFF [Catania flatfoot (CTF) score] and a measure of internal consistency; to evaluate interobserver and intra-observer reliability of the CTF Score; to provide a strong tool for proper FFF surgical indication.

Research methods

CTF is a medically compiled score of four main domains for a total of twelve items: Patient features, Pain, Clinical Parameters, and Functionality. Each item refers to a specific rate. Five experienced observers answered 10 case reports according to the CTF. To assess inter- and intra-observer reliability of the CTF score, the intra-class correlation coefficients' (ICCs) statistics test was performed, as well as to gauge the correlation between the CTF score and the surgical or conservative treatment indication. Values of 75% were chosen as the score cut-off for surgical indication. Sensitivity, specificity, positive likelihood ratio (PLHR), negative likelihood ratio (NLHR), positive predictive value (PPV), and

negative predictive value (NPV).

Research results

Overall interobserver reliability ICC was 0.87 (95%CI: 0.846-0.892; $P < 0.001$). Overall intra-observer reliability ICC was 0.883 (95%CI: 0.854-0.909; $P < 0.001$). A direct correlation between the CTF score and surgical treatment indication [Pearson correlation coefficient = 0.94 ($P < 0.001$)] was found. According to the 75% cut-off, the sensitivity was 100% (95%CI: 83.43%-100%), specificity was 85.71% (95%CI: 75.29%-92.93%), PLHR was 7 (95%CI: 3.94-12.43), NLHR was 0 (95%CI: 0-0), PPV was 75% (95%CI: 62.83%-84.19%) and NPV was 100% (95%CI: 100%-100%).

Research conclusions

CTF represents a useful tool for orthopedic surgeons in the FFF evaluation. The CTF score is a quality questionnaire to reproduce suitable clinical research, survey studies, and clinical practice. Moreover, the 75% cut-off is an important threshold for surgical indication and helps in the decision-making process.

Research perspectives

CTF needs further multicentric studies to increase its validity for diagnostic and surgical indications in FFF.

FOOTNOTES

Author contributions: Vescio A and Testa G contributed equally to this work; Vescio A, Testa G and Pavone V designed the research study; Caldaci A and Sapienza M performed the research; Vescio A contributed new reagents and analytic tools; Vescio A and Testa G analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Total hip arthroplasty following the failure of intertrochanteric nailing: First implant or salvage surgery?

Giuseppe Solarino, Davide Bizzoca, Pasquale Dramisino, Giovanni Vicenti, Lorenzo Moretti, Biagio Moretti, Andrea Piazzolla

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Abstract

BACKGROUND

Proximal femur fractures, including both intracapsular (femoral neck fractures) and extracapsular fractures (intertrochanteric femoral fractures, IFFs), affect around 1.5 million people per year worldwide. Mechanical failures of intertrochanteric nailing in IFFs could be managed with revision total hip arthroplasty (THA).

AIM

To describe the surgical complexity and the procedure-related complication rates in patients with trochanteric nailing failure and treated with THA.

METHODS

Patients referred to our level I trauma center between April 2012 and July 2018 with failed cephalomedullary nailing following trochanteric fractures were retrospectively recruited. All patients underwent a salvage surgical procedure, *i.e.*, cephalomedullary nail removal and conversion to THA. The same surgical and anesthesiology team performed the surgical procedures under spinal anesthesia. All patients underwent clinical and radiographic follow-ups for at least 24 mo. Complications and re-operations were recorded.

RESULTS

Seventy-four patients met the inclusion criteria (male: 29; female: 45; mean age: 73.8-years-old; range: 65-89) and were included in the current study. The average operative time was 117 min (76-192 min). The average blood loss was 585 mL

(430-1720 mL). Among the 74 patients, 43 (58.1%) required transfusion of three or more blood units. Two patients died within the 4th d after surgery because of pulmonary embolism, and 1 patient died 9 mo after surgery due to ischemic myocardial infarction. The complication rate in the 71 patients who completed the minimum 24-mo follow-up was 22.5%. In 3 cases out of 71 (4.2%) periprosthetic acetabular fracture was observed during the follow-up. One of these periacetabular fractures occurred intraoperatively. An intraoperative periprosthetic femur fracture was observed in 5 patients out of 71 (7.0%). Four of these patients needed a re-operation to fix the fracture with plates and cerclages; in one of these patients, femoral stem revision was also necessary. In 4 patients out of 71 (5.6%), an early THA dislocation was observed, whereas in 1 case (1.4%) a late THA dislocation was observed. Three patients out of 71 (4.2%) developed a periprosthetic joint infection during the study follow-up.

CONCLUSION

The present study demonstrated that salvage options for IFF fixation failure are complex procedures with a relevant intraoperative and postoperative complication rate.

Key Words: Femoral nailing; Total hip arthroplasty; Proximal femur fractures; Osteoporosis; Fragility fractures; Geriatric patients; Hip traumatology; Hip replacement

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Core Tip: The present study demonstrated that salvage options for intertrochanteric femoral fracture fixation failure deal with intraoperative and postoperative complications at a higher rate compared to primary elective total hip arthroplasty.

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INTRODUCTION

Proximal femur fractures (PFFs), including both intracapsular (femoral neck fractures, FNFs) and extracapsular fractures (intertrochanteric femoral fractures, IFFs), affect around 1.5 million people per year worldwide, thus constituting a major public health problem[1]. PFFs are the most common traumatic injuries in elderly people and significantly impact patients' health status, potentially leading to a reduced quality of life, increased disability and higher mortality rate[1,2]. In Italy, PFFs have an estimated annual prevalence of 78000, with 90% of injuries occurring in patients older than 65 years [3]. Nonetheless, as life expectancy is constantly increasing, the annual number is supposed to steadily increase by reaching 8.2 million fractures in 2050 worldwide[3-6].

IFFs, accounting for more than 60% of PFFs, have an annual mortality rate of 15%-20%[4]. It has also been reported that the incidence of IFF is increasing more than the incidence of PFF in the elderly[7]. Fox *et al*[7], in a prospective study on 923 elderly patients comparing patients with IFF and FNF, observed that patients with IFFs were older and showed a worse pre-injury health status. They also were less likely to recover to the pre-fracture level of functioning at the 2-mo follow-up.

IFFs need surgical management and could be treated both with intramedullary and extramedullary implants[1,3]. However, a recent meta-analysis by Zhang *et al*[8] stated that the current evidence indicates short intramedullary nails may be a better choice than dynamic hip screws in the treatment of IFFs. Compared to dynamic hip screws, intramedullary nailing has the theoretical advantages of being less invasive and biomechanically superior, providing a buttress to limit fracture collapse[1]. Moreover, in patients managed with cephalomedullary nails, a better recovery to pre-injury activity level, less blood loss, and fewer complications have been reported[1,3,8].

The surgical planning of IFFs and implant choice is critically influenced by the stability of the fracture pattern[9]. A stable fracture resists displacement after adequate reduction and fixation and generally includes two fragment fractures with an intact posteromedial cortical calcar[9]. The intact medial buttress allows the proximal femur to redistribute stress and resist medial compressive loads[10]. On the other hand, an unstable fracture may collapse even after adequate reduction and fixation[10]. Unstable patterns include fractures with a compromised medial calcar (comminuted patterns or fractures with a large posteromedial fragment), fractures with a subtrochanteric extension, reverse obliquity fractures, or intertrochanteric fractures that involve the lateral cortical wall[9,10].

Treatment of unstable fractures is still challenging, and several factors may influence the surgical technique and implant choice[9,10]. Cephalomedullary nailing revealed a biomechanical superiority compared with an extramedullary fixation for unstable fracture patterns since it can resist higher loading forces and provide greater stability reducing the distance from the implant and the hip joint diminishing the bending moment across the implant/fracture construct[11-15]. Fixation failure after surgery to treat IFF is a serious complication. Many factors seem to influence the stability of the fixation during follow-up including the patient's age, female sex, poor bone quality, device choice, fracture reduction

Table 1 Main data of the study

Item	Patients, *n* = 74
Age in yr	
mean ± SD	73.80 ± 7.85
Range	65-89
Sex	
Female	45 (60.8)
BMI in kg/m^2	
mean ± SD	28.70 ± 4.43
Side	
Right	43 (58.1)
Mean operating time in min, mean ± SD	77.0 ± 35.5
Patients undergoing ≥ 3, blood transfusion	43 (58.1)

Data are *n* (%) unless otherwise indicated. BMI: Body mass index; SD: Standard deviation.

quality, and presence of neurological comorbidities that may affect the rehabilitation process[16].

This study aimed to describe the surgical complexity and the procedure-related complication rates, in patients referring with trochanteric nailing failure and treated with total hip arthroplasty (THA) or hemiarthroplasty.

MATERIALS AND METHODS

Patients referred to our level I trauma center between April 2012 and July 2018 with failed trochanteric nailing were retrospectively recruited according to inclusion and exclusion criteria. Ethical clearance was obtained from our center's clinical research ethics board as per the 1964 Declaration of Helsinki, and all patients gave informed consent before enrolment in the study.

The inclusion criteria included: age greater than 65-years-old; good cognitive state; and osteoporosis, defined as lumbar T-score ≤ -2.5 (all patients performed a DEXA scan during hospitalization). The exclusion criteria included: Moderate cognitive impairment (defined as mini-mental state examination < 19); a history of malignant neoplasm; hemoglobin < 10 g/dL at baseline; severely obese patients, *i.e.*, body mass index ≥ 35 kg/m^2; a life expectancy of fewer than 3 mo; medical illness or cognitive disorders precluding participation in the follow-up examination; concomitant lower-limb fractures; and traumatic head injury.

Patient demographics, including age, sex, body mass index, and comorbidities were recorded at recruitment. All patients underwent THA *via* the Hardinge approach, with the patient positioned in lateral decubitus. Adhesions were cleared around scar tissue, fully exposing the trochanter and enabling assessment of the greater and lesser trochanters and calcar femoral. The surgical procedures were performed by the same surgical and anesthesiology team under spinal anesthesia.

Cefazolin (2 g intravenously) or, if contraindicated, clindamycin (600 mg i.v.) was given 60 min before incision. Subcutaneous injection of low molecular-weight heparin (enoxaparin 4000 UI once a day, started 12 h after surgery) was administered for antithrombotic prophylaxis in all patients until the return to full weight-bearing.

Surgical time, blood transfusion rate and perioperative and major complications were assessed. All patients underwent a minimum 24-mo clinical and radiographic follow-up. Complications and reoperations were recorded.

Statistical analysis was performed using STATA/MP 14 for Windows (StataCorp LP, College Station, United States). All data were described as mean, median, and standard deviation.

RESULTS

The main data of the study are reported in Table 1. Seventy-four patients met the inclusion and exclusion criteria (male: 29; female: 45; mean age: 73.8-years-old; range: 65-89) and were included in the current study. The recruited patients were originally referred with the following fracture patterns: 31-A1.2 (58 out of 74; 78.38%); 31-A1.3 (9 out of 74; 12.16%); 31-A2.2 (5 out of 74; 6.76%); and 31- A2.3 (2 out of 74; 2.7%).

The trochanteric nail failure modality included: cut-out in 39 cases out of 74 (50.65%); non-union in 13 patients out of 74 (17.56%); peri-implant fracture in 12 patients out of 74 (16.20%); cut-through in 8 patients out of 74 (10.80%); and femoral head avascular necrosis in 2 patients out of 74 (2.70%).

The average operation time was 117 min (76-192 min). The average blood loss was 585 mL (430-1720 mL). Among the 74 patients, 43 patients (58.10%) required transfusion of three or more blood units.

All the patients underwent nail conversion to THA. Cemented stems were used in 19 patients out of 64 (25.68%), whereas uncemented stems were employed in 55 patients out of 74 (74.32%). Among the latter, long stems were used in 39 patients out of 74 (52.70%). Cemented cups were implanted in 18 patients out of 74 (24.32%), whereas in 56 patients out of 74 (75.68%) cementless cups were used. Dual-mobility cups were implanted in 16 patients out of 74 (21.62%).

Table 2 shows the complications observed during the study follow-up. Seventy-one patients completed the minimum 24 mo of clinical and radiological follow-up (range: 25-85 mo). Two patients (2.70%) died within 4 d after surgery because of pulmonary embolism. One patient (1.35%) died 9 mo after surgery due to ischemic myocardial infarction. The overall complication rate in the 71 patients who completed the minimum 24-mo follow-up was 22.5%.

In 3 cases (4.23%) periprosthetic acetabular fracture was observed during the follow-up. One of these periacetabular fractures occurred intraoperatively. In 5 patients (7.00%), an intraoperative periprosthetic femur fracture was observed. Four of these patients needed a re-operation to fix the fracture with plates and cerclages; in one of these patients, femoral stem revision was also necessary. In 4 patients (5.60%) an early THA dislocation was observed, and 1 case (1.40%) a late THA dislocation was observed.

Three patients (4.23%) developed a periprosthetic joint infections (PJI) during the study follow-up. Two of them were early treated with debridement, antibiotics, irrigation, and retention of the prosthesis protocol; the other one was a late-onset infection requiring the THA explant and definitive conversion to Girdlestone procedure.

Table 3 shows the study data detailed by patients' sexes. Note that a higher percentage of perioperative complications was observed in male patients.

Figure 1 shows a case of complex femoral nailing failure in a female patient aged 81.

DISCUSSION

IFF is a common fracture injury among the elderly. Conservative treatment can result in prolonged periods in bed and/or lower limb shortening with varus deformity and is limited to very unstable patients with high perioperative risk[17]. Surgical treatment with cephalomedullary nails, compression hip screws, and the paracortical proximal plate has become the standard of care[9]. Despite the advanced acknowledge and skills in the surgical management of IFF, internal fixation is often associated with significant failure, ranging from 3%-12%.

The patients at increased risk of failure are the elderly, females, and osteoporotic patients[18,19]. Fixation failure depends on several factors, including poor bone quality, fracture comminution and biomechanical stability, quality of reduction, and fixation. Despite several technological improvements that have been produced in the last two decades, fixation failure due to mechanical and biological complications still occurs and can lead to potentially devastating scenarios[20-23]. Mechanical complications are cut-out, cut-through, peri-implant fractures, or implant fractures.

The most common mechanical complication observed in our study was the lateral mobilization of the cephalic screw, *i.e.*, cutting out (55.71% of cases). Many factors are associated with a higher risk of cut-out, including a tip-to-apex distance greater than 25 mm, an unstable fracture pattern, an inadequate fracture reduction that may lead to a varus deformity of the femoral neck, and positioning of lag screw outside of the center-center or inferior center of the femoral neck[24-26]. The medial mobilization of the cephalic screw or blade toward the hip joint is also called cut-through.

Salvage procedures currently used for failed internal fixation of IFF are revision osteosynthesis or conversion to hip arthroplasty. The term salvage procedures in patients undergoing salvage surgeries are used to indicate a considerable decrease in pain level and an increase in functional recovery after treatment[27-34].

Revision osteosynthesis is mostly utilized in patients younger than 50-years-old, with high life expectancy and satisfactory bone quality[27,28]. It implies femoral head sparing and re-fixation performed *via* hardware exchange (blade/screw), bone graft augmentation (autologous or allograft) acting as a plug-in case of joint perforation, and a new blade/screw insertion either cemented or uncemented[29]. On the other hand, conversion to THA as a salvage option is preferred for elderly patients with severely impaired articular surfaces allowing early weight bearing and mobilization [20,21,29]. As already mentioned, salvage THA is a complex procedure and includes several technical hurdles hindering successful surgical outcomes including bone loss and/or deformity, poor bone stock, and the presence of non-union or malunion[20].

Our study differentiated salvage procedure-related complications into intraoperative and postoperative complications. Intraoperatively, we considered major complications, such as an increased skin-to-skin operative time compared to primary THA implant, intraoperative blood loss, and intraoperative fractures. Intraoperative fractures were the most common intraoperative complication including one acetabular fracture and five femoral fractures occurring during acetabular reaming and femoral canal broaching, respectively. They may be related to a combination of factors such as previous osteoporosis, incomplete fracture union, and weakening of the bone after hardware removal.

Intraoperative acetabular fractures may be related to disuse osteopenia and/or the presence of previous osteoporosis. Great trochanter fractures may be attributable to an amount of bone loss to the medial aspect of the greater trochanter due to a wider diameter of proximal nails, a lateral entry site of the lag screw in the greater trochanter, and excessive stress during hardware removal[35].

Skin-to-skin operative time and intraoperative bleeding were higher. Compared to patients undergoing primary THA, salvage procedures require two steps. The first operative time includes adhesion clearance around scar tissue, exposure of the greater trochanter, and hardware removal. The second operative time includes prosthetic joint implantation. This procedure is challenging and technically demanding because of distorted proximal femur anatomy, poor bone stock,

Table 2 Recorded complications, *n* (%)

Item	Patients, *n* = 74
Dead	3 (4.00)
Periprosthetic acetabular fractures	3 (4.00)
Periprosthetic femoral fractures	5 (6.76)
THA dislocation	5 (6.76)
Periprosthetic joint infections	3 (4.00)

THA: Total hip arthroplasty.

Table 3 Study data reported by sex

Item	Males, *n* = 29	Females, *n* = 45	*P* value
Age in yr			
mean ± SD	72.90 ± 9.85	74.40 ± 8.65	0.087
Range	67-89	65-87	
BMI in kg/m^2			
mean ± SD	28.60 ± 4.03	28.90 ± 4.55	0.650
Side			
Right	17 (58.62)	26 (57.78)	0.580
Operating time in min, mean ± SD	84.0 ± 41.50	72.22 ± 32.34	0.003[a]
Patients undergoing ≥ 3, blood transfusion	19 (65.50)	24 (53.30)	0.002[a]
Complications			
Dead	2 (6.89)	1 (2.22)	0.001[1]
Periprosthetic acetabular fractures	2 (6.89)	1 (2.22)	0.001[a]
Periprosthetic femoral fractures	1 (3.45)	4 (8.90)	0.001[a]
THA dislocation	2 (6.89)	3 (6.70)	0.630
Periprosthetic joint infections	2 (6.89)	1 (2.22)	0.001[a]

[a]Statistical significance.
Data are *n* (%) unless otherwise indicated. BMI: Body mass index; SD: Standard deviation; THA: Total hip arthroplasty.

medial or lateral wall incompetence, and the presence of screw holes causing potential cement extrusion[30,31].

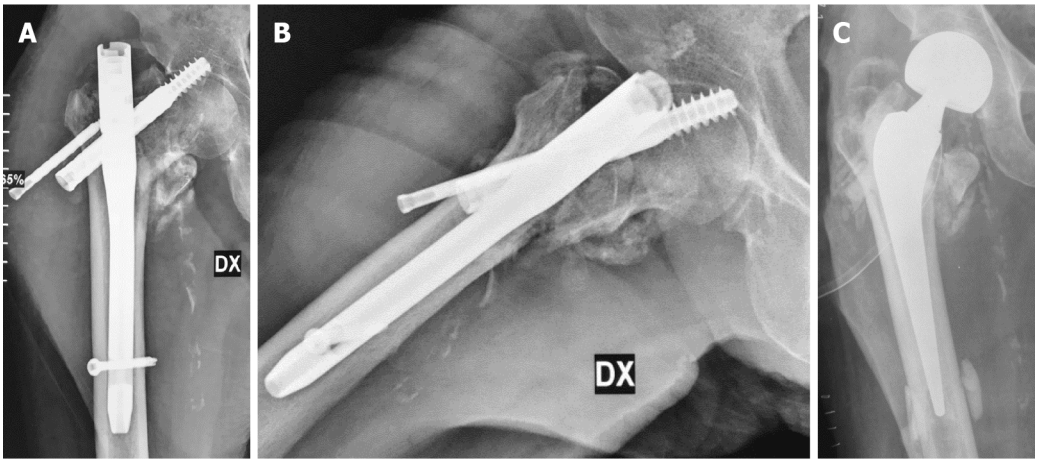
During the postoperative period after patient discharge, complications were further categorized as early major and late major complications. Early major complications included four cases of dislocation and two PJIs. Late major complications included 1 case of late dislocation and 1 case of periprosthetic infection.

Early postoperative dislocation is an important orthopedic complication after the salvage of THA. The dislocation rate in patients undergoing salvage arthroplasty after fixation failure of IFF seems to be higher compared to patients undergoing primary THA or salvage arthroplasty for FNF. This complication may be related to many factors: loss of abductor mechanism; shortening of limb length; and misorientation of prosthetic components[32].

The surgical site infection risk rate increases with an increasing number of revision surgeries performed. Our results (two early and one late PJI), similar to other results available within the current literature, revealed an increased PJI rate in salvage options compared to primary elective THA[36,37].

CONCLUSION

Surgical treatment for IFF fixation failure is a challenging procedure. Despite updated surgical skills in the surgical management of IFF, internal fixation failure rates are diagnosed in up to 12% of cases. Salvage options are the mainstay of their treatment allowing early weight bearing and stimulating functional recovery to the pre-injury level. This study analyzed difficulties during a salvage procedure, *i.e.*, cephalomedullary nail removal and THA implant, after failed



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Figure 1 A case of complex femoral nailing failure in a female patient aged 81 years. A and B: Anti-rotational screw cut-out, concomitant varus deformity of the neck, and cephalic screw cut-through; C: The patient underwent cemented bipolar hemiarthroplasty. Note the cement leakage through the former distal screw hole.

fixation of IFF. The present study demonstrated that salvage options for IFF fixation failure deal with intraoperative and postoperative complications at a higher rate than primary elective THA. Based on the present study findings, it is mandatory to adequately plan the surgical treatment in patients with PFFs since high rates of perioperative local and systemic complications are more common during revision surgery (or a salvage procedure).

ARTICLE HIGHLIGHTS

Research background

Proximal femur fractures (PFFs), including both intracapsular (femoral neck fractures) and extracapsular fractures (intertrochanteric femoral fractures, IFFs), affect around 1.5 million people per year worldwide. Mechanical failures of intertrochanteric nailing in IFFs could be managed with revision total hip arthroplasty (THA).

Research motivation

To assess if the conversion of failed nailing to THA in patients with previous PFFs has a high perioperative complication rate.

Research objectives

To describe the surgical complexity and the procedure-related complication rates, in patients referring with trochanteric nailing failure and treated with THA

Research methods

Patients referred to our level I trauma center between April 2012 and July 2018 with failed cephalomedullary nailing following trochanteric fractures were retrospectively recruited. All patients underwent a salvage surgical procedure, *i.e.*, cephalomedullary nail removal and conversion to THA. The surgical procedures were performed by the same surgical and anesthesiology team under spinal anesthesia. All patients underwent clinical and radiographic follow-ups for a minimum of 24 mo. Complications and re-operations were recorded.

Research results

Seventy-four patients met the inclusion criteria (male: 29; female: 45; mean age: 73.8-years-old; range: 65-89) and were included in the current study. The average operative time was 117 min (76-192 min). The average blood loss was 585 mL (430-1720 mL). Of the 74 patients, 43 patients (58.1%) required transfusion of three or more blood units. Two patients died within the 4th d after surgery because of pulmonary embolism. One patient died 9 mo after surgery due to ischemic myocardial infarction. The complication rate in the 71 patients who completed the minimum 24-mo follow-up was 22.50%. In 3 cases (4.23%) periprosthetic acetabular fracture was observed during the follow-up. One of these periacetabular fractures occurred intraoperatively. An intraoperative periprosthetic femur fracture was observed in 5 patients (7.00%). Four of these patients needed a re-operation to fix the fracture with plates and cerclages; in one of these patients, femoral stem revision was also necessary. In 4 patients (5.60%) an early THA dislocation was observed, whereas in 1 patient (1.40%) a late THA dislocation was observed. Three patients (4.23%) developed a periprosthetic joint infection during the study follow-up.

Research conclusions

The present study demonstrated that salvage options for IFF fixation failure are complex procedures with a relevant intraoperative and postoperative complication rate.

Research perspectives

Based on the present study findings, it is mandatory to adequately plan the surgical treatment in patients with PFFs since a revision surgery has a risk of high rates of perioperative local and systemic complications.

FOOTNOTES

Author contributions: Bizzoca D and Solarino G contributed to the investigation, data analysis, and writing; Dramisino P, Vicenti G, and Moretti L contributed to writing the first draft; Moretti B and Piazzolla A contributed to supervision and funding acquisition.

Institutional review board statement: Ethical clearance was obtained from our center's clinical research ethics board as per the 1964 Declaration of Helsinki.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors declare having no conflicts of interest.

Data sharing statement: No additional data are available.

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CASE REPORT

Vancomycin flushing syndrome in orthopaedic practice: A case report

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Abstract

BACKGROUND

Vancomycin flushing syndrome (VFS), also known as red man syndrome, is an allergic reaction to vancomycin. It typically presents as a rash on the face, neck, and upper torso after intravenous administration of vancomycin. VFS is blamed on rapid intravenous infusion of vancomycin during management and rarely happens after local use. A review of the literature showed that in the last 23 years, 4 such cases have been reported. Here, we add another case of VFS developed after slow local absorption of vancomycin in cement beads.

CASE SUMMARY

A 44-year-old male with a known case of hypertension, no history of allergies to medications, and a history of chronic osteomyelitis of the right tibia with discharging sinus over the anterolateral aspect of the leg. The pus culture grew *Staphylococcus aureus*, which was sensitive to clindamycin and vancomycin. The patient underwent irrigation and debridement with the placement of vancomycin cement beads made from 4 g of vancomycin powder and 40 g of polymethyl methacrylate. Three hours postoperatively, the patient developed a pruritic, erythematous, macular rash predominantly on his face, neck, chest, and lower extremities and to a lesser extent his upper extremities. A diagnosis of VFS was made and was successfully treated with cetirizine (10 mg, oral) and methylprednisolone sodium succinate (125 mg, intravenous). The patient continued to have itching with a facial rash for 12 h with gradual improvement. A decision was made to not remove the beads as the patient continued to improve. Gradually, the rash disappeared after 96 h with no further sequela.

CONCLUSION

VFS can occur not only after rapid intravenous injection of vancomycin but also

with local release, as in our case. As orthopaedic surgeons routinely use vancomycin with polymethyl methacrylate in chronic osteomyelitis and revision arthroplasty, they should be aware of such a complication occurring.

Key Words: Vancomycin; Anaphylactic reactions; Red man syndrome; Vancomycin flushing syndrome; Case report

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Core Tip: Vancomycin-related allergic skin reactions are not uncommon and are typically reported to occur after rapid intravenous infusion. However, this complication can also occur when vancomycin is implanted for slow release. Since orthopaedic surgeons routinely use vancomycin with polymethyl methacrylate, they should be aware of this complication occurring despite its rarity.

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INTRODUCTION

Vancomycin inhibits cell wall synthesis of bacteria, making it a potent bactericidal against the majority of Gram-positive cocci[1]. Even though it has its own complications of resistance and other allergic reactions, it is still in use. One of the serious complications of using vancomycin is vancomycin flushing syndrome (VFS), also known as Red man syndrome (RMS), which is an anaphylactoid reaction. It presents as a pruritic, erythematous rash on the face, neck, and upper torso, hypotension, angioedema, and cardiac arrest[2-5]. The initial reports of this complication were reported due to rapid infusion of vancomycin at 1000 mg over 1 h[6]. Later reports did suggest it can happen even after slow infusion as well[7].

Vancomycin is routinely used in orthopaedic practice preoperatively as a prophylactic antibiotic and postoperatively to treat bone and joint infections[8,9]. Serious allergic reactions like VFS can occur. VFS developed in our patient with chronic osteomyelitis after the insertion of vancomycin-impregnated beads. A review of the literature on VFS in orthopaedic patients showed that 4 cases of VFS occurring after local implantation have been reported in the last 23 years (Table 1)[10-13].

CASE PRESENTATION

Chief complaints

A 44-year-old male presented with chronic osteomyelitis of the right tibia. The patient presented to the orthopaedic clinic due to right leg pain and swelling, the inability to bear weight, and multiple attacks of subjective fever. The right leg pain suddenly progressed over the prior 3 mo, without a history of recent trauma. The pain increased at night and later became constant even during rest. The pain was located mainly on the proximal right tibia with radiation to the right knee and middle third of the right leg. The patient also experienced multiple attacks of fever and night sweats.

History of present illness

The patient had an open fracture 22 years ago with an infection and was diagnosed with chronic osteomyelitis with a discharging sinus. The sinus had closed, but the pain continued. He was treated with evacuation of the abscess and courses of antibiotics.

History of past illness

The patient had a history of hypertension.

Personal and family history

No personal or family history relevant to the presentation. No history of allergy to medications was reported.

Physical examination

On inspection, there was swelling of the right leg and skin redness on the anterior aspect of the proximal third of the right leg. We observed a skin scar with thin scar tissue over the tibia directly. There was no underlying soft tissue on the anterior aspect of the proximal right tibia with massive swelling and tenderness around this area. The patient had an intact neurovascular examination.

Table 1 Review of literature of vancomycin flushing syndrome after local implantation of vancomycin

Ref.	Vancomycin used	Outcome
Hinarejos *et al*[10], 2015	Bone cement	Recovered
Juyal *et al*[12], 2015	Bone cement beads	Recovered
Chen *et al*[11], 2018	Cement spacer	Recovered
Harper and Incavo[13], 2019	Cement spacer	Recovered
Present case, 2023	Bone cement beads	Recovered

Laboratory examinations

Laboratory findings included slightly increased leukocytes (12.3 × 10^9/L; normal range: 4.5-11.0 × 10^9/L), haematocrit (40.2%; normal range: 41%-50%), platelets (522,000 mcL; normal range: 150,000 to 450,000 mcL), elevated erythrocyte sedimentation rate (95 mm/h, normal range: < 20 mm/h), and high C-reactive protein (133 mg/L; normal range: 0-10 mg/L). The patient had a discharging sinus on the anterior proximal third of the right leg in the centre of the previous scar. Culture from the sinus grew *Staphylococcus aureus*.

Imaging examinations

Anteroposterior and lateral X-ray views showed multiple opacities, and magnetic resonance imaging showed a collection with high signal intensity in the proximal right tibia. The radiological studies revealed an intramedullary collection of the proximal right tibia with the impression of subacute osteomyelitis with multiple Brodie's abscesses of the proximal right tibia (Figure 1).

FINAL DIAGNOSIS

Chronic osteomyelitis of the right tibia.

TREATMENT

The patient underwent irrigation and debridement with the placement of vancomycin cement beads made from 4 g of vancomycin powder and 40 g of cement (1 g of vancomycin for each 10 g of cement) attached to size 1 proline and was placed intramedullary in the cavity through the two bone windows on the proximal and mid right tibia. Three hours postoperatively, the patient developed a pruritic, erythematous, macular rash predominantly on his face, neck, chest, and lower extremities and to a lesser extent his upper extremities. There were no signs of vital instability observed at the time (maximum area of skin rash was the infected, right lower limb and the patient's face and chest) (Figure 2). The patient started to become agitated due to itchiness. However, he remained clearly conscious, and the fine oxygen saturation was 98% in room air. The patient remained stable.

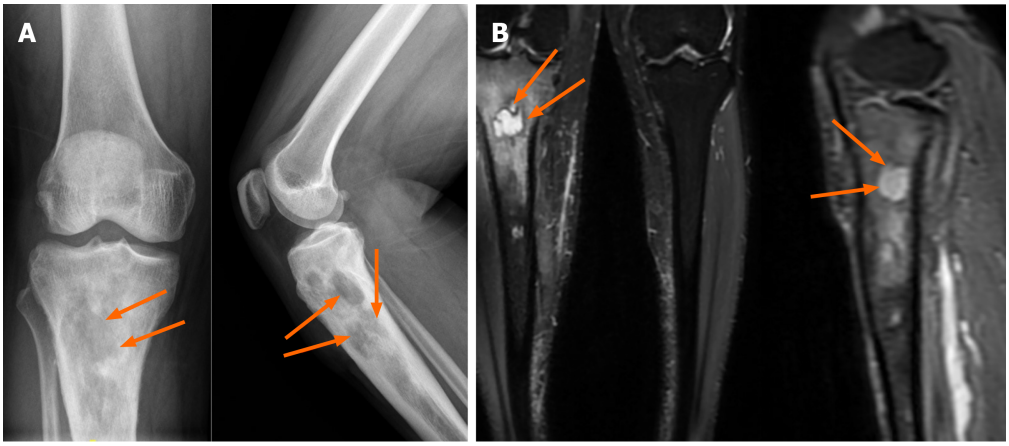
Urgent consultation of the on-call medical and infectious disease teams was completed; they examined the patient and recommended starting the patient immediately on cetirizine (10 mg, oral) and methylprednisolone sodium succinate (125 mg, intravenously). The patient continued to experience itching with a facial rash for 12 h with gradual improvement after therapy. He remained on close observation with close monitoring of respiration and other vital signs. The orthopaedic team made the decision to remove the antibiotics beads only if the patient hemodynamically deteriorated. The patient showed marked improvement 18 h after starting the medications; gradually, the rash started to decrease until it completely disappeared after around 96 h with no further sequela.

OUTCOME AND FOLLOW-UP

The beads were removed 4 mo postoperatively. The patient also received progressive irrigation and debridement with bone graft to the distal metaphyseal bone defect (window). The patient completed the antibiotics course according to the infectious disease team's recommendation (2 wk parenteral and 10 wk oral).

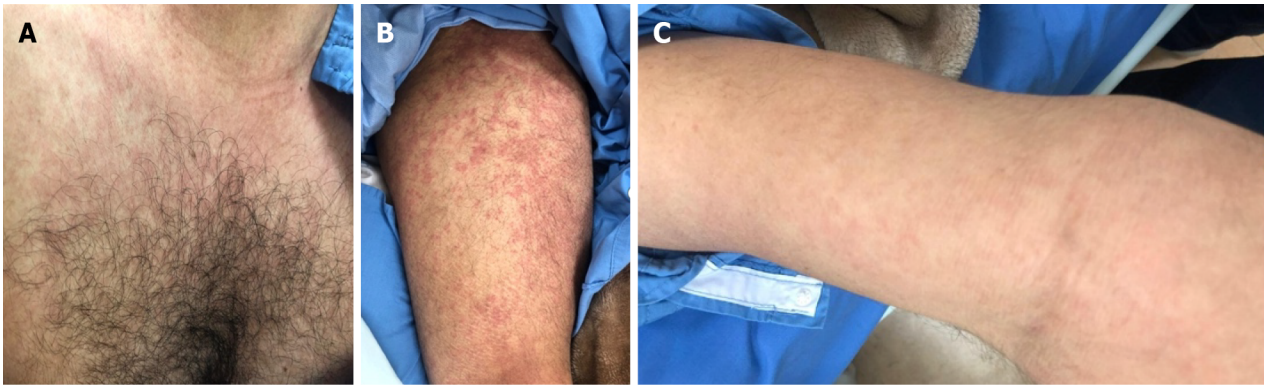
DISCUSSION

Our patient who developed VFS due to vancomycin exposure during after a prolonged release was contrary to the initial reports of rapid infusion being the cause of VFS. Only 4 other orthopaedic cases in the last two decades have been reported where the complication occurred due to the slow release of vancomycin. It is believed that the side effects are



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Figure 1 Imaging examinations. A: An X-ray showed changes of chronic osteomyelitis in the right upper tibia; B: Magnetic resonance imaging showed changes of chronic osteomyelitis with abscess formation in the right upper tibia. The arrows indicate cavitation and changes due to chronic osteomyelitis.



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Figure 2 Allergic reactions due to vancomycin. A: Chest; B: Legs; C: Forearm.

due to impurities. However, even after increasing the purity, the side effects still occur. At present, it is recommended that vancomycin should be infused at a rate no faster than 1 g/h or 10 mg/min[13,14].

There are two issues that need to be addressed. Vancomycin induces allergic reactions due to its activation of mast cells, which release histamine independent of preformed immunoglobin E or complement. The side effects range from pruritis to angioedema to cardiac arrest. It is prudent that antihistamines are started at the same time as vancomycin to avoid the reactions.

Secondly, the term "RMS" needs to be retired from the medical language as this term has racial implications relating to native American nations. Because reactions to vancomycin are not known to be race dependent and occur in children and women, RMS is a misnomer. Hence the term VFS should be used.

CONCLUSION

In conclusion, VFS can occur either through rapid infusion or slow release of vancomycin, as in our patient. Since vancomycin-impregnated cement beads and spacers are routinely used in orthopaedic service, orthopaedic surgeons and trainees should be aware of such complications and should be ready to recognize and treat them early.

FOOTNOTES

Author contributions: Al-Anii FM, Sadat-Ali M, Al-Tabash KW, AlMulhim AI, AlMousa SA, and AlHawas AM participated in the study of the case, review of the literature, and the writing of the manuscript.

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CASE REPORT

Late brachial plexopathy after a mid-shaft clavicle fracture: A case report

Mohammad M Alzahrani

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Abstract

BACKGROUND

Clavicle fractures can rarely be associated with brachial plexus injury. These are commonly caused by tractional injury at the time of trauma, but unfrequently can be caused by compression of the brachial plexus from excessive callus or granulation tissue formation.

CASE SUMMARY

We report a rare case of an adult male who sustained a mid-shaft clavicle fracture and had a late presentation of brachial plexus palsy due to compression from excessive callus formation.

CONCLUSION

We reported a case of a rare occurrence of delayed brachial plexus palsy due to compression from excessive callus formation in a midshaft clavicle fracture. Early diagnosis and surgical decompression of the brachial plexus is critical, as when managed efficiently, a full recovery of the brachial plexus palsy can be expected in these patients.

Key Words: Clavicle; Fracture; Brachial plexus; Palsy; Case report

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Core Tip: Brachial plexus palsy due to compression from excessive callus formation in a midshaft clavicle fracture is a rare occurrence. We reported a case of a of delayed brachial plexus palsy due to compression from excessive callus formation in a midshaft clavicle fracture. Early diagnosis and surgical decompression of the brachial plexus is critical for improved patient outcomes.

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INTRODUCTION

Clavicle fractures are a common injury in the adult population, accounting for 2%-3% of all fractures[1-3]. While these injuries are common, an associated brachial plexus injury is considered rare with an incidence of less than 1%, while this incidence can reach 2% in displaced fractures[4,5]. These brachial plexus injuries commonly occur due to tractional injury at the time of trauma. A rare cause of brachial plexus lesion is compression due to excessive callus or granulation tissue formation and these patients typically have a late presentation[6,7].

CASE PRESENTATION

Chief complaints

A 58-year-old male was involved in a frontal impact motor vehicle accident as a restrained driver. Patient had no history of loss of consciousness and was brought by ambulance to the emergency department. Primary survey was found to be normal, while on secondary survey patient was found to have tenderness over the right clavicle with obvious deformity. In addition, patient had limited right shoulder range of motion in all planes due to severe pain. Plain radiographs diagnosed multiple right sided rib fractures (which were managed conservatively) and a right mid-shaft comminuted clavicle fracture. Neurological and vascular exam was found to be normal at the time of the initial assessment and there was no sign of skin tenting or skin breakage over the clavicle fracture.

History of present illness

Patient was immobilized in a sling and discharged with a follow up in the orthopaedic clinic in 2 wk. At the time of the follow up 2 wk post-injury, plain radiographs were performed again and re-documented a displaced mid-shaft comminuted clavicle fracture (Figure 1A). Patient again was found to have tenderness over a deformed right clavicle with pain and limited right shoulder range of motion. The neurological and vascular exam of the right upper extremity was still found to be normal. Patient was offered open reduction and internal fixation of the clavicle fracture, but patient declined surgery and opted for conservative management and was given follow up in 4 wk.

At the time of the 4 wk follow up, patients' tenderness over the right clavicle improved and follow up imaging showed progression of callus formation at the fracture site (Figure 1B). Interestingly, patient was complaining to intermittent right upper extremity mild to moderate shooting pain but was found to have a normal motor and sensory exam of the extremity.

History of past illness

There was no significant past medical illness.

Personal and family history

There was no significant personal and family history.

Physical examination

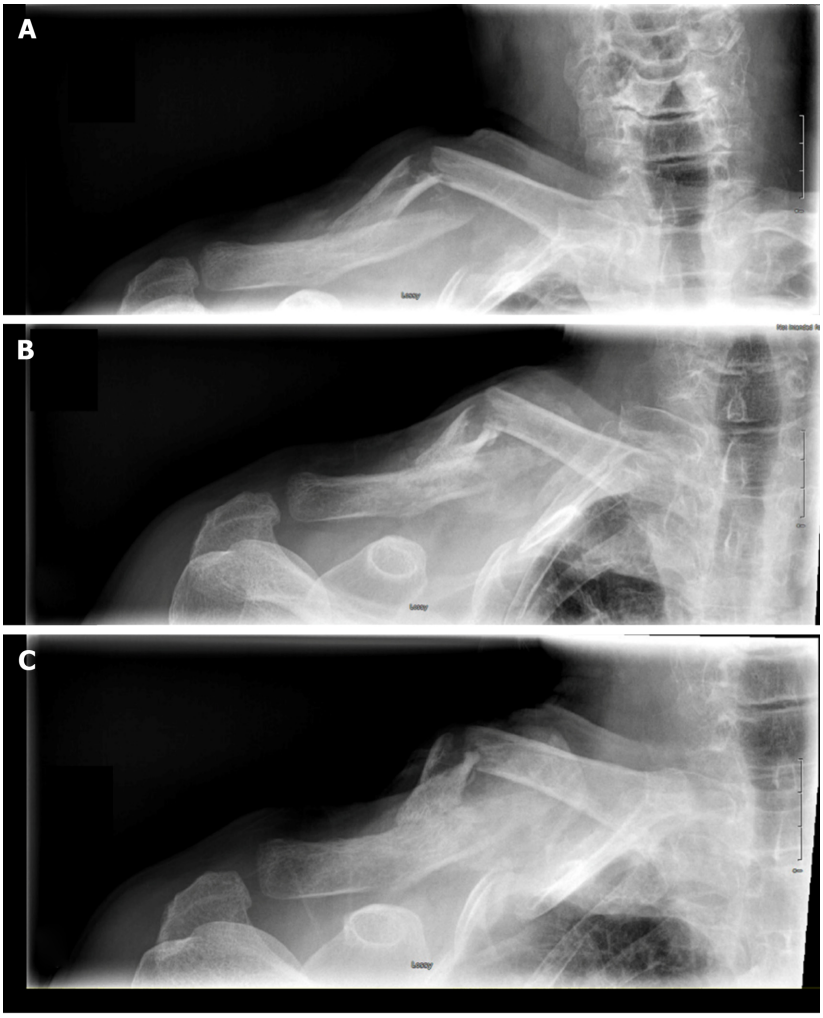
At the following office visit at 3 mo post-injury, the patient's shoulder and clavicle pain resolved, but patient was complaining of significant right upper extremity weakness, with inability to hold a cup in his hand and decreased grip strength. On further history, patient also gave history of loss of sensation in the hand and forearm region (C7, C8 and T1 distribution). On physical exam there was resolution of the localized right clavicle tenderness with a large bony deformity in the region. Motor power showed weakness in right upper extremity muscle power globally, but more pronounced in finger flexion, adduction and abduction, in addition to weakness in thumb flexion and adduction. On sensory exam, there was loss of sensation over the ulnar aspect of the hand and medial forearm. Distal pulses were present, including radial and ulnar pulses at the wrist.

Laboratory examinations

There were no significant laboratory examinations.

Imaging examinations

Plain radiograph of the clavicle showed large formation of callus at the fracture site (Figure 1C). A computed tomography (CT) scan was performed which confirmed the midshaft comminuted fracture with hypertrophic callus formation around the fracture site (Figures 2 and 3). Due to the patient's neurological deficit, a magnetic resonance imaging (MRI) of the region was performed and showed that the hypertrophic callus formation was causing compression of the brachial plexus



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Figure 1 Antero-posterior right clavicle radiograph 2 wk, 6 wk and 3 mo post-injury. A: 2 wk; B: 6 wk; C: 3 mo.

trunks in the infraclavicular region (Figure 4).

A nerve conduction study was arranged for the patient. But as the patient was exhibiting significant neurological deficits due to brachial plexus compression from the hypertrophic callus formation, an urgent surgical decompression and clavicle open reduction internal fixation was planned.

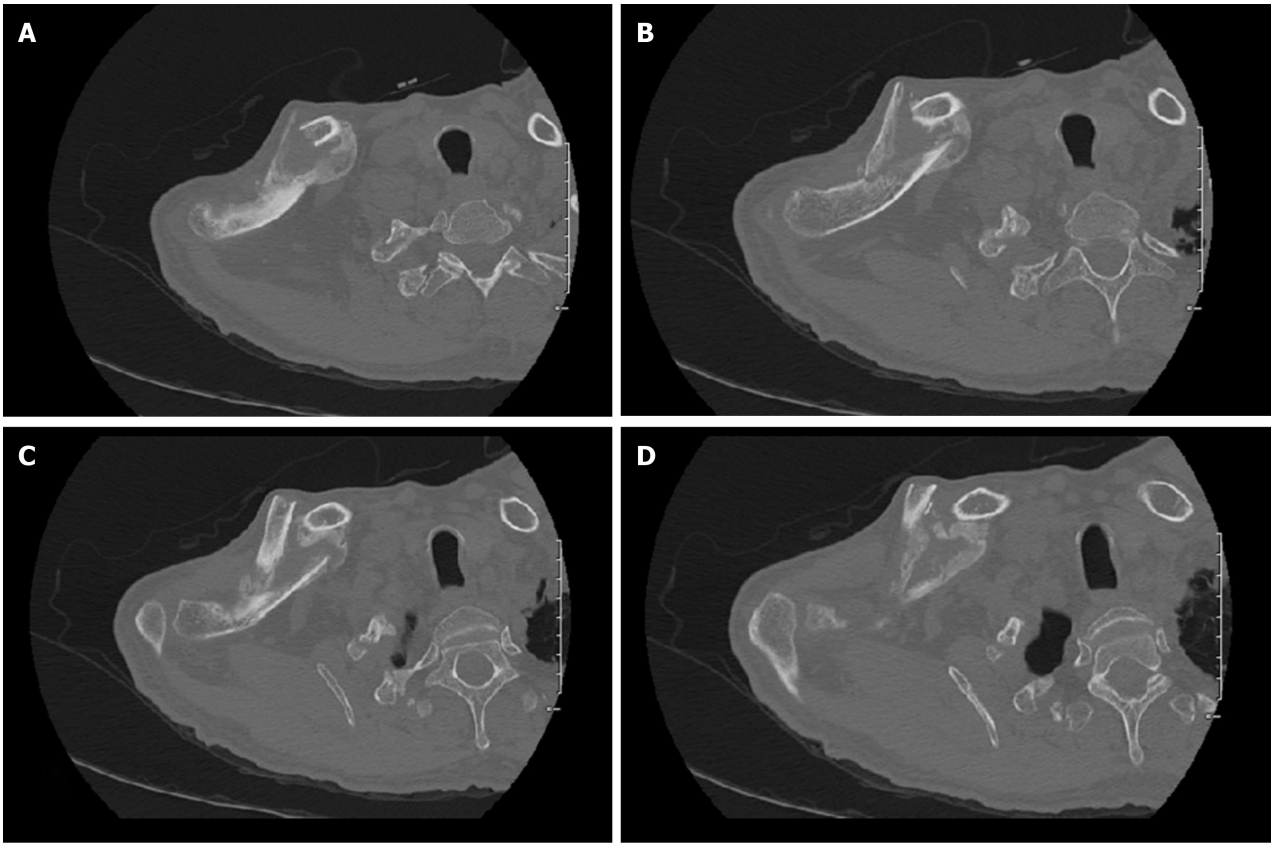
FINAL DIAGNOSIS

Right mid-shaft clavicle fracture with hypertrophic callus formation causing compression of the brachial plexus trunks in the infraclavicular region.

TREATMENT

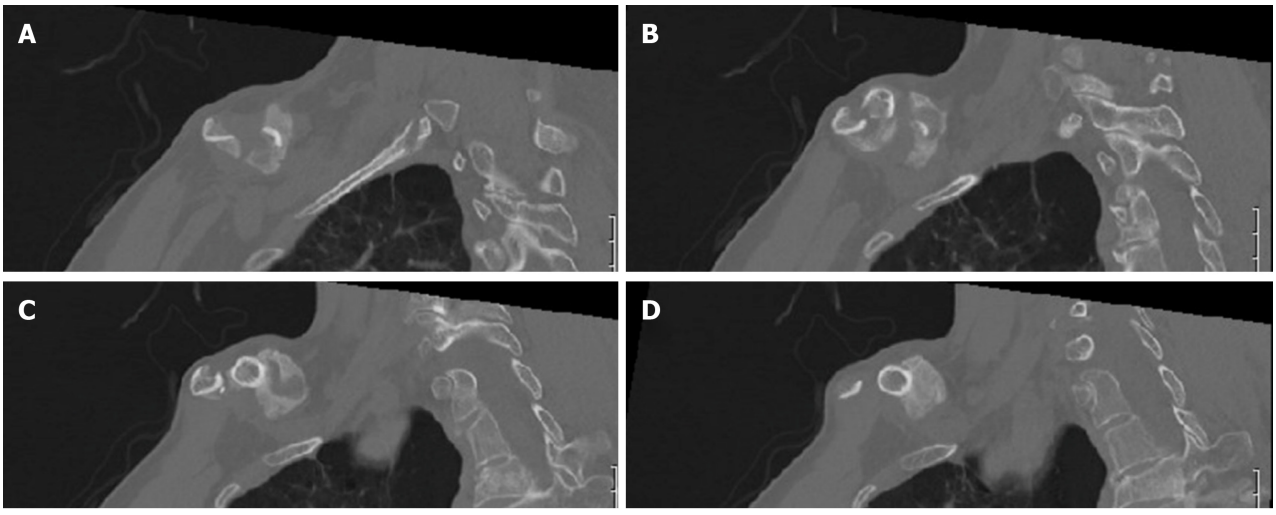
The surgery was performed under general anesthesia. After 2 g of intravenous cefazolin was administered, the patient was positioned in the supine position and the right upper extremity was sterilely prepped and draped up to the mid-sternal region. A direct surgical incision over the right clavicle was performed extending from the sternoclavicular joint medial to the distal clavicle laterally. The incision was performed through skin and subcutaneous tissue and hemostasis was obtained. Due to the mass effect of the callus formation over the fracture site, only a thin layer of muscle and fascia was identified and was sharply dissected through. Normal clavicle bone both medial and laterally to the fracture site was exposed to allow application of the internal fixation.

Once adequate exposure was obtained, the area of the bridging callus was carefully osteotomized using small osteotomes and a small handheld burr. The callus was then excised using the burr and small rongeur until the native fracture site was identified. After complete removal and decompression of the hypertrophic callus (Figure 5), we identified the medial and lateral end of the fracture with a small butterfly piece. We confirmed that the infra-clavicular



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Figure 2 Sequential axial images of non-contrast computed tomography scan. A-D: At 3 mo post-injury showing mid-shaft clavicle fracture with abundant callus formation.

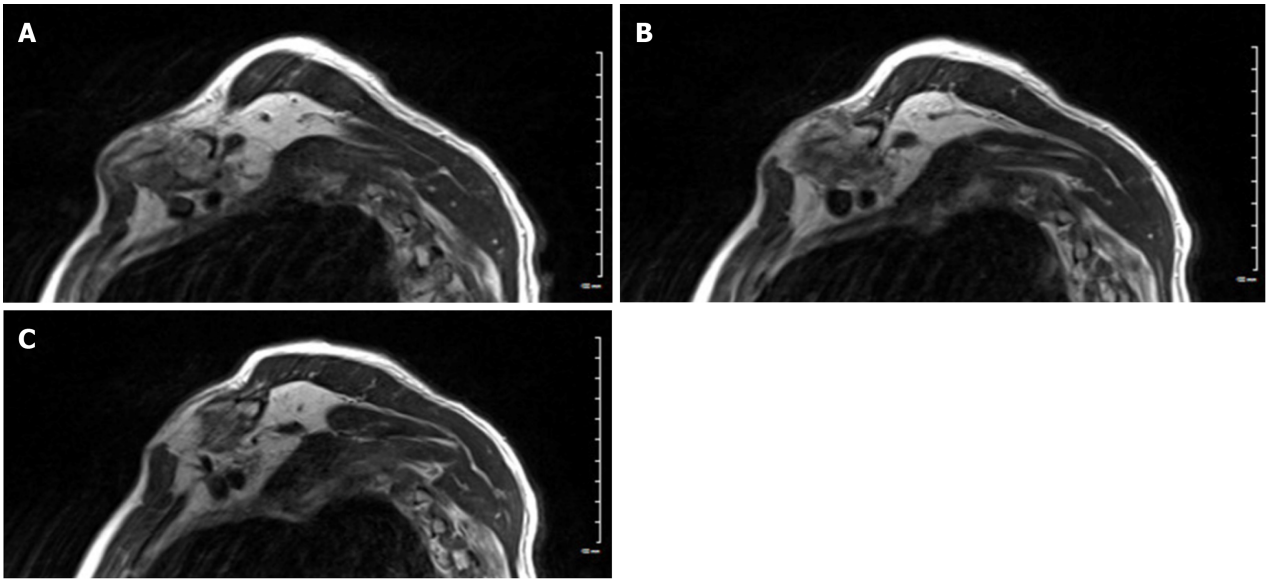


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Figure 3 Sequential sagittal images of non-contrast computed tomography scan. A-D: At 3 mo post-injury showing mid-shaft clavicle fracture with abundant callus formation.

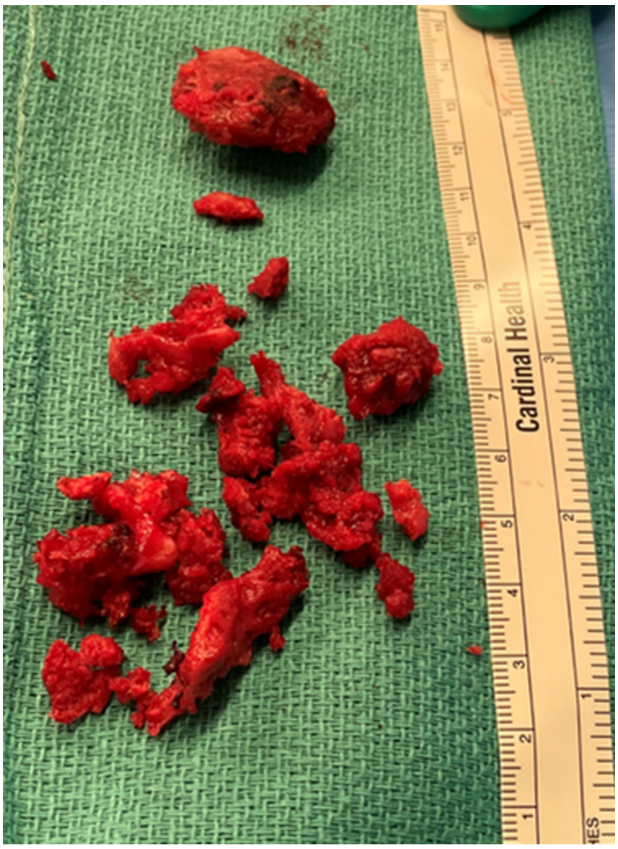
region was decompressed, and no remanent callus or granulation tissue was still present.

The comminuted fracture was then reduced and held provisionally with pointed reduction clamps and then provisionally fixed with an anterior contoured 2.7 mm reconstruction plate and then a superior pre-contoured 3.5 mm clavicular plate was applied. Intra-operative fluoroscopic images were obtained confirming adequate fracture reduction and implant positioning (Figure 6). The wound was then copiously irrigated with normal saline. The wound was closed in layers and a sterile dressing was applied.



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Figure 4 Sequential sagittal T2 weighted images of magnetic resonance imaging scan. A-C: At 3 mo post-injury showing mid-shaft clavicle fracture with abundant callus formation causing a mass effect on adjacent brachial plexus trunks.

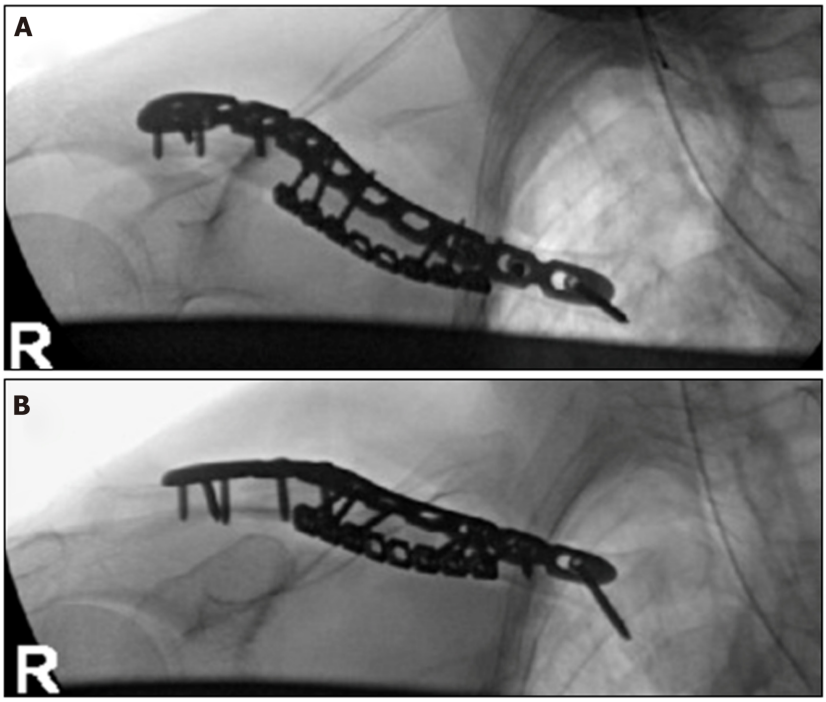


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Figure 5 Clinical intra-operative picture showing the excised hypertrophied callus after surgical decompression.

OUTCOME AND FOLLOW-UP

Patient was allowed gentle shoulder range of motion but instructed to avoid any weight bearing through the right upper extremity for the first six weeks post-operatively. In the early post-operative phase, patient noted significant improvement in his symptoms and formal physical therapy was initiated at 6 wk post-operatively.



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Figure 6 Superior and anteroposterior radiographs of right clavicle after open reduction and internal fixation. A: Superior radiographs; B: Anteroposterior radiographs.

At both 3 and 6 mo follow ups the patient noted improved motor function of the hand and gradual resolution of his sensory deficits. He also indicated improvement of the radiculopathic pain in the right upper extremity. Plain radiographs of the right clavicle showed progression of the fracture healing and maintained implant fixation (Figure 7).

DISCUSSION

Brachial plexus injuries are rarely caused by clavicle fractures with the majority of cases being caused by tractional injury at the time of trauma, which commonly affect the supraclavicular region of the brachial plexus. Della Santa *et al*[7] reported an incidence of only 1% of clavicle fractures associated with brachial plexus palsy during a 20-year period.

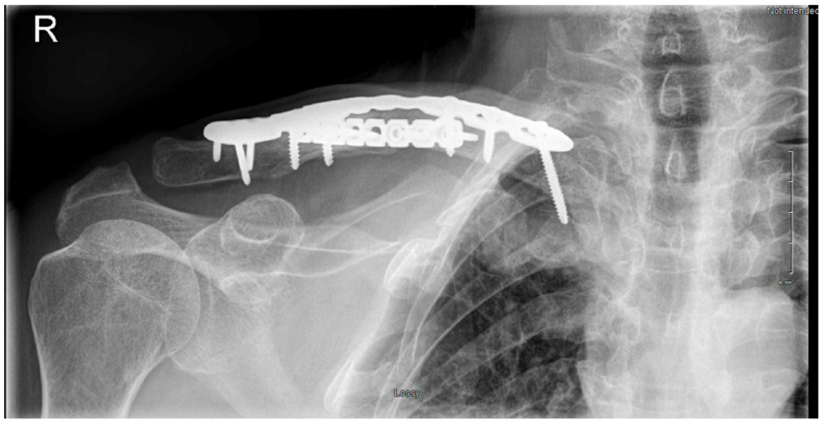
In our case report, the patient had a delayed palsy of the brachial plexus due to compression from the excessive callus formation. This entity is considered extremely rare, with only some case reports and case series reported in the literature [6-9]. The resultant compression can be due to excessive callus or granulation tissue formation, hypertrophic nonunion or vascular pseudo-aneurysm[10-12]. Commonly this compression affects the infra- or retroclavicular region of the brachial plexus, and these patients have a delayed presentation with late onset neurological deficits in the ipsilateral upper extremity[8,11,13].

A high index of suspicion and careful physical exam are required to avoid misdiagnosis and delay in management. Documentation of motor and sensory exam both at the time of injury and in subsequent visits is critical to identify any evidence of brachial plexus palsy in the early phase. In addition, adequate plain radiographs and CT scan can identify any excessive callus formation or hypertrophic nonunion as the cause of compression. A CT angiogram can be indicated to rule out a subclavian pseudoaneurysm as the cause of compression[12]. Documentation of brachial plexus compression can be identified with an MRI of the clavicular and brachial plexus region, which can also identify other causes of compression (*i.e.*, excessive granulation tissue). Nerve conduction studies and electromyography can also help identify level of compression and involved brachial plexus region.

Management of these injuries involves decompression of the brachial plexus and open reduction internal fixation of the associated clavicle fracture. Typically, these injuries have good prognosis when compared to injuries due to tractional injuries[7,8,13]. The majority of patients can be expected to have a complete neurological recovery once the brachial plexus is decompressed, and fracture adequately stabilized[4,9,14].

CONCLUSION

We reported a case of a rare occurrence of delayed brachial plexus palsy due to compression from excessive callus formation in a midshaft clavicle fracture. Early diagnosis and surgical decompression of the brachial plexus is critical, as when managed efficiently, a full recovery of the brachial plexus palsy can be expected in these patients.



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Figure 7 Anteroposterior radiographs of right clavicle at 3 mo post-surgery showing progression of the fracture healing and maintained implant fixation.

FOOTNOTES

Author contributions: Alzahrani MM contributed to the concept, design, study execution, manuscript writing and review.

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ORIGINAL ARTICLE

Retrospective Study

Safety and outcomes of hip and knee replacement surgery in liver transplant recipients

Mohamed Ahmed, Abdelrhman Abumoawad, Fouad Jaber, Hebatullah Elsafy, Saqr Alsakarneh, Laith Al Momani, Alisa Likhitsup, John H Helzberg

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Abstract

BACKGROUND

Liver transplant (LT) is becoming increasingly common with improved life expectancy. Joint replacement is usually a safe procedure; however, its safety in LT recipients remains understudied.

AIM

To evaluate the mortality, outcome, and 90-d readmission rate in LT patients undergoing hip and knee replacement surgery.

METHODS

Patients with history of LT who underwent hip and knee replacement surgery between 2016 and 2019 were identified using the National Readmission Database.

RESULTS

A total of 5046119 hip and knee replacement surgeries were identified. 3219 patients had prior LT. Mean age of patients with no history of LT was 67.51 [95% confidence interval (CI): 67.44-67.58], while it was 64.05 (95%CI: 63.55-64.54) in patients with LT. Patients with history of LT were more likely to have prolonged

length of hospital stay (17.1% *vs* 8.4%, $P < 0.001$). The mortality rate for patients with no history of LT was 0.22%, while it was 0.24% for patients with LT ($P = 0.792$). Patients with history of LT were more likely to have re-admissions within 90 d of initial hospitalization: 11.4% as compared to 6.2% in patients without history of LT ($P < 0.001$). The mortality rate between both groups during readmission was not statistically different (1.9% *vs* 2%, $P = 0.871$) respectively.

CONCLUSION

Hip and knee replacements in patients with history of LT are not associated with increased mortality; increased re-admissions were more frequent in this cohort of patients. Chronic kidney disease and congestive heart failure appear to predict higher risk of readmission.

Key Words: Liver transplant; Hip replacement surgery; Knee replacement surgery

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Core Tip: Patients receiving liver transplants (LTs) are having longer life expectancy. This resulted in an increasing number of patients with LTs requiring hip and knee surgery, with data about their outcomes being limited. The aim of this analysis is to evaluate the safety of these procedures in LT patients and provide more guidance on expected outcomes. This study concluded that LT patients are not at risk of higher mortality albeit increased morbidity.

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INTRODUCTION

Joint replacement surgery is one of the most performed elective surgical procedures. Both total hip arthroplasty (THA) and total knee arthroplasty (TKA) have proven to be highly beneficial orthopedic procedures[1]. Liver cirrhosis is an established risk factor for complications after THA and TKA. Patients with cirrhosis had longer lengths of stay, more frequent discharges to nursing facilities, increased 90-d readmission rate, and higher medical complications including urinary tract infections, acute kidney injury (AKI), need for blood transfusions, gastrointestinal hemorrhage, dislocations, infections, and revisions within 90 d[1]. One-year and longer-term mortality rates were higher in patients with cirrhosis. A model for end-stage liver disease score of 10 or higher predicted a three-fold increased likelihood of complications[1]. A recent meta-analysis examining 527 patients with history of liver pathology undergoing total joint arthroplasty (TJA) showed higher risk of infection and mortality[2].

Liver transplant (LT) is the only curative treatment for patients with liver cirrhosis and end stage liver disease[3]. The prevalence of liver transplantation, which ranks second only to kidney transplantation among solid organ transplantations in the United States, has increased[4]. The increasing 5-year graft survival rate of more than 70% has led to better outcomes with LT[3-5]. With increased life expectancy in the LT cohort, reduced bone mineral density, and higher risk of hip osteonecrosis from immunosuppressive drugs, this cohort becomes at higher risk of needed TKA[6-10].

Arthroplasty is generally safe in healthy, immunocompetent individuals, but its safety in LT patients remains controversial[11]. Previously, a meta-analysis examined the complication rates in 3024 LT patients undergoing THA or TKA [12]. This demonstrated that LT patients benefit functionally from both THA and TKA, but at the cost of increased infection-related complications, reoperation/revision, arthrotomy, and specific medical complications, including AKI and blood transfusion[12]. Other previous studies from small cohorts have addressed the issue of safety but had demonstrated conflicting results[13-17].

Current data describing the mortality rates and readmission rates of these patients after total joint replacement are insufficient to adequately assess complications due to the small cohort size. This makes it difficult to draw conclusions when considering the decision for joint replacement. As more LT patients seek evaluation for degenerative hip disease, a better understanding of the mortality rate and 90-d readmission rates in this high-risk cohort is needed. The aim of this study is to evaluate the mortality outcome and 90-d readmission rates in LT patients undergoing THA and TKA using the National Readmission Database (NRD). Compared to a control cohort, we hypothesize that LT patients undergoing THA or TKA will show a measurable increase in mortality and 90-d readmission rates.

MATERIALS AND METHODS

Patients with history of LT who underwent hip and knee replacement surgery between 2016 and 2019 were included in

the study. Patients were selected from the Healthcare Cost and Utilization Project databases (HCUP). The HCUP databases are sponsored by the Agency for Healthcare Research and Quality. The NRD database is the largest HCUP database and contains unweighted data from over 7 million hospital admissions each year. The data represent a 20% random sample of participating hospital discharges from 46 states. The NRD database is de-identified and available to the public. Thus, it is not considered human subject research and is exempted from review by the institutional review board. To assure a meaningful study cohort the investigators agreed upon a minimum study cohort of 250000 admissions. The International Classification of Diseases Code, 10th Revision Clinical Modification (ICD-10) was used to identify the patients. 90-d readmission rates and diagnoses were identified (Supplementary material). Multiple logistic regression model was used to identify the factors associated with readmission.

Statistical analysis

Continuous variables were described using mean ± SD, while categorical variables were described using proportion (percentage). Categorical variables were compared using the Rao-Scott χ^2 test, and continuous variables were compared using a survey-weighted Student's *t*-test. Multivariate analysis was performed using logistic regression models to decrease bias and adjust for possible confounding factors. Statistical analysis was performed by a biomedical statistician. All analyses were performed using STATA BE 17.

Inclusion criteria

The inclusion criteria including: (1) Patients > 18 years old; (2) Patient with history of LT; and (3) Patient needing hip and/or knee replacement surgery from 2016-2019.

Exclusion criteria

The exclusion criteria including: (1) Patient < 18 years old; (2) Patient needing any other kind of transplant; (3) Patients admitted for other type of orthopedic surgeries; and (4) Patients admitted after more than 90 d of initial admission.

RESULTS

General characteristics

A total of 5046119 hip and knee replacement surgeries were identified between the year 2016 and 2019. 3219 patients had prior LT. Mean age of patients with no history of LT was 67.51 [95% confidence interval (CI): 67.44-67.58], while it was 64.05 (95%CI: 63.55-64.54) in patients with LT. Patients without history of LT had mean length of hospital stay (LOS) 2.87 d (95%CI: 2.84-2.91) as compared to 3.86 d (95%CI: 3.62-4.11), $P < 0.001$. Medicare was the most common primary expected payer. Urban teaching hospitals were the most common (Table 1).

Outcomes

Patients with history of LT were more likely to have prolonged LOS (17.1% *vs* 8.4%, $P < 0.001$), develop AKI (11.1% *vs* 3.2%, $P < 0.001$), and have sepsis (1.2% *vs* 0.3%, $P < 0.001$). The mortality rate for patients with no history of LT was 0.22%, while it was 0.24% for patients with LT. No significant difference was found ($P = 0.792$). Patients with history of LT were more likely to have readmissions within 90 d of initial hospitalization: 11.4% compared to 6.2% in patients without history of LT ($P < 0.001$). The mortality rate between both groups during readmission was not statistically different (1.9% *vs* 2%, $P = 0.871$) respectively. Mortality was mainly caused by sepsis, pulmonary embolism and AKI. There was no significant statistical difference between the 2 groups in rate of prosthetic infections during readmission (10.1% *vs* 12.1%, $P = 0.34$) and gastrointestinal (GI) bleed (4.7% *vs* 5.9%, $P = 0.47$).

Multivariate analysis

Multiple logistic regression analysis showed that the odds ratio (OR) for 90-d readmission in LT patients was 1.54 (95%CI: 1.29-1.84). These readmissions were statistically associated with the presence of chronic kidney disease (CKD) (OR = 1.416, 95%CI: 1.39-1.44) and underlying congestive heart failure (OR = 1.72, 95%CI: 1.69-1.76) (Table 2).

DISCUSSION

Liver transplantation is a lifesaving treatment for patients with end-stage liver disease. With increasing advances in surgical technique, patient/graft selection, and immunosuppression, long-term survival after LT continues to improve. More LT patients are likely to become candidates for THA and TKA due to the increased risk of avascular necrosis and longer patient longevity. Postoperative complications and higher readmission rates are significant concerns in this cohort. While only a few small-cohort studies have reported postoperative complications in LT patients undergoing THA or TKA, no available data suggest readmission rates and predictors of readmissions. This study found 3219 LT patients identified among 5046119 patients who underwent hip and knee replacement surgeries between 2016 and 2019. The mean age of the LT cohort was 64.05 compared to 67.51 in the non-LT cohort. Overall, the LT cohort had a higher readmission rate at 90 d, longer hospital stays, and a higher risk of AKI and sepsis. CKD and congestive heart failure appear to predict a higher risk of readmission at 90 d. No significant difference in mortality rate, prosthesis infection, and gastrointestinal

Table 1 Compares demographics and main outcomes between the two groups during index admission

General characteristics	Patients with history of LT, *n* = 3218	Patients without LT, *n* = 5042901	*P* value
Mean age at admission	64.05 ± 0.49	67.51 ± 0.46	< 0.001
LOS	2.87 ± 0.03	3.86 ± 0.25	< 0.001
Mortality	8 (0.24%)	11154 (0.22%)	0.792
Primary expected payer			
1: Medicare	2104	3056650	< 0.001
2: Medicaid	189	212763	
3: Private	837	1592682	
4: Self-pay	13	26225	
5: No charge	4	3057	
6: Other	71	149442	
Location/teaching status of hospital			
1: Rural	191	498918	< 0.001
2: Urban nonteaching	509	1278335	
3: Urban teaching	2517	3268866	
CHF	263	260627	< 0.001
Renal failure	1461	434965	< 0.001
Coronary artery disease	454	661069	0.276

LT: Liver transplant; CHF: Chronic heart failure; LOS: Length of hospital stay.

Table 2 Predictors of readmissions at 90-d (multivariate analysis)

	Odds ratio, 95%CI	*P* value
Liver transplant	1.54 (1.29-1.83)	< 0.0001
Age	1.01 (1.009-1.01)	< 0.0001
Female	0.86 (0.85-0.87)	< 0.0001
DM	1.19 (1.16-1.22)	< 0.0001
CHF	1.72 (1.69-1.76)	< 0.0001
LOS	1.05 (1.04-1.06)	< 0.0001
Renal failure	1.42 (1.39-1.44)	< 0.0001
Rheumatoid arthritis	1.26 (1.23-1.29)	< 0.0001
Chronic pulmonary disease	1.34 (1.32-1.36)	< 0.0001
Obesity	0.98 (0.97-1.01)	0.78

Multivariate logistic regression model for predictors of readmissions at 90-d for patients with history of liver transplant. CI: Confidence interval; DM: Diabetes mellitus; CHF: Chronic heart failure; LOS: Length of hospital stay.

bleeding was observed.

Recent studies examining the outcomes of THA or TKA after LT are small and limited. There is little data on readmission rates and mortality in this population. It appears that LT patients were more likely to be readmitted within 90 d than control patients (11.4% *vs* 6.2%, $P < 0.001$). Multiple logistic regression analysis showed that the OR for 90-d readmission in LT patients was 1.54 (95%CI: 1.29-1.84). Predictors of increased 90-d readmission rates were also analyzed, including patient's age, LOS, chronic heart failure (CHF), CKD, lung disease, and diabetes mellitus with complications. Among these factors, CHF (OR = 1.72, 95%CI: 1.69-1.76, $P < 0.001$) and CKD (OR = 1.42, 95%CI: 1.39-1.44, $P < 0.001$) predicted a higher risk of readmission.

Mortality during this short follow-up period was also analyzed to better capture the mortality rate associated with TKA/THA compared to other causes. Few studies have reported short-term mortality risk. Inacio *et al*[18] reported a 1-year mortality rate of 0.5% in the 45-54 age group. Another meta-analysis reported that 1-year mortality year for the LT cohort undergoing THA or TKA was 4.35%. The observed one-year mortality rate in LT patients is more like cirrhotic patients undergoing THA and TKA, which was measured at 5% in 115 patients by Tiberi *et al*[1]. This study did not find an increased mortality rate among the LT group (0.24% in LT compared to 0.22 % in controls, $P = 0.792$). In addition, there was no significant difference in mortality rates between the two groups during readmission (1.9% *vs* 2%, $P = 0.871$).

Suppression of humoral immunity by lifelong immunosuppressants increases postoperative complications[17,19,20]. The incidence of systemic infections, particularly sepsis and AKI was significantly increased in the LT cohort after 90 d compared to the control group. The LT cohort in our study had a higher risk of AKI than controls (11.1% *vs* 3.2%, $P < 0.001$). A meta-analysis of 3024 LT patients reported a higher risk of complications in the LT group, with AKI being the highest OR among all complications[12]. The trend towards higher AKI rates has also been reported in patients with cirrhosis after arthroplasty. Tiberi *et al*[1] found a higher risk of AKI in patients with cirrhosis compared to controls after 90 d (10% *vs* 1%). In addition, significantly higher AKI rates were found in other types of transplantation. Choi *et al*[21] reported higher odds (OR = 22.25, $P < 0.001$) of developing AKI in the kidney and LT after THA compared to controls. Cavanaugh *et al*[22] reported a higher incidence in the kidney (OR = 3.48) and in cardiac, lung, and pancreas transplant patients (OR = 4.42) receiving TKA and THA, while Klement *et al*[19] reported significantly higher AKI rates in the kidney (OR = 6.03), lung (13.180), heart (19.660) and pancreas (7.780) transplanted patients who received TKA at 90 d. Post operative AKI can be linked to poor patient outcomes, including increased length of stay, cost and increased probability of discharging to extended-care facilities. Additionally, postoperative AKI is responsible for 25%-90% of in-hospital deaths[23].

Increased susceptibility to systemic and local infections is a major concern in LT patients undergoing THA or TKA. A meta-analysis by Han *et al*[12] reported higher rates of local and systemic infections both at 90 d and at all time points in the LT cohort compared to the control group. Additionally, this study found that LT patients undergoing TKA, compared to those undergoing THA, had a higher rate of joint infection at all time points. Onochie *et al*[24] had similar findings, a meta-analysis of chronic liver disease patients undergoing THA *vs* controls, demonstrated infection rates of 0.5% at a mean follow-up of 13.5 mo. The finding of higher rates of infection in patients with cirrhosis after arthroplasty is a general trend. While Jiang *et al*[25] found that a diagnosis of cirrhosis is the highest independent risk factor for periprosthetic infection, Deleuran *et al*[26] reported higher rates of infection in cirrhotic patients undergoing THA or TKA at one year with an incidence of 3.1% *vs* 1.4% in controls. Higher infection rates after arthroplasty are also observed in other types of organ transplant patients[19,22]. Our study found an increased risk of sepsis in the LT group (1.2% *vs* 0.3%, $P < 0.001$), but no significant difference between prosthetic infections was observed (10.1% *vs* 12.1%, $P = 0.34$). Delayed infection, however, remains a known risk.

The risk of bleeding tendency remains a paramount consideration with THA and TKA after LT. Hepatic reserve is a major concern, as a decrease in liver functions can lead to a decrease in platelets and clotting factors, and an increased risk of bleeding. Oya *et al*[16] study reported an increased incidence of intraoperative blood loss in a small cohort of 7 patients (303.6 mL *vs* 163.4 mL, $P < 0.01$). A few studies have also reported increased blood transfusion rates in the LT group[13,19,20,22]. This study reported no significant difference in GI bleeding between the two groups (4.7% *vs* 5.9%, $P = 0.47$). Nevertheless, careful assessment and evaluation of the bleeding profile should be performed in this population before considering THA or TKA.

In summary, LT patients appear to have longer hospital stays compared to nontransplant recipient patients (17.1% *vs* 8.4%, $P < 0.001$). This is consistent with the study of Aminata *et al*[13], which found a significant difference between the LOS in 33 LT who underwent THA compared to non-transplant patients (16 d *vs* 10 d).

Strengths of this study include an adequate sample size to report readmission rates, predictors of readmission, short-term mortality risk, and complication rates statistically and accurately in the LT cohort. To the authors' knowledge, this is the first study to examine the 90-d readmission rates in LT *vs* a control cohort for patients after THA or TKA. The coding and size of the database allowed comparison between the LT cohort and a large control cohort. This also enabled multiple logistic regression analysis to analyze predictors of readmissions.

This study is not free from limitations. Surgical variables unique to transplantation were not available, such as the regimen, dose and duration of immunosuppression, and the type of transplant (related donor). Also, the indication of joint replacement is not available. Another limitation is unavailability of the temporal relationship between the timing of LT and joint replacement in addition to degree of immunosuppression and performance status of patients and laboratory results.

Like any database query using ICD-10 codes, the quality of the data depends on the accurate coding at the time of the patient encounter. Although this data was collected by the United States NRD, this could encourage other countries with national registries to perform a similar analysis to see if these results can be generalized outside the United States. Finally, patient satisfaction, hip and knee outcome scores, and functional measurements were not included in this database.

CONCLUSION

In conclusion, THA or TKA after LT is not associated with measurably increased mortality but has an increased risk of 90-d readmission. The most prominent risk factors for readmissions are CHF and CKD. While the LT cohort showed an increased risk of AKI and sepsis, there was no increased risk of gastrointestinal bleeding and prosthesis infection. Careful patient selection and medical optimization can reduce readmission rates, risk of mortality, and postoperative complic-

ations in LT patients undergoing THA or TKA. Hopefully the results of this study will provide orthopedic surgeons with accurate readmission profiles to appropriately counsel their patients about the inherent readmission risks after THA and TKA, in LT patients.

ARTICLE HIGHLIGHTS

Research background

Solid organ transplants are rising with recipients having longer life span. This puts them at risk of needing joint replacement surgery during their life time. The outcomes of these surgeries are understudied which raises the need for studies to evaluate benefits and risks in this cohort.

Research motivation

The question is whether patients with liver transplant (LT) are at increased risk of developing complication or have a higher mortality when needing hip or knee replacement surgery.

Research objectives

The main objective is to prove the LT patients are not at increased risk of complications when needing hip or knee replacement surgery which will allow these patients to get this surgery when needed. Also, this study aims to identify factors associated with increased morbidity which can help modify these factors.

Research methods

Patients were selected from the Healthcare Cost and Utilization Project databases (HCUP). The HCUP databases are sponsored by the Agency for Healthcare Research and Quality. The International Classification of Diseases Code, 10th Revision Clinical Modification was used to identify the patients.

Research results

Patients with a history of LT undergoing knee or hip replacement have longer hospital stay, increase morbidity but no increase mortality as compared to patient with no history of LT.

Research conclusions

The results show that hip and knee replacement are safe procedures in patients with LT.

Research perspectives

More research is needed in identifying risk scores to stratify LT patients as either high or low risk for joint replacement surgery.

FOOTNOTES

Author contributions: Ahmed M contributed to the conception and literature review of the manuscript; Ahmed M, Abumoawad A, and Elsafy H designed this study; Ahmed M and Jaber F drafted the manuscript; Abumoawad A collected the data; Jaber F, Al Momani L, Likhitsup A, and Helzberg JH involved in the critical reviewing of the manuscript; Elsafy H contributed to the analytic plan; Helzberg JH supervised and edited the manuscript.

Institutional review board statement: This study is performed based on the Healthcare Cost and Utilization Project databases. The HIPAA Privacy Rule sets national standards for patient rights with respect to health information. This rule protects individually identifiable health information by establishing conditions for its use and disclosure by covered entities.

Informed consent statement: This study is performed based on the Healthcare Cost and Utilization Project databases. The HIPAA Privacy Rule sets national standards for patient rights with respect to health information. This rule protects individually identifiable health information by establishing conditions for its use and disclosure by covered entities.

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ORIGINAL ARTICLE

Retrospective Study

Time of surgery and surgeon level in supracondylar humerus fractures in pediatric patients: A retrospective study

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Abstract

BACKGROUND

Supracondylar humerus fractures account for more than 60% of all elbow fractures and about 1/5 of all pediatric fractures. Unfortunately, these fractures can be associated with risk of complications including neurovascular injuries, malunions and limb deformities. Controversy exists regarding the effect of time of surgical intervention and/or level of surgeon performing the surgery on outcome of these fractures.

AIM

To determine whether time of surgical intervention and/or surgeon level influence the outcomes of surgically managed pediatric supracondylar humerus fractures.

METHODS

We retrospectively studied 155 pediatric patients presenting with a supracondylar humerus fracture in a level 1 trauma center from January 2006 to December 2019. The data extracted included demographic data, fracture characteristics, surgical data, and follow-up outcomes. The collected data was analyzed and *P* values of < 0.05 were considered statistically significant.

RESULTS

Of the cohort, 11% of patients had documented post-operative complications, of which the majority occurred in surgeries performed after day time working hours and in fractures requiring open reduction. While the lowest complication rate was

found in surgeries performed by pediatric orthopaedic surgeons, this did not reach statistical significance.

CONCLUSION
In pediatric patients undergoing surgery for supracondylar fractures, we found a higher complication rate when surgeries were not performed during working hours. Surgeon level and training had no significant effect on the risk of post-operative complications.

Key Words: Supracondylar humerus; Fracture; Time of surgery; Level; Complications

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Core Tip: In our pediatric cohort of surgically treated supracondylar humerus fractures we found a higher complication rate when surgeries were not performed during working hours. Surprisingly, surgeon level and training had no significant effect on the risk of post-operative complications.

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INTRODUCTION

Supracondylar humeral fractures (SCHF) account for 16% of all paediatric fractures and are commonly sustained by children younger than eight years of age[1-4]. These injuries commonly occur after a fall on an outstretched hand irrespective of forearm position[5-7]. The majority of these fractures require closed reduction and pinning, while open reduction is reserved for some complex patterns, delayed presentation or when closed reduction fails[8-10]. When compared to closed reduction and fixation, open reduction carries higher risk of complications, especially infection and loss of elbow range of motion[8,11-13].

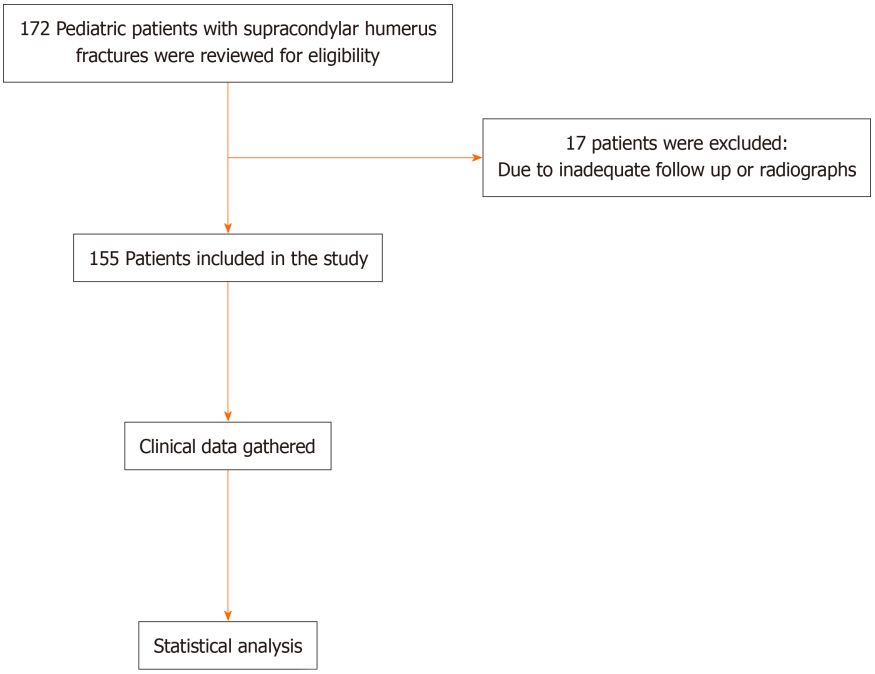
Timing of surgical intervention for these injuries is an area of controversy, as proponents for emergent intervention prefer it before any surgical site swelling occurs to minimize complications including nerve injury and compartment syndrome. In addition, it is believed that early surgical management can improve the success of closed reduction in these patient[12]. Surgeons who prefer a more delayed but urgent approach believe that operating on these fractures with an experienced team and during the daytime hours will lead to a quicker and more efficient surgical experience and decrease the associated post-operative complications[14,15].

The purpose of our study was to explore outcomes of surgical management of SCHF in pediatric patients and to assess if timing of surgical intervention and/or surgeon level would influence the outcomes of these patients post-operatively.

MATERIALS AND METHODS

This is a retrospective cohort study conducted in a level 1 trauma center from January 2006 to December 2019. After ethical approval was obtained from the institutional review board in our institute (IRB-UGS-2019-01-333), all pediatric patients 1 to 14 years old who sustained a SCHF and were treated surgically with a follow up period of at least 24 mo were included. Exclusion criteria were patients who were lost to follow up, had incomplete data points in their charts or had inadequate radiographs. In addition, Gartland type I fractures were excluded as these all were managed non-surgically in our institution.

All surgeries were performed by pediatric orthopaedic trained consultants, board certified orthopaedic consultants, fellows, or residents (with consultant supervision). Cases were booked in the dedicated emergency room by the admitting consultant and surgery is performed according to urgency level decided by the admitting consultant. Cases admitted after day time working hours by non-pediatric orthopaedic consultants are repatriated to a pediatric orthopaedic consultant the next morning if not done. Operative fixation was performed under general anaesthesia, with the patients in supine position. The operative extremity was prepped and draped in standard fashion and pre-operative weight appropriate prophylactic antibiotics were administered. A trial of closed reduction was performed and if adequate percutaneous fixation with k-wires was performed (configuration and number were left to surgeon discretion). If closed reduction was unsuccessful, an open reduction was performed. After fixation, a sterile dressing was applied to the pin sites and an above elbow back-slap was applied in neutral position. Patients were followed up in clinic at 2 wk post-operatively, then at the 6-week post-operative mark where pins were removed, and patients were allowed to start range of motion of the elbow. Patients were then seen at 3-, 6- and 12-mo post-surgery.



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Figure 1 Patient flowchart.

Data was extracted from the hospital electronic medical records, which included patient demographics data (age and gender), in addition to fracture characteristics and outcome variables. The collected variables included Gartland classification, time of surgery (during working hours "08:00-15:00" *vs* after day time working hours "15:00-8:00"), surgeon level (trainees "fellows or residents under supervision", non-pediatric orthopedic surgeons, and pediatric orthopedic surgeons), nerve or vessel injury (both pre- and post-operative), associated complications (including compartment syndrome and pin site infection) and fixation construct. Post-operative radiographic alignment was assessed on plain antero-posterior and lateral elbow radiographs. Inadequate reduction was defined according to Flynn's criteria (Baumann angle < 10°, displacement > 4 mm and anterior humeral line not bisecting the capitellum)[16].

A power analysis was performed with data from Saarinen *et al*[17], using a power of 80% and $\alpha = 0.05$, we estimated that we would require a sample size of 59 patients. Data was analyzed using Statistical Package for Social Sciences version 27 (IBM Corp, 2017). Categorical variables were described as frequencies and percentages, while continuous variables were described as mean and standard deviation. Bivariate analysis was tested using Chi-square test and ANOVA were applicable, with a *P* value of less than 0.05 considered as significant. Odds ratios with 95% confidence intervals were calculated to examine the association between the outcome variables and patient or fracture factors.

RESULTS

A total of 172 patients were reviewed and 155 were included in the study with a mean age of 5.36 years old (range 1-13 years old) (Figure 1). More than half of the patients were males 105 (67.7%). Of the patients included in the cohort, 2.6% had a documented nerve injury pre-operatively (half of which were managed during working hours), these injuries included two cases of median and two cases of radial nerve palsies. An absent radial pulse was found in 9% of patients (half of which were also managed during working hours), all patients regained pulses after manual reduction during the operative procedure (Table 1). More than half of patients (56.1%) were managed during working hours, while 43.9% were managed after day time working hours. The majority of fractures were managed by closed reduction and k-wire fixation (84.5%) and parallel K-wires were the most applied construct (48.4%) (Table 1).

Twenty-four cases (15.5%) required an open reduction, 3 of which had an absent pulse pre-operatively which was regained after fracture reduction. More than half of the open reduction cases were performed by trainees with consultant supervision (58.3%), while 20.8% were performed by pediatric orthopaedic surgeons and 20.8% performed by non-pediatric orthopaedic surgeons.

Of the cohort, 17 patients (11%) had documented post-operative complications. These complications included four cases of nerve palsy post-operatively, three of which were fixed with two lateral and one medial k-wires (two had a median nerve injury and one ulnar nerve injury) and one fixed with two lateral parallel k-wires (sustained a median nerve injury). The remaining complications were 12 cases of unacceptable angular deformity post-fixation and one case of bony spur requiring operative management. Patients who were managed after day time working hours were associated with more complications when compared with daytime surgeries (5.7% *vs* 17.6%, *P* value < 0.05). Patients who had their surgeries done after day time working hours were nearly at a 3 times higher risk of developing complications (OR = 2.8, *P*

Table 1 Demographic data of supracondylar fracture cohort

Variables, *n* (%)		
Time of surgery	During working hours	87 (56.1)
	After working hours	68 (43.9)
Surgeon level	Pediatric orthopedic consultant	44 (28.4)
	Non-pediatric orthopedic consultant	38 (24.5)
	Trainee	73 (47.1)
Gender	Male	105 (67.7)
	Female	50 (32.3)
Mechanism	Fall on outstretched hand	112 (72.3)
	Fall on flexed elbow	17 (11)
	Direct	15 (9.7)
	Motor vehicle accident	8 (5.2)
	Others	3 (1.9)
Pre-operative nerve injury	Yes	4 (2.6)
	No	151 (97.4)
Pulse	Intact	141 (91)
	Absent	14 (9)
Classification	Gartland type 2	32 (20.6)
	Gartland type 3	115 (74.2)
	Flexion type	8 (5.2)
Procedure	Open reduction	24 (15.5)
	Close reduction	131 (84.5)
K-wire arrangement	Parallel	75 (48.4)
	Medial & lateral	35 (22.6)
	Two lateral & one medial	34 (21.9)
	Others	11 (7.1)

value < 0.05) when compared to surgeries done during the daytime.

In addition, patient who required an open reduction had a higher rate of complications (33.3%) when compared to closed reduction (6.9%, *P* value < 0.001) (Table 2). Complications recorded with open reduction were 5 cases of angular deformity, one case of ulnar nerve palsy and one case of boney spur. The odds of a complication occurring was more than 6 times greater with an open reduction when compared to a closed reduction (OR = 6.8, *P* value < 0.005). We found no difference in rate of complication between Gartland type 2, type 3 and flexion type SCHFs.

Interestingly, although the lowest rate of complications was in surgeries performed by pediatric orthopaedic surgeons, this was not statistically significant (Table 2). There was no significant difference in Gartland classification, K-wire arrangement, pre-operative nerve injury and absent pulse between cases done by different levels of surgeons. Concerning timing of surgery and the surgeon performing the surgery, the majority (57.4%) of after day time working hours surgeries were performed by trainees, while only 25% were performed by non-pediatric orthopaedic surgeons and 17.6% by pediatric orthopaedic surgeons (*P* value < 0.05).

We also assessed the effect of surgeon level on complication rate in surgeries performed during working hours and surgeries performed after day time working hours, separately, and found no statistically significant difference.

DISCUSSION

The aim of this study was to investigate and analyze factors that could have an influence on outcomes of SCHF in pediatric patients, including time of surgery and surgeon level. In our cohort, we found that majority of complications occurred in cases performed after day time working hours, this may be attributed to that more severe injuries or cases with associated neurovascular compromise may be taken more urgently during the night. Aydoğmuş *et al*[18] reported

Table 2 Percentages of complications by variable and *P* value

Variables		Complication, *n* (%), *n* = 155		
		Yes, *n* = 16 (10.3)	No, *n* = 139 (89.7)	*P* value
Time of surgery	During working hours	5 (5.7)	82 (94.3)	**0.019**
	After working hours	12 (17.6)	56 (82.4)	
Surgeon level	Pediatric orthopaedic consultant	4 (9.1)	40 (90.9)	0.841
	Non-pediatric orthopaedic consultant	5 (13.2)	33 (86.8)	
	Trainee	8 (11)	65 (89)	
Gender	Male	10 (9.5)	95 (90.5)	0.404
	Female	7 (14)	43 (86)	
Classification	Gartland type 2	2 (6.3)	30 (93.7)	0.308
	Gartland type 3	13 (11.3)	102 (88.7)	
	Flexion type	2 (25)	6 (75)	
Procedure	Open reduction	8 (33.3)	16 (66.7)	**0.001**
	Close reduction	9 (6.9)	122 (93.1)	
K-wire arrangement	Parallel	6 (8)	69 (92)	0.154
	Medial & lateral	4 (11.4)	31 (88.6)	
	Two lateral & one medial	7 (20.6)	27 (79.4)	
	Others	0 (0)	11 (100)	

inferior fixation of 91 pediatric patients with operatively managed SCHF during after-hours when compared to cases performed during the daytime. In their cohort, they found no difference operative time, requirement of open reduction nor patient outcomes. When comparing early (< 12 h) and delayed (> 12 h) surgical fixation of pediatric SCHF, Suganuma *et al*[19] and Gupta *et al*[20] found no difference in rate of open reduction, post-operative complications nor surgical time between the two groups. In addition, Mehlman *et al*[15] found no difference in rate of open reduction, pin tract infection nor iatrogenic nerve injury between pediatric SCHF performed within 8 h of injury and more than 8 h of injury. Multiple other studies explored differences in outcomes and complication rates when surgery is done early or in a delayed fashion for SCHF, with the majority finding no statistically significant differences (Table 3).

Considering the higher complication rate in after day time working hours surgery and the lack of increased risk of adverse events in delayed fixation of SCHF, it seems clear that unless the extremity is pulseless with lack of perfusion, the fracture is open or there are signs of compartment syndrome, SCHF in pediatric patients should preferably be done during a reasonable time of day and not late after day time working hours.

While the majority of the complications in our cohort were in the surgeries that were conducted by trainees and non-pediatric orthopaedic surgeons, this was not statistically significant. When exploring the literature, we find that this is an area of controversy, as several studies have shown that the level and training of the surgeon has a significant effect on both outcome and complication rate of pediatric SCHF (Table 4). In addition, studies have also shown that when the procedure is supervised by a pediatric orthopedic surgeon, the outcomes are excellent with very low complication and revision rates irrespective of the level of the surgeon performing the surgery[21,22]. On the other hand, several studies have shown no difference in complication rate and risk of malreduction when the surgery is performed by a trained orthopaedic surgeon without pediatric fellowship training[17,23,24].

Limitations of the study include that it is a retrospective cohort, but we believe that we were successful in data collection from the patients' medical records with good accuracy. Another possible limitation is the small sample size, but we believe that our study is adequately powered based on the sample size analysis using previous published studies. In addition, the number of complications in our study was relatively low, but the proportion of complications was similar in previously published studies.

CONCLUSION

In pediatric patients undergoing surgery for SCHF, we found a higher complication rate when surgeries were not performed during working hours, or when an open reduction is required. Although pediatric orthopaedic surgeons had the lowest rate of complications, this difference did not reach statistical significance. We believe the data presented in this study can help in reaching a better-informed decision about the timing of surgery for pediatric patients with SCHF.

Table 3 Previous studies assessing effect of time of surgery on outcomes of pediatric supracondylar humeral fractures

Ref.	Sample size	Groups	Results
Suganuma *et al* [19], 2020	120 Gartland type II and III SCHF	Surgeries within 12 h of injury and > 12 h	No difference in: Operative time; Early complications; Post-operative radiographic parameters
Aydoğmuş *et al* [18], 2017	91 Gartland type III SCHF	Daytime *vs* after hours surgery	Poor fixation rate in after hour surgery; No difference in operative time or residual deformity
Schmid *et al*[25], 2015	343 Gartland type II and III SCHF	Surgeries within 6 h, 6-12 h, 12-24 h and > 24 h from injury	No difference in: Outcome; Complications; Requiring open reduction
Mayne *et al*[26], 2014	115 Gartland type II and III SCHF	Surgeries within 12 h of injury and > 12 h	No difference in: Infection rate; Iatrogenic nerve injury; Requiring open reduction
Larson *et al*[27], 2014	399 Gartland type II SCHF	Surgeries within 24 h of injury and > 24 h	No difference in complication rate
Yildirim *et al*[28], 2009	190 Gartland type III SCHF	Time from injury to surgery	4 fold increase in requiring open reduction for each 5 hour delay
Walmsley *et al*[29], 2006	171 Gartland type III SCHF	Surgeries within 8 h of injury and > 8 h	No difference in complication rate; Higher risk of requiring open reduction in > 8 h group
Sibinski *et al*[30], 2006	77 Gartland type III SCHF	Surgeries within 12 h of injury and > 12 h	No difference in: Operative time; Outcome; Risk of open reduction
Gupta *et al*[20], 2004	150 operatively treated SCHF	Surgeries within 12 h of injury and > 12 h	No difference in: Pin tract infection; Iatrogenic nerve injury
Mehlman *et al*[15], 2001	198 operatively treated SCHF	Surgeries within 8 h of injury and > 8 h	No difference in: Pin tract infection; Iatrogenic nerve injury
Iyengar *et al*[31], 1999	58 Gartland type III SCHF	Surgeries within 8 h of injury and > 8 h	No difference in: Open reduction rate; Clinical outcomes

SCHF: Supracondylar humeral fractures.

Table 4 Previous studies assessing effect of surgeon level on outcomes of pediatric supracondylar humeral fractures

Ref.	Sample size	Groups	Results
Fisher *et al*[23], 2021	231 patients who underwent CRPP for SCHF	Pediatric orthopaedic fellowship trained *vs* other orthopaedic surgeons	Shorter operative and fluoroscopy time; No difference in complications
Osateerakun *et al* [32], 2019	87 Gartland type II and III SCHF	Pediatric orthopaedic fellowship trained *vs* other orthopaedic surgeons	Higher risk of complications in Gartland type III when not performed by pediatric orthopaedic surgeon; Overall complication rate and acceptable alignment were similar
Saarinen *et al* [17], 2019	108 operatively treated SCHF	Residents, pediatric surgeons and orthopaedic surgeons	Orthopaedic surgeons had the least complications and inadequate reductions; Residents had less complications and inadequate reductions when compared to pediatric surgeons
Pesenti *et al*[33], 2018	236 Gartland type III SCHF	Surgeons with < 1 yr *vs* > 1 yr experience	Less experienced had longer operative time; No difference in complication and malalignment rate
Tuomilehto *et al* [34], 2018	210 operatively treated SCHF	Consultants *vs* registrars	Higher complications and poorer outcomes in surgeries done by registrars
Liu *et al*[22], 2011	654 operatively treated SCHF	Fellows progression through fellowship training	No difference in complications and malunions throughout the fellowship year; Spike of malreductions at case 7 which improves at case 15
Padman *et al*[21], 2010	71 Gartland type II and III SCHF	Consultants *vs* trainees	Poorer outcome and more complications in surgeries performed by trainees without consultant supervision
Farley *et al*[24], 2008	444 operatively treated SCHF	Pediatric orthopaedic surgeon *vs* non-pediatric orthopaedic surgeon	No difference in complication rate and outcomes

CRPP: Closed reduction percutaneous pinning; SCHF: Supracondylar humeral fractures.

ARTICLE HIGHLIGHTS

Research background

Pediatric supracondylar humerus fractures can be associated with risk of complications including neurovascular injuries, malunions and limb deformities. Surgical timing and level of surgeon performing the surgery may have an effect on outcome of these fractures.

Research motivation

Explore the effect of time of surgery and level of surgeon on pediatric supracondylar humerus fractures.

Research objectives

The objective of this study was to determine whether time of surgical intervention and/or surgeon level influence the outcomes of surgically managed pediatric supracondylar humerus fractures.

Research methods

We retrospectively studied 155 pediatric patients presenting with a supracondylar humerus fracture in a level 1 trauma center from January 2006 to December 2019. The data extracted included demographic data, fracture characteristics, surgical data, and follow-up outcomes. The collected data was analyzed and P values of < 0.05 were considered statistically significant.

Research results

Of the cohort, 11% patients had documented post-operative complications, of which the majority occurred in surgeries performed after day time working hours and in fractures requiring open reduction. While the lowest complication rate was found in surgeries performed by pediatric orthopaedic surgeons, this did not reach statistical significance.

Research conclusions

In pediatric patients undergoing surgery for supracondylar fractures, we found a higher complication rate when surgeries were not performed during working hours. Surgeon level and training had no significant effect on the risk of post-operative complications.

Research perspectives

We believe the data presented in this study can help in reaching a better-informed decision about the timing of surgery for pediatric patients with supracondylar humeral fractures.

FOOTNOTES

Author contributions: Albrahim IA, Alomran AK, and Bubshait DA contributed to concept; Albrahim I, Alomran AK, Bubshait DA, Tawfeeq Y, Alsayigh J, Abusultan A, Altalib A, Alzaid ZA, Alzahrani MM contributed to design; Albrahim I, Alomran AK, and Bubshait DA, Tawfeeq Y, Alumran A, Alsayigh J, Abusultan A, Altalib A, Alzaid ZA, and Alsubaie SS contributed to study execution; Albrahim I, Alomran AK, and Bubshait DA, Tawfeeq Y, Alumran A, Altalib A, Alzaid ZA, Alsubaie SS, Alzahrani MM contributed to manuscript writing and review; Alumran A contributed to statistical analysis; Alsubaie SS contributed to statistical analysis.

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ORIGINAL ARTICLE

Basic Study

Automated decision support for Hallux Valgus treatment options using anteroposterior foot radiographs

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Abstract

BACKGROUND

Assessment of the potential utility of deep learning with subsequent image analysis to automate the measurement of hallux valgus and intermetatarsal angles from radiographs to serve as a preoperative aid in establishing hallux valgus severity for clinical decision-making.

AIM

To investigate the accuracy of automated measurements of angles of hallux valgus from radiographs for further integration with the preoperative planning process.

METHODS

The data comprises 265 consecutive digital anteroposterior weightbearing foot radiographs. 181 radiographs were utilized for training (161) and validating (20) a U-Net neural network to achieve a mean Sørensen–Dice index > 97% on bone segmentation. 84 test radiographs were used for manual (computer assisted) and automated measurements of hallux valgus severity determined by hallux valgus (HVA) and intermetatarsal angles (IMA). The reliability of manual and computer-based measurements was calculated using the interclass correlation coefficient (ICC) and standard error of measurement (SEM). Inter- and intraobserver reliability coefficients were also compared. An operative treatment recommendation was then applied to compare results between automated and manual angle measurements.

RESULTS

Very high reliability was achieved for HVA and IMA between the manual measurements of three independent clinicians. For HVA, the ICC between manual measurements was 0.96-0.99. For IMA, ICC was 0.78-0.95. Comparing manual against automated computer measurement, the reliability was high as well. For HVA, absolute agreement ICC and consistency ICC were 0.97, and SEM was 0.32. For IMA, absolute agreement ICC was 0.75, consistency ICC was 0.89, and SEM was 0.21. Additionally, a strong correlation (0.80) was observed between our approach and traditional clinical adjudication for preoperative planning of hallux valgus, according to an operative treatment algorithm proposed by EFORT.

CONCLUSION

The proposed automated, artificial intelligence assisted determination of hallux valgus angles based on deep learning holds great potential as an accurate and efficient tool, with comparable accuracy to manual measurements by expert clinicians. Our approach can be effectively implemented in clinical practice to determine the angles of hallux valgus from radiographs, classify the deformity severity, streamline preoperative decision-making prior to corrective surgery.

Key Words: Computer-aided diagnosis; Artificial intelligence in orthopedics; Automated preoperative decision support; Deep learning; Medical imaging

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Core Tip: This study presents an accurate method for automated assessment of angles of hallux valgus on high-resolution weight-bearing anteroposterior feet radiographs. Reference points are estimated according to the AOFAS standard on automatically segmented bones of the foot. The proposed method accurately calculates angles even in the case of significant toe deformity automating preoperative decision-making. Experimental results revealed high reliability of hallux valgus angle and intermetatarsal angle measurements between the proposed algorithm and medical doctors, achieving a correlation of almost 80%.

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INTRODUCTION

Hallux valgus (HV) is a foot deformity that affects a considerable percentage of the population[1,2]. It is a complex positional deformity of the first ray that leads to altered joint mechanics, dysfunction, and progressive pain. The technique of weightbearing dorsoplantar radiographs was standardized and determined in the AOFAS research committee report[3-6]. Orthopedic surgeons frequently use radiographic angles to make clinical decisions for patients with symptomatic HV[7-9]. Various radiographic measurements used in hallux valgus treatments were discussed[3,10]. The reliability of radiographic measurements in HV was also studied[11]. Through the use of WBCT scans, it has been demonstrated that up to 87% of hallux valgus cases exhibit metatarsal bone pronation, emphasizing the intricate multiplanar nature of this deformity. This metatarsal pronation explains the perceived metatarsal bone shape and the misalignment of the medial sesamoid bone in radiological studies, which has been recognized as a significant factor contributing to recurrence following treatment. As a result, distal metatarsal articular angle has proved unreliable, demonstrating a poor interobserver agreement[12,13]. Further research is needed to develop effective approaches for addressing the rotational deformity in individuals with HV[2,14,15].

Key angles utilized in clinical practice to establish the severity of HV are the hallux valgus angle (HVA) and the intermetatarsal angle (IMA)[8,12,13,16-18]. Intra- and inter-observer agreement for radiographic measurement of HVA/IMA is reportedly good using various digital techniques[11,17,19]. The HVA is between the longitudinal axes of the first metatarsal and the proximal phalanx (PP). The IMA is between the longitudinal axes of the first and second metatarsal bones (Figure 1). Many methods were used to facilitate and accelerate manual or computer-assisted determination of the longitudinal axes of the first, second metatarsal (1,2MT) and the hallucial PP bones, *e.g.*, establishing reference points, to make measurements more repeatable[7,20].

Traditionally, these angles were manually measured on hard-copy radiographs. Nowadays, computer-assisted measurement methods are being developed, that reduce the measurement error of HVA[21-23]. New possibilities for radiographic images analysis have emerged thanks to recent advances in clinical applications of deep learning[24-29]. This study is among the first forays into automated HVA/IMA measurements from radiographs.

Kwolek *et al*[30] introduced an algorithm for the automatic recognition of radiographs of the hallux valgus using U-Net neural network with promising outcomes. A study on hallux valgus measurement with a deep convolutional neural

network based on landmark detection has been discussed by Li *et al*[31]. In contrast to our approach based on the toe bones segmentation and reference points estimation, their method is based on a small number of landmark points. Moreover, their database contains mainly radiographs without hallux valgus (almost 50%) or with small deformation, *i.e.* only 5/340 (1.5%) radiographs have IMA > 16° (severe hallux valgus deformation).

In this study, we significantly expanded algorithms to automate HV assessment from foot radiographs[30]. The necessary bones (first, second metatarsal, and hallucial PP) were segmented and labelled by a U-Net to set reference points and calculate HVA/IMA automatically. Expert clinicians also determined these angles manually, with outcomes being compared later. Moreover, our algorithm was evaluated only on patients' radiographs who subsequently underwent hallux valgus surgery. Our dataset contains a considerable percentage of radiographs with severe forefoot deformations including toe overlap, severe pronation, and sesamoid dislocation. Our bone segmentation-based algorithm is sufficiently robust to handle even such challenging circumstances anatomy as toes overlapping.

Classification systems

Traditional classification methods rely upon weightbearing anteroposterior radiographs to determine the severity of HV based on the HVA, and IMA (Figure 1)[17]. More than 100 different operative techniques were described for the correction of HV[32-34]. The overall clinical picture together with the degree of deformity determine the surgical decisions made. A suitable intervention is selected by considering the overall clinical picture along with the degree of deformity, potential degenerative changes of the first metatarsophalangeal joint, size, and shape of the metatarsal, and joint congruency.

Our algorithm is based on operative treatment algorithm proposed by EFORT (Figure 2)[35]. A convolutional neural network was trained to segment bones, with subsequent image analysis to automatically estimate angles and recommend appropriate surgical decisions. Digital radiographs were managed using a picture archiving and communication system and the IMPAX software suite.

MATERIALS AND METHODS

Algorithm outline

The measurements of the HVA/IMA were performed automatically on bones segmented and labelled by the U-Net neural network (Figure 3)[36]. To achieve this, the U-Net was first trained using anteroposterior foot radiographs and corresponding images with manually segmented and labelled bones. By providing automatically segmented and labelled bones, the required reference points were likewise automatically measured and the HVA/IMAs ultimately calculated.

The U-Net was trained only on right feet radiographs to reduce the cost and time of model training. Radiographs with the left feet were mirrored and then incorporated into the database. At the angle measurement stage, the segmented images with the left feet were back-mirrored to perform the measurements on the feet in the original orientation.

Dataset

133 patients were randomly selected between 2014 and 2021. A total of 265 pre-operative (unilateral or bilateral) anteroposterior feet radiographs were sourced from the electronic database of the authors' institution (demographics in Table 1). Inclusion criteria were: available weight-bearing radiographs, sole indication: symptomatic hallux valgus. Exclusion criteria were: No available weight-bearing radiographs, prior osteotomies, radiographs with severe osteoarthritis and first metatarsophalangeal joint deformation, and/or severe, *e.g.*, rheumatoid forefoot deformations or Charcot diabetic foot, visible plates, and other artificial elements distorting the image of the bone. Radiographs were obtained using standard radiology equipment Eidos RF439 and Luminos DRF unit and digitally transmitted *via* a picture archiving and communication system.

The data was divided randomly into three subsets: training, validation, and testing (Figure 3B). Both the patient's right and left feet were included in these subsets. The training and validation subsets were used to train and validate the U-Net for bone segmentation, while the testing subset was used to evaluate the performance of the trained U-Net and automatically measure the HVA/IMA.

Training and validation subset

We initially applied a 71/29 percent random split between training and validating subsets to develop the U-Net. After achieving the Sørensen–Dice index (SDI) greater than the cutoff value, the final training set was established.

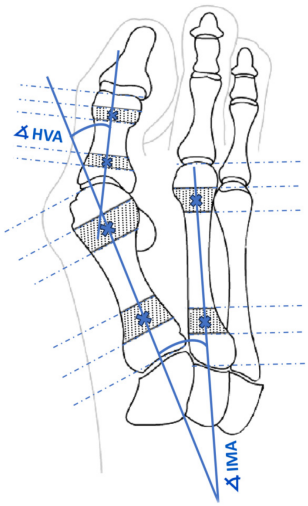
Testing subset

According to Zou *et al*[37], the minimum number of subjects (testing subset) to estimate the agreement of the measurements between the two methods is 80. Our testing subset consisted of 84 randomly selected anteroposterior foot radiographs. Apart from the input radiographs, the testing subset also contained manually segmented radiographs to evaluate the quality of bone segmentation by the U-Net network. We calculated the SDIs using radiographs with automatically and manually segmented bones. There were no duplicate patient radiographs between the training, validation, and testing subsets. The validation radiographs were used to select the best neural network model, and validate the performance of the selected network during its training. The HVA/IMA were estimated only on the testing radiographs.

Table 1 Demographics

	Age	Sex	Hallux valgus angle			Intermetatarsal angle		
			All feet	Right feet	Left feet	All feet	Right feet	Left feet
Number of subjects	133	133, 16M (12%)/117F (88%)	265	133	132	265	133	132
Number of measurements	-	-	243	120	123	212	105	107
Range	23-81 yr	-	4-68°	4-68°	10-61°	4-26°	4-26°	7-22°
Average	55.8 yr	-	31.2°	31.3°	31.1°	13.8°	14°	13.7°

M: Male; F: Female; -: Not applicable.



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Figure 1 Determination of angles of hallux valgus as described by AOFAS. HVA: Hallux valgus angle; IMA: Intermetatarsal angle.

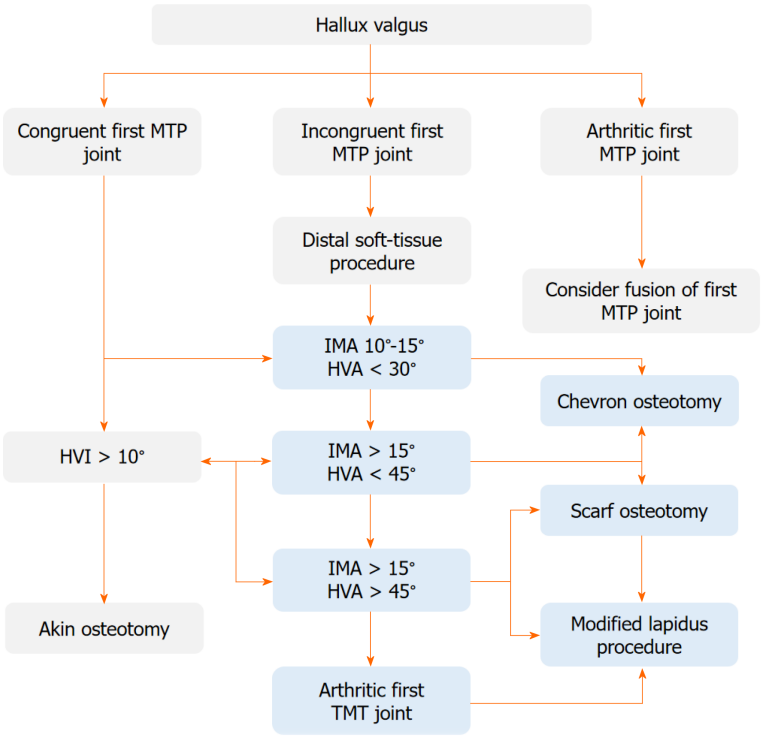
Anonymization and manual labelling

The input radiographs were anonymized (Figure 3A) and stored in .png image format with lossless compression. Radiographs were digitally anonymized with unique IDs. To train a U-Net network that would achieve high bone segmentation accuracy, bones were manually annotated on original high-resolution radiographs. Initially, seventy radiographs were manually segmented and labelled by the first author in Adobe Photoshop. The radiographs with labelled bones were randomly split into a set of 50 training and 20 validation images. Manual segmentation of bones on radiographs is a very time-consuming task with considerable effort necessary to properly separate the border of bone from surrounding soft tissue. Considering the current understanding of pronation and variable shape of the first metatarsal head in hallux valgus deformation described by Wagner *et al*[14], the first metatarsal head and the sesamoid bones were delineated carefully and precisely by a foot surgeon to achieve precise measurements of the HVA/IMA[11]. The complex structure of bones in anteroposterior feet radiographs makes automated segmentation (delineation) particularly difficult[38]. Radiographs are contaminated by noise, artifacts, insufficient contrast, resolution, and/or intensity. These factors made preparing the dataset and developing the algorithm particularly challenging.

Various bone segmentation strategies were considered during algorithm development. We started with a binary segmentation of bones with bone extraction[30]. However, this approach produced clinically unreliable results in cases of cross-over toe with higher HVA. To overcome these difficulties, and simplify the algorithm to achieve robust automated separation of each required bone even in "difficult" radiographs, we established main regions on each foot radiograph *via* multi-class segmentation (Figure 3A). This approach allowed us to select and process just the three bones forming the HVA/IMA (1,2MT, and hallucial PP) and exclude all remaining structures and radiograph background. Considering that the region of interest on a given foot may have varying aspect ratios (height to width), some images were padded vertically with rows of black pixels to standardize the image size to 768 × 1024 pixels without changing the resolution (Figure 4).

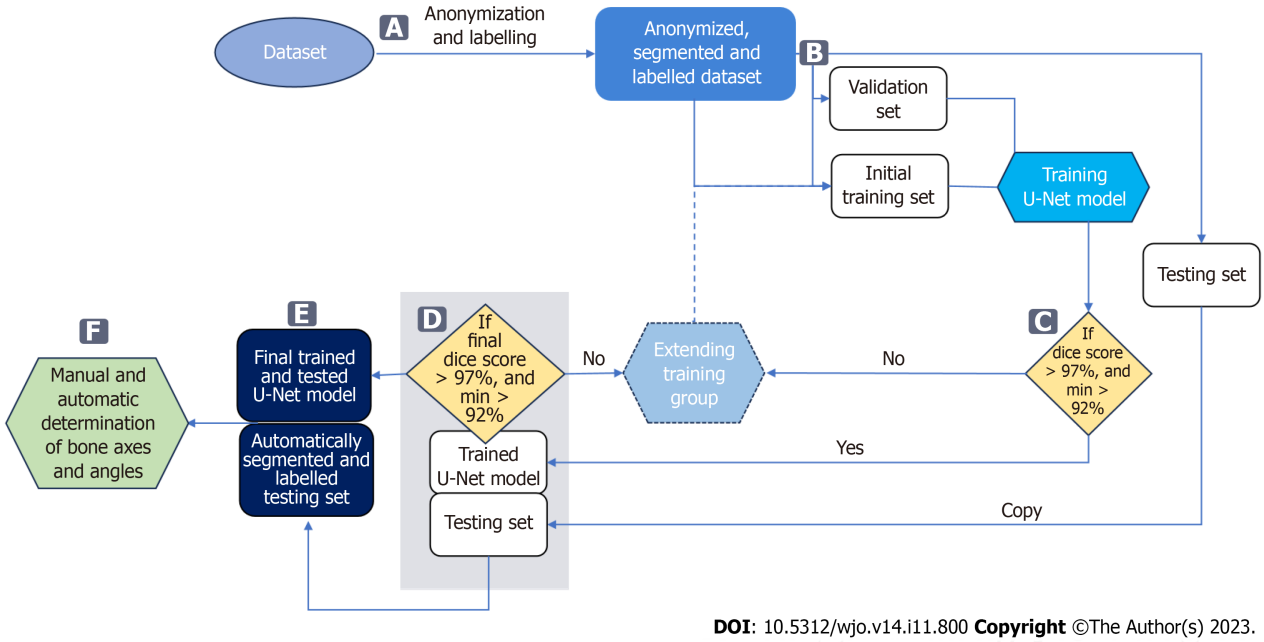
U-Net training and validation

Radiographs pre-processing: The radiographs were prepared as described above to training a U-Net neural network[36]. We designed a U-Net neural network for bone segmentation that operates on grey images sized 768 × 1024 px (Figure 4). In contrast to the U-Net proposed by Ronneberger *et al*[36] our network is symmetric one, *i.e.* the input image size is equal to output map size, it performs multi-class segmentation, and relies on the Dice loss and score for training and evaluation,



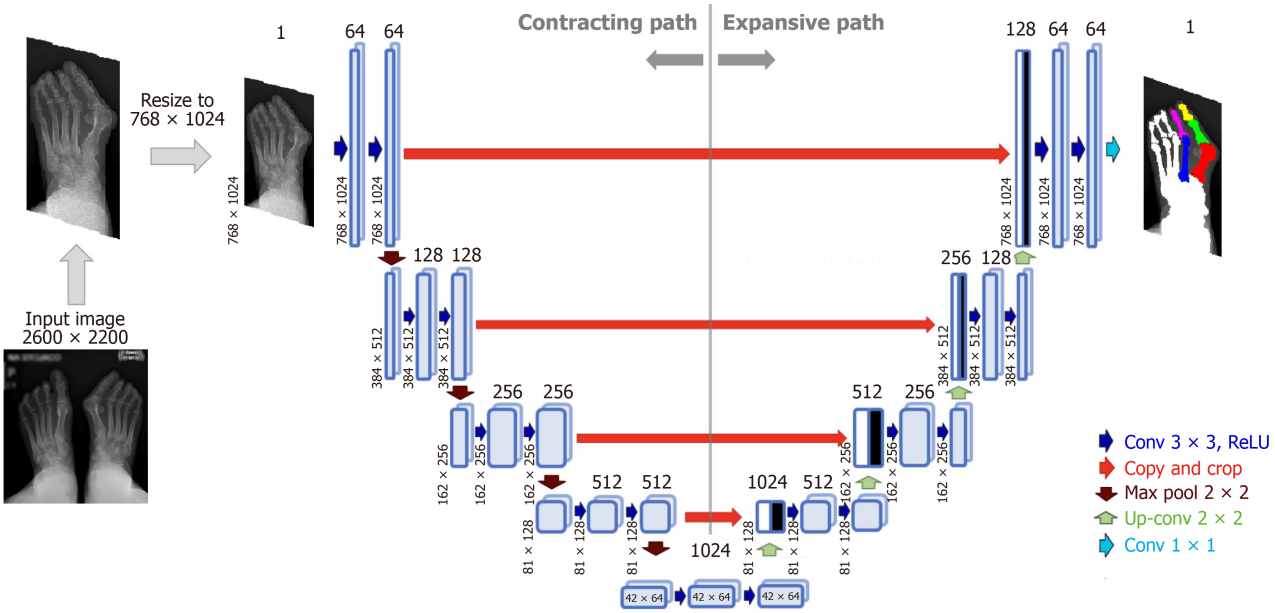
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Figure 2 Operative treatment algorithm of hallux valgus. D1 - decision for intermetatarsal angle (IMA) 10°-15° and hallux valgus angle (HVA) < 30°, D2 - decision for IMA > 15° and HVA < 45°, D3 - decision for IMA > 15° and HVA > 45°. HVA: Hallux valgus angle; HVI: Hallux valgus interphalangeus; IMA: Intermetatarsal angle; MTP: Metatarsophalangeal; TMT: Tarsometatarsal.



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Figure 3 Data flow in the proposed approach. A: Bones are manually segmented and labelled from anonymized input radiographs to perform multi-class segmentation using a U-Net neural network; B: Radiographs are then randomly assigned to three subsets: training, validation, and testing; C: The accuracy of bone segmentation in each training cycle of the U-Net is validated on a fixed validation subset consisting of 20 radiographs. The U-Net network is trained on a training subset initially consisting of 50 radiographs, which is increased by 10 each training cycle until achieving average Sørensen–Dice index (SDI) > 97% on the validation set; D: Once the network achieves an SDI > 0.97, calculated on the testing subset, the U-Net model completes. If SDI is not > 0.97, the training subset is extended and the U-Net is retrained; E: The final U-Net model is used to segment and label bones on all testing radiographs; F: These are used to automatically determine reference points and measure hallux valgus and intermetatarsal angles.



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Figure 4 Architecture of U-Net neural network for bone segmentation from radiographs. The network consists of an encoder (contracting path), which encodes an input image size of 768 × 1024 pixels to 42 × 64 × 1024 feature tensor at the bottleneck, and a decoder (expanding path) that decodes the feature tensor to the segmented image of the same size as the input image. The decoder follows the typical architecture of a convolutional network. Each block in the decoder consists of two 3 × 3 convolutions, each followed by a rectified linear unit (ReLU) and a 2 × 2 max pooling with stride 2 for down-sampling. Each down-sampling step of the encoder doubles the number of feature channels and decreases the image resolution by half. Every block in the decoder comprises upsampling the feature map followed by a 2 × 2 convolution that halves the number of feature channels - a concatenation with the correspondingly cropped feature map from the contracting path - and two 3 × 3 convolutions, each followed by a ReLU.

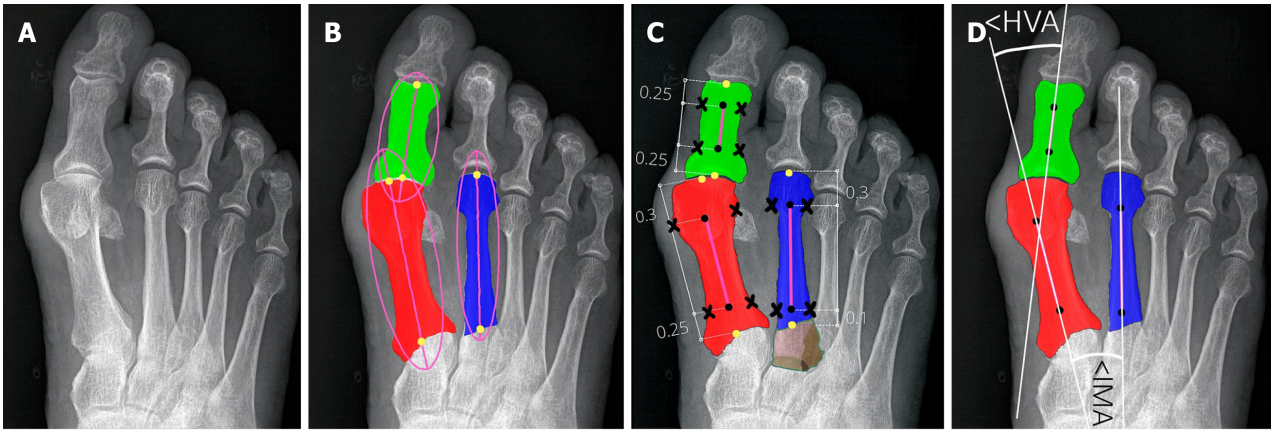
respectively. The accuracy of the bone segmentation was evaluated using SDI which is the most used metric in medical image segmentation[37,39]. We assumed that the threshold SDI should have a mean greater than 97%, with a minimum value greater than 92%. SDIs were determined only for the three bones required to estimate HVA/IMA. During U-Net training, the calculated SDI was used to check whether U-Net training should be stopped or continued on an extended training subset containing more images. After U-Net training was complete, the SDI was checked on the testing subset to verify whether the U-Net achieved the required generalizability. The initial training subset consisted of 50 anteroposterior foot radiographs with corresponding bone masks and labels. The initial training set was increased by 10 images after each training round until the threshold SDI was achieved on the validation subset (Figure 3C). The validation subset was fixed during training and used to compare the segmentation abilities of networks trained on incrementally larger training subsets. The threshold SDI was achieved on a training set of 150 radiographs with corresponding bone masks and labels. After adding an additional radiographs, the final training set consisting of 161 training images and 20 validation images (90% and 10%, respectively) was used to train the final U-Net. The dataset is available upon request.

Architecture and training U-Net: The neural network for bone segmentation follows the standard U-Net architecture established by Ronneberger *et al*[36]. Each U-Net encoder and decoder contains four layers (Figure 4). The validation SDI was calculated at the end of each epoch during the training of the U-Net, and the training was stopped when the SDI did not increase over 10 following epochs. This served as an early stop technique to avoid overfitting, where the value of early stop (patience) was set to 10. The U-Net was trained using Adam optimizer with Dice loss, learning rate (LR) set to 0.0001 (with reducing LR on plateau) and batch size equal to 8. The number of epochs was set to 80, and a callback was used to save the best U-Net model and its weights. The training data was augmented using mirroring, rotations, and contrast enhancement. Training of neural networks was performed on NVIDIA A100 GPU, whereas the testing was performed on the notebook's GPU (RTX2060).

Final validation of U-Net: Before measuring HVA/IMA, the trained U-Net was evaluated on the testing subset to assess its generalizability (Figure 3D). As the average SDI was larger than 97% on the testing subset with a minimal score larger than 92%, we used the trained U-Net to segment bones on all test radiographs (Figure 3E). In image post-processing, small holes in bones segmented by the U-Net were filled using morphological operations, and artifacts such as small blobs were deleted. Our algorithm first segmented and labeled bones that it then used to automate determining reference points and HVA/IMA measurements (Figure 3F, Figure 5). The programmer who trained the U-Net did not parti-cipate in manual measurements of HVA/IMA and did not see any results before statistical analysis.

Measurement of HVA and IMA

Automatic determination of reference points and angles: Using the anteroposterior feet radiographs, the U-Net segmented bones and labelled them with different colors (Figure 4). Using these labels our algorithm selected three bones



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Figure 5 Determining reference points of first and second metatarsals and hallucial proximal phalanx. A: Input radiograph; B: Three bones of interest: 1,2MT, and hallucial PP were approximated by ellipses to estimate bone axes, which were then used to determine bone endpoints; C: The elliptical axes were split into three parts with specific proportions to determine segment endpoints (marked by black dots) and reference points of the respective bone being established on a transverse line perpendicular to the longitudinal at a point equidistant from the outer border of the medial and lateral cortices (black crosses). Brown color show unsegmented (bone overlap) areas of the proximal epiphyseal of the second metatarsal bone; D: The central axes (white lines) were automatically determined through reference points (marked by black dots).

of interest: 1,2MT, and hallucial PP. HVA/IMA were automatically measured using reference points from these bones.

According to AOFAS (Figure 1) all reference points on the 1,2MT, and hallucial PP are the metaphyseal/diaphyseal points from which a guideline had to be determined to automate measurement of bone axes[18]. The final bone split ratios were selected following various combinations of bone split ratios to obtain the points closest to the diaphysis (Figure 5). For the 1MT, the reference points were located at 0.3 of the bone length proximal to the distal articular surface and at 0.25 of the bone length distal to the proximal articular surface. For the 2MT: 0.30 and 0.10, and for the hallucial proximal phalanx: 0.25 and 0.25, respectively.

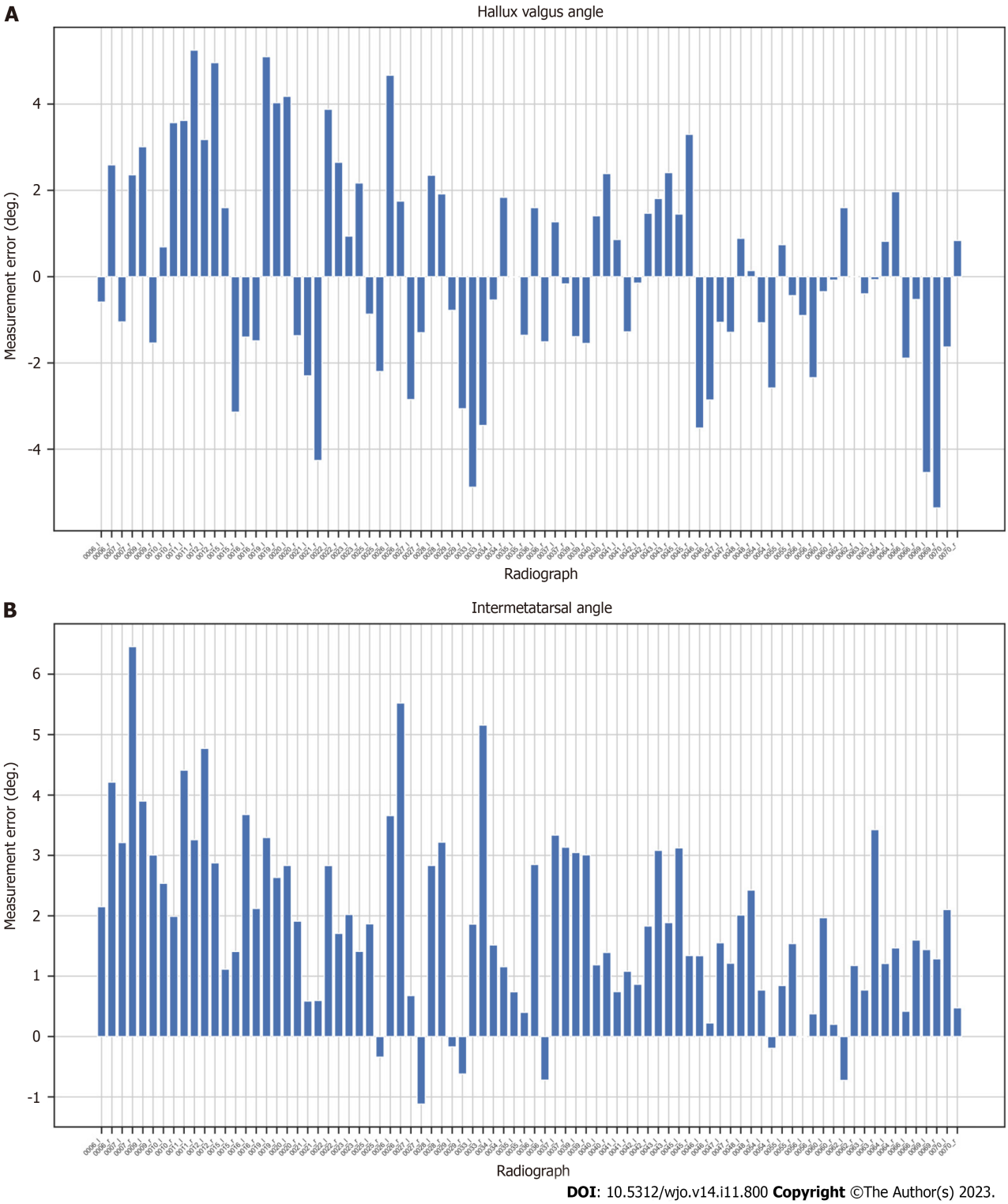
Statistical analysis

Eighty-four radiographs of patients were used to measure HVA/IMA both manually by clinicians (reference method) and automatically by our algorithm. The reliability of the measurements between these two approaches was calculated using ICC and the standard error for a single measurement (SEM). Manual measurements (HVA/IMA) were performed by: an orthopedic surgeon (O_A) with 7 years' experience and repeated at 2 mo in blinded test (O_{A1} and O_{A2}), an orthopedic surgeon (O_B) with 15 years of experience; and by musculoskeletal radiologist (R) with 15 years of experience. Interobserver and intraobserver reliability coefficients (ICC) were calculated. The observers were not aware of any clinical results. Assessment of the HVA/IMA was performed according to the guidelines of the AOFAS *ad hoc* Committee on Angular Measurements (Figure 1) and digital technique using Radiant/Carestream[7,18,40]. Our algorithm then classified the appropriate severity (Figure 2) and operative decisions were compared against the orthopedic surgeon (O_{A2}). All statistical calculations were performed using MedCalc.

RESULTS

We proposed a novel automated HVA/IMA measurement method using deep learning algorithms. To measure these angles, the 1,2MT, and hallucial PP bones were automatically segmented, with reference points then automatically assigned. We obtained high interobserver and intraobserver correlations between manual measurements of HVA and IMA, and great agreement between artificial intelligence (AI) (our algorithm) and clinician angle measurements (Table 2). We analyzed HVA and IMA measurement errors for each patient's radiograph finding (Figures 6 and 7). Standard Error of the Mean for HVA was 0.26 and 0.16 for IMA. The accuracy of angles measured by the U-Net is similar to that of orthopedic surgeons.

A decision system was developed and tested according to the EFORT operative treatment algorithm (Figure 2)[35]. Operative decisions were taken (D1- chevron, D2- chevron or scarf, D3- scarf or Lapidus) based on calculated angles. The AI decisions were compared to O_{A2} decisions for concordance. The agreement of clinician decisions was also compared. The ratio of same pre-operative surgical decisions among AI and O_{A2} was almost 0.80 (67/84), which was higher than the ratio among clinicians (Table 2). A key achievement of our algorithm is that it saves radiologist and orthopedic surgeon's time while providing a clinically actionable HVA/IMA measurement that supports preoperative planning.



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Figure 6 Measurement errors (in degrees) for AI (our algorithm) compared to orthopedic surgeon (O_{A2}) for each radiograph. A: Hallux valgus angle; B: Intermetatarsal angle.

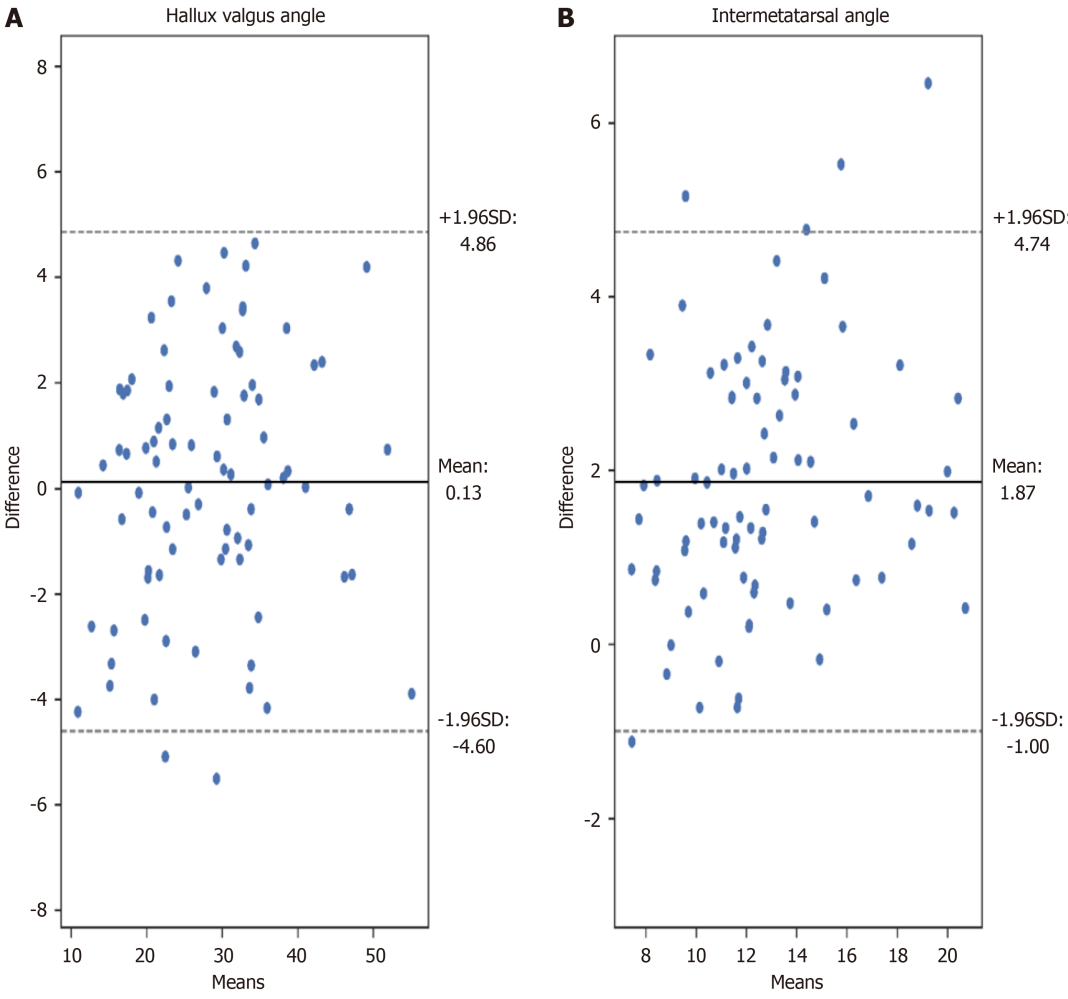
DISCUSSION

Some initial work on deep-learning radiographic and WBCT foot analysis was recently published[41-44]. While WBCT is arguably the future of hallux valgus preoperative qualifications, X-ray remains the standard as it is cheap, and widely available for symptomatic HV[38,45]. This work is in line with emerging research and substantially improves upon our previous algorithm. As demonstrated experimentally, the proposed approach can estimate HV angles on high-resolution radiographs and classify the severity of HV as a preoperative decision-making tool. Moreover, this work may expedite novel developments in forefoot surgery. This will provide a reliable opportunity to compare preoperative and posto-perative measurements and analyze the effects of surgical correction to produce better HV treatment standards.

Table 2 Correlation of hallux valgus angle, intermetatarsal angle, and pre-operative surgical decisions between clinicians, and against artificial intelligence

	Hallux valgus angle correlation (ICC)	Intermetatarsal angle correlation (ICC)	Pre-operative surgical decisions correlation
R-O_B	0.96	0.79	0.73 (61/84)
R-O_{A1}	0.96	0.81	0.62 (52/84)
R-O_{A2}	0.96	0.78	0.73 (61/84)
O_B-O_{A1}	0.96	0.91	0.75 (63/84)
O_B-O_{A2}	0.99	0.95	0.88 (74/84)
O_{A1}-O_{A2}	0.98	0.91	0.82 (69/84)
AI-O_{A2}	0.97 (AA-ICC)	0.89 (AA-ICC)	0.80 (67/84)
	0.97 (C-ICC)	0.75 (C-ICC)	

AI: Artificial intelligence; AA-ICC: Absolute agreement interclass correlation coefficient; C-ICC: Consistency interclass correlation coefficient; ICC: Interclass correlation coefficient; O_{A1}, O_{A2}, O_B: Orthopedic surgeons; R: Musculoskeletal radiologist.



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Figure 7 Bland-Altman plots illustrating the differences between measurements achieved by our algorithm (AI) and orthopedic surgeon (O_{A2}). A: Hallux valgus angle measurements; B: Intermetatarsal angle measurements.

Coughlin *et al*[19] found that only 83.8% of IMA measurements made by physicians were within 3 degrees of concordance. AI overcomes the issue of clinician intra-observational and inter-observational reliability in terms of repeatable angular measurements of HV[46].

Considering that collecting a dataset of radiograms of patients with HV who were subsequently operated is not easy, we decided to rely on HV measurements on the segmented bones. Our initial research demonstrated that such an approach permits achieving better accuracy of HVA/IMA measurements on limited numbers of radiographs compared to key point-based ones. The difficulties associated with segmentation of proximal epiphyseal of 2MT bones due to anatomical overlap inclined us to apply a simplified segmentation with the exclusion of this bone area (Figure 5C). Consequently, the IMA measurements have an irrelevant bias (Figure 6B, Figure 7B).

Foot surgeons are aware that the decision to perform osteotomies or first tarsometatarsal joint (TMTJ) fusions (Lapidus procedure) depends on more than just HVA and IMA. Rather, it depends on the patients' clinical picture, concomitant deformities of the foot such as lesser toe deformities, pes planus, metatarsus adductus, first TMTJ instability, the width of the 1st MT shaft, pronation of the first ray, presence of first metatarsophalangeal joint osteoarthritis, and the surgeons' own skill level. The lateral view is also critical in evaluating the first TMTJ instability or presence of osteoarthritis which may necessitate a fusion rather than a 1st MT osteotomy. According to Lee *et al*[11] the HVA, IMA, interphalangeal angle, sesamoid rotation angle, and first metatarsal protrusion distance are worth measuring in HV considering three-dimensional role in this deformity. Presently the above-mentioned requirements may limit the applicability of our method in some cases. Nonetheless, our algorithm establishes itself as a fast and clinically effective tool in the assessment of many HV cases. In order to fully automate preoperative HV planning, further research and development remain necessary.

In future work, more radiographs will be labeled to train more advanced U-Net to distinguish bones under challenging areas better. A multi-center database of radiographs should be created. Due to recent developments and a deeper understanding of pronation, enhanced segmentation and further research on manual and automatic estimation of the distal metaphyseal/diaphyseal 1MT reference point is necessary. We plan to train and evaluate different networks on our dataset, which will be extended to new images from other hospitals.

CONCLUSION

The proposed automated, AI-assisted determination of angles of hallux valgus based on deep learning is an accurate tool that produces measurements comparable to manual measurements performed by experienced clinicians in significantly less time. Automation can be used in clinical practice to determine angles of hallux valgus on X-ray images, classify the degree of deformity, and streamline preoperative decisions-making prior to HV surgery.

ARTICLE HIGHLIGHTS

Research background

Recent advances in artificial intelligence and deep learning has spurred innovations in medical imaging modalities, resulting in enhanced visualisation possibilities. Additionally, there is a growing interest in the automation of regular diagnostic procedures alongside orthopedic measurements.

Research motivation

So far, no reliable and automated method has been developed for measuring angles of foot bones in significant deformities of the big toe from radiographs according to AOFAS. Likewise, there is no system for automated preoperative decision-making.

Research objectives

The aim of our research was to develop a robust automated method for measuring angles of hallux valgus on radiographs according to AOFAS guidelines, to determine the accuracy of this method, to compare it against expert clinician measurements, and to develop a preoperative decision-making systems.

Research methods

The bones which are necessary to determine the angles of hallux valgus, obtained on anteroposterior weight-bearing feet radiograms were segmented by a U-Net. The bone axes were determined, and then the reference points for determining the hallux valgus angles (HVA) and intermetatarsal angles (IMA) were found. The interclass correlation coefficient and standard error for single measurements were used to calculate the agreement between manual and automatic measurements. Finally, the correlation between the decisions of our algorithm and clinical adjudication for preoperative planning of hallux valgus was investigated.

Research results

The key foot bones were segmented from anteroposterior feet radiograms by the U-Net neural network with high accuracy (average Sørensen–Dice index larger than 97%). Such a precise segmentation enabled the accurate determination

of bone axes and the required reference points. Excellent agreement was achieved between manual and automated measurements of both angles. For HVA, absolute agreement interclass correlation coefficient (AA-ICC) and consistency ICC (C-ICC) were 0.97, and standard error of measurement (SEM) was 0.32. For IMA, AA-ICC was 0.75, C-ICC was 0.89, and SEM was 0.21. The proposed hallux valgus treatments based on HVA and IMA measured automatically correlated well with those proposed by orthopedic surgeons performing manual angle measurements.

Research conclusions

The proposed artificial intelligence powered automation for evaluating angles of hallux valgus through deep learning is a precise, yielding measurements akin to those conducted manually by experienced clinicians. This offers promising clinical applications such as facilitating the automated determination of angles of hallux valgus from X-ray images, categorizing the extent of deformity, and recommending a specific protocol for corrective surgery.

Research perspectives

Future research will focus on automating the measurements of remaining angles and parameters of forefoot deformation along its greater clinical implementation to further enhance diagnostic accuracy and improve patient outcomes.

FOOTNOTES

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META-ANALYSIS

Long head of biceps tendon transposition for massive and irreparable rotator cuff tears: A systematic review and meta-analysis

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Abstract

BACKGROUND

Superior capsular reconstruction (SCR) with long head of biceps tendon (LHBT) transposition was developed to massive and irreparable rotator cuff tears (MIRCTs); however, the outcomes of this technique remain unclear.

AIM

To perform a systematic review of biomechanical outcomes and a meta-analysis of clinical outcomes after LHBT transposition for MIRCTs.

METHODS

We performed a systematic electronic database search on PubMed, EMBASE, and Cochrane Library. Studies of SCR with LHBT transposition were included according to the inclusion and exclusion criteria. Biomechanical studies were assessed for main results and conclusions. Included clinical studies were evaluated for quality of methodology. Data including study characteristics, cohort demographics, and outcomes were extracted. A meta-analysis was conducted of the clinical outcomes.

RESULTS

According to our inclusion and exclusion criteria, a total of six biomechanical studies were identified and reported an overall improvement in subacromial contact pressures and prevention of superior humeral migration without limiting range of motion (ROM) after LHBT transposition for MIRCTs. A total of five clinical studies were included in the meta-analysis of LHBT transposition outcomes, consisting of 253 patients. The results indicated that compared to other surgical methods for MIRCTs, LHBT transposition had advantages of more significant improvement in ROM (forward flexion mean difference [MD] = 6.54, 95% confidence interval [CI]: 3.07-10.01; external rotation [MD = 5.15, 95%CI: 1.59-8.17]; the acromiohumeral distance [AHD] [MD = 0.90, 95%CI: 0.21-1.59]) and reducing retear rate (odds ratio = 0.27, 95%CI: 0.15-0.48). No significant difference

in American Shoulder and Elbow Surgeons score, visual analogue scale score, and University of California at Los Angles score was demonstrated between these two groups for MIRCTs.

CONCLUSION
In general, SCR with LHBT transposition was a reliable and economical technique for treating MIRCTs, both in terms of biomechanical and clinical outcomes, with comparable clinical outcomes, improved ROM, AHD, and reduced the retear rates compared to conventional SCR and other established techniques. More high-quality randomized controlled studies on the long-term outcomes of SCR with LHBT transposition are required to further assess.

Key Words: Massive and irreparable rotator cuff tears; Long head of biceps tendon transposition; Rotator cuff repair; Superior capsular reconstruction

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Core Tip: Superior capsular reconstruction (SCR) with long head of biceps tendon (LHBT) transposition was developed to massive and irreparable rotator cuff tears (MIRCTs). However, the outcomes of this technique remain unclear. SCR with LHBT transposition is a reliable and economical technique for treating MIRCTs, both in terms of biomechanical and clinical outcomes, with comparable clinical outcomes, improved range of motion, acromiohumeral distance, and reduced the retear rates compared to conventional SCR and other established techniques.

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INTRODUCTION

Rotator cuff tears are one of the most common musculoskeletal disorders, affecting between 15% and 50% of the population, and increasing in prevalence with age[1]. The prevalence of massive and irreparable rotator cuff tears (MIRCTs) is reportedly as high as 40% in rotator cuff tears[2,3]. The rotator cuff works as a dynamic stabilizer of the glenohumeral joint, and MIRCTs will cause the absence of this stabilizer, with the head migrating superiorly and anteriorly, leading to abnormal wear and tear of the head and glenohumeral joint[4,5]. If left untreated, the MIRCTs may lead to permanent pain and loss of function, eventually resulting in rotator cuff arthropathy.

The repair of MIRCTs still remains a surgical challenge due to muscle fat infiltration, tendon retraction, and tissue degeneration. Numerous surgical management options for MIRCTs are available, including debridement and sub-acromial decompression, partial rotator cuff repair, biceps tenodesis or tenotomy, an allograft or autograft (patch, fascia or dermis), tendon transfer (latissimus dorsi, pectoralis major, or pectoralis minor), balloon technique, and reverse total shoulder arthroplasty, have been reported[6-13]. If complete repair cannot be accomplished, partial repair may still improve pain and function of the shoulder. However, the risk of retear rate after partial repair is as high as 52%[14]. Compared to partial repair, arthroscopic patch grafting has better clinical efficacy, but patch grafting has no significant benefit for patients with high-grade fatty degeneration[15,16]. Tendon transfer is a good option for young, active patients with MIRCTs, minimal glenohumeral arthritis and severe functional limitations. However, the surgical trauma of tendon transfer is relatively large and the rehabilitation process is complicated. In patients with advanced cuff tear arthropathy and/or painful pseudoparalysis, a reverse total shoulder can provide predictable pain relief and function improvement but is associated with more complications and higher failure rate[17].

Superior capsular reconstruction (SCR) is considered a possible option for treating MIRCTs and restoring superior glenohumeral stability and shoulder function, which was first described by Mihata *et al*[18] in 2013. The graft used is a tensor fasciae lata (TFL) autograft that attaches medially to the superior glenoid and laterally to the greater tuberosity. Recently, the long head of biceps tendon (LHBT) has been proposed as an alternative to the standard SCR graft, which seems to overcome the problems of donor site morbidity, feasibility of grafting, and additional costs of allografting[19]. When performing the LHBT transposition technique, the native LHBT connection on the glenoid side was preserved. The proximal portion of the LHBT, was then transposed posteriorly and fixed on the supraspinatus tendon footprint as the SCR.

Currently, biomechanical studies have been carried out to observe the biomechanical effects of LHBT transposition for MIRCTs[20-22]. Meanwhile, few previous clinical studies have reported promising clinical outcomes after LHBT transposition for MIRCTs[23-25]; however, it remains unknown about the reliability of this technique. The purpose of this study was to perform a systematic review of biomechanical outcomes and a meta-analysis of clinical outcomes after LHBT transposition for MIRCTs. We hypothesized that LHBT transposition would effectively restore joint biomechanics compared with the unrepaired state and improve overall shoulder function, the acromiohumeral distance (AHD) and

decrease the retear rate of repaired rotator cuff.

MATERIALS AND METHODS

This meta-analysis and systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[26].

Search strategy

Two independent authors (Wan RW and Luo ZW) performed an electronic search in three databases between their inception date and May 20, 2022: MEDLINE (PubMed), EMBASE (Ovid), and Cochrane Library. The Boolean search phrase was "(superior capsul* reconstruction OR superior capsul* repair OR superior labr* reconstruction OR superior labr* repair OR rotator cuff repair) AND (biceps)." The reference lists of correlational studies were also reviewed.

Eligibility criteria

Inclusion criteria consisting of biomechanical studies were as follows: (1) Cadaveric shoulders with massive or irreparable rotator cuff tears; (2) LHBT transposition was used in cadaveric shoulders; and (3) articles written in English or with an English translation.

Inclusion criteria consisting of clinical studies were as follows: (1) LHBT transposition was used to treat rotator cuff tears; (2) Rotator cuff tears were large to massive or irreparable; (3) Postoperative functional outcomes were reported; and (4) Articles were written in English or had an English translation.

The exclusion criteria were as follows: (1) Computational-based or animal studies; (2) editorial letters or letters to the editor, case reports, technical notes, expert consensuses, systematic and narrative reviews, pilot studies, unpublished manuscripts, book chapters, lectures, meeting abstracts, conference proceedings, or dissertations; (4) superior labrum anterior and posterior (SLAP) injury or LHBT injury; (5) SCR without using LHBT transposition; and (6) clinical studies not reporting preoperative and postoperative outcomes or without enough information for data analyses.

Study selection

After duplicates were removed, two independent authors (Wan RW and Luo ZW) evaluated all titles and abstracts for relative articles. If these data were inadequate, full texts were assessed to judge if studies met the inclusion criteria. If there was an objection concerning the inclusion of studies, studies were judged by the senior author (Shang XL) to make the final decision.

Data extraction

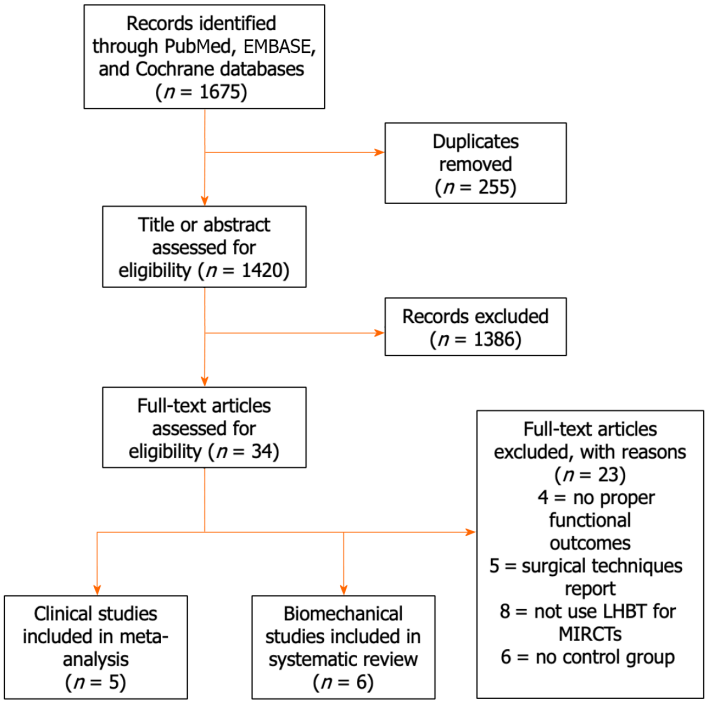
After assessing full-text articles for eligibility and applying the inclusion/exclusion criteria, the following information were extracted: study type, level of evidence, first author, publication year, country, number of patients, mean age, mean duration of follow-up, surgical technique, and postoperative clinical outcomes, and postoperative retear rates. The primary outcomes of interest were American Shoulder and Elbow Surgeons (ASES) score, visual analogue scale (VAS) score (0-10 [10 = severe pain]), University of California at Los Angles (UCLA) score, range of motion (ROM) including active external rotation at side (ER_0; degrees), active forward flexion (FF; degrees), AHD, and retear rates. For studies with insufficient information, the reviewers contacted the primary authors, when possible, to acquire and verify the data.

Quality assessment

Given the abundance of nonrandomized studies in the available literature, two independent reviewers (Wan RW and Luo ZW) critically appraised all eligible studies using Methodological Index for Nonrandomized Studies (MINORS) to evaluate their quality[27]. If a consensus was not achieved, a senior reviewer (Shang XL) made the final decision on the assessment. The MINORS instrument consists of 12 items: 4 for comparative studies only and 8 for noncomparative and comparative studies. A score of 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate) was suggested for each item, resulting in an ideal maximum score of 16 for noncomparative studies and 24 for comparative studies. For nonrandomized comparative studies, the methodologic quality was classified as follows: 0-12, low quality; 13-18, fair quality; and 19-24, good quality. The outcomes of the risk of bias and quality assessment offered context for the conclusions to be drawn from this review.

Statistical analyses

Statistical analyses were performed by using Review Manager, version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration). The mean difference (MD) and odds ratio (OR) were used to compare continuous and dichotomous variables, respectively. All results were reported with 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant. I^2 test was performed to assess the impact of study heterogeneity on the results of the meta-analysis. According to the Cochrane review guidelines, if severe heterogeneity was present at $I^2 > 50\%$, the random effect models were chosen. If $I^2 \leq 50\%$, multiple similar studies were considered to be homogeneous, and the fixed effects model was used to combine the statistical values. The results are summarized in forest plots.



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Figure 1 Flowchart diagram of the electronic search. Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. LHBT: Long head of biceps tendon; MIRCTs: Massive and irreparable rotator cuff tears.

RESULTS

Study selection

The initial literature search yielded 1675 articles (Figure 1). After removing duplicates, 1420 studies were screened for title and abstract, resulting in 34 full-text articles being assessed for eligibility. After the application of inclusion and exclusion criteria, six articles[21,28-32] reported biomechanical outcomes and five articles[33-37] reported clinical outcomes were identified for further analysis.

Risk of bias

The MINORS scores of two retrospective control clinical studies[33,34] were ≥ 19 points, indicating good quality of evidence. The MINORS scores of three other retrospective control clinical studies[35-37] were > 13 points, indicating fair quality of evidence (Table 1).

Systematic review of biomechanical studies

The characteristics and main results of included biomechanical studies are shown in Table 2. Because of the heterogeneity of testing conditions and outcome reporting, no meaningful statistical analyses could be performed. Overall, LHBT transposition for MIRCTs was reported to improve subacromial contact pressures and prevent superior humeral migration without limiting ROM.

Meta-analysis of clinical outcomes

A total of five studies meeting inclusion criteria were included in the meta-analysis of LHBT transposition outcomes, consisting of 253 patients. The study characteristics are presented in Table 3. We considered LHBT transposition for MIRCTS as the intervention group and other surgical methods for MIRCTs, *i.e.* the double-row repair, the transosseous-equivalent technique with absorbable patch reinforcement, the traditional SCR with a fascia lata autograft, arthroscopic rotator cuff repair (ARCR) alone, ARCR and tenotomy of LHBT, as the control group.

Patients were clinically assessed both preoperatively and postoperatively on a number of outcome-based scores that included ASES score, VAS score, UCLA score, ROM, AHD, and retear rates. ASES score was measured in five studies including a total of 253 patients: 127 in the LHBT transposition group and 126 in the control group. The results of the heterogeneity analysis indicated that these five studies had good homogeneity (P = 0.27, I^2 = 22%). A mean difference of 0.51, 95%CI: -1.91 to 2.93 was calculated, with a P value of 0.68. No significant difference was observed between the two groups regarding the ASES score (Figure 2A).

VAS score was measured in four studies including a total of 231 patients: 115 in the LHBT transposition group and 116 in the control group. The results of the heterogeneity analysis indicated that these four studies had good homogeneity (P = 0.33, I^2 = 13%). A mean difference of -0.13 (95%CI: -0.33 to 0.06) was calculated, with a P value of 0.18, indicating that no significant difference was found between the two cohorts (Figure 2B).

Table 1 Methodological Index for Nonrandomized Studies scores of the clinical studies

Ref.	Study type/LOE	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Score
Barth *et al* [37], 2020	III, retrospective control study	2	1	2	2	1	2	1	0	2	1	2	0	16
Kocaoglu *et al*[34], 2020	III, retrospective control study	2	2	2	2	2	2	2	0	2	2	2	0	20
Rhee *et al* [33], 2021	III, retrospective control study	2	1	1	2	2	2	1	1	2	2	2	1	19
Chiang *et al* [36], 2021	III, retrospective control study	2	1	2	2	1	2	1	0	1	1	2	0	15
Kawashima *et al*[35], 2022	III, retrospective control study	2	1	2	2	1	2	1	0	1	2	2	0	16

UCLA score was measured in three studies including a total of 163 patients: 89 in the LHBT transposition group and 74 in the control group. The results of the heterogeneity analysis indicated that these three studies had good homogeneity (P = 0.19, I^2 = 41%). A mean difference of 0.36, 95%CI: -0.67 to 1.39 was calculated, with a P value of 0.50. This suggested that no significant difference was found between the two cohorts (Figure 2C).

ROM was evaluated in five studies including a total of 253 patients: 127 in the LHBT transposition group and 126 in the control group. The results of the heterogeneity analysis in FF and ER0 indicated that these five studies had good homogeneity (P = 0.61, I^2 = 0%, P = 0.32, I^2 = 14%). In terms of FF, a mean difference of 6.54, 95%CI: 3.07-10.01 was calculated, with a P value of 0.0002, indicating that the FF was significantly better in the LHBT transposition group (Figure 2D). Regarding ER0, a mean difference of 5.15, 95%CI: 1.59-8.17 was calculated, with a P value of 0.005, indicating that the ER0 was significantly better in the LHBT transposition group (Figure 2E).

AHD was measured in four studies including 199 patients: 103 in the LHBT transposition group and 96 in the control group. The results of the heterogeneity analysis indicated that these four studies had good homogeneity (P = 0.13, I^2 = 48%). A mean difference of 0.90, 95%CI: 0.21-1.59 was calculated, with a P value of 0.01, indicating that LHBT transposition can significantly improve AHD (Figure 2F).

Retear rate was reported in five studies including a total of 253 patients: 127 in the LHBT transposition group and 126 in the control group. The results of the heterogeneity analysis indicated that these five studies had good homogeneity (P = 0.42, I^2 = 0%). An odds ratio of 0.27, 95%CI: 0.15-0.48 was measured (P < 0.0001), thereby indicating that the retear rate in LHBT transposition group was lower (Figure 3).

Table 2 Biomechanical outcomes after long head of biceps transposition

Ref.	Number of shoulders	Age, yr	Surgical technique	Testing conditions/groups	Testing method	Main results	Main conclusion
Park *et al*[22], 2018	9	58 (33-77)	ACR using autologous proximal biceps tendon for large to massive rotator cuff tears	(1) Intact; (2) Stage II tear (complete tear of the supraspinatus); (3) ACR for stage II tear; (4) Stage III tear (complete tear of the supraspinatus and anterior one-half of the infraspinatus); and (5) ACR for stage III tear	Range of motion, superior translation of the humeral head, and subacromial contact pressure were measured at 0°, 30°, 60°, and 90° of ER with 0°, 20°, and 40° of glenohumeral abduction	ACR for both stage II and stage III showed significantly higher total range of motion compared with intact at all angles. ACR significantly decreased superior translation for stage II tears at 0°, 30°, and 60° ER for both 0° and 20° abduction and for stage III tears at 0° and 30° ER for both 0° and 20° abduction. ACR for stage III tear significantly reduced peak subacromial contact pressure at 30° and 60° ER with 0° and 40° abduction and at 30° ER with 20° abduction	ACR using autologous biceps tendon biomechanically normalized superior migration and subacromial contact pressure, without limiting range of motion
El-shaar *et al*[21], 2018	10 (5 matched pairs)	63 (59-67)	SCR utilizing a LHB autograft or TFL autograft	(1) After a massive RC tear without SCR; and (2) After SCR with either a TFL autograft or an LHB autograft	Cadaveric demographics, mean force required to superiorly translate the humerus, and change in mean force when normalized to the torn condition were recorded	SCR with an LHB autograft required 393.2% ± 87.9% of the force needed for superior humeral migration in the massive RC tear condition, while SCR with a TFL autograft required 194.0% ± 21.8%. The LHB reconstruction group trended toward a stronger reconstruction when normalized to the torn condition	SCR with an LHB autograft is a feasible procedure that is shown to be biomechanically equivalent and potentially even stronger than SCR with a TFL autograft in the prevention of superior humeral migration
Han *et al*[30], 2019	7	50-65	SCR using the LHBT or using the LHBT with side-to-side repair	(1) Intact; (2) Simulated complete supraspinatus tendon tear; (3) Modified SCR using LHB; and (4) Modified SCR using LHB and side-to-side repair augmentation	Superior translation of the humerus, subacromial contact pressure and area, and glenohumeral range of motion were tested at 0°, 30°, and 60° of glenohumeral abduction	The complete cuff tear shifted the humeral head superiorly as compared to the intact shoulder. Subacromial peak contact pressure was also increased at 30° and 60° while contact area was increased at 0° and 30°. The modified SCR both with and without side-to-side repair shifted the humeral head inferiorly at 30° and 60°, with contact area further reduced at 60°. Both techniques had	The LHB with appropriate distal insertion on the greater tuberosity restores shoulder stability in irreparable rotator cuff tears by re-centering the humeral head on the glenoid

						comparable results for contact pressure and total rotational range of motion	
Han *et al*[29], 2020	8	65 (56-69)	PR, BR and BRSS	(1) Intact; (2) IRCT; (3) PR; (4) BR; and (5) BRSS	Total rotational range of motion was measured at 40°, then 20°, and finally 0° of glenohumeral abduction. Superior humeral translation and subacromial contact pressure were measured at 0°, 30°, 6 0°, and 90° of external rotation at each abduction angle	Superior humeral translation was significantly decreased in the BR and BRSS conditions compared with the IRCT and PR conditions at 0° and 20° of GH abduction ($P < 0.001$). BR and BRSS significantly reduced subacromial contact pressure compared with IRCT and PR at 0° of GH abduction ($P < 0.001$). There was no significant decrease in total rotational range of motion after BR at any abduction angle	BR biomechanically restored shoulder stability without over constraining range of motion in an IRCT model
Berthold *et al*[32], 2021	8	53.4 ± 14.2 (20-64)	SCR with V- shaped LHBT reconstruction, box-shaped LHBT reconstruction or single-stranded LHBT reconstruction	(1) Intact; (2) Irreparable psRCT; (3) V-shaped LHBT reconstruction; (4) Box-shaped LHBT reconstruction; and (5) Single-stranded LHBT reconstruction	ghST, MAA, maximum cDF, and sCP were accessed and recorded in each condition	Each of the 3 LHBT techniques for reconstruction of the superior capsule significantly increased MAA while significantly decreasing ghST and cDF compared with the psRCT. Additionally, the V-shaped and box-shaped techniques significantly decreased sCP compared with the psRCT. The V-shaped technique further showed a significantly increased MAA and decreased cDF when compared with the box-shaped and single-stranded techniques, as well as a significantly decreased ghST when compared with the box-shaped technique	Using the LHBT for reconstruction of the superior capsule improved shoulder function by preventing superior humeral migration, decreasing deltoid forces and sCP
Denard *et al*[31], 2021	8	62 (46-70)	SCR with box-shaped LHBT reconstruction or single-limb LHBT reconstruction	(1) Intact state; (2) A stage III MCT model (complete supraspinatus and anterior one-half of the infraspinatus); (3) Box Biceps SCR; and (4) Single-limb biceps	A custom testing system used to evaluate range of motion, superior translation, and subacromial contact pressure at 0°, 20°, and 40° of abduction	Range of motion was not impaired with either repair construct ($P > 0.05$). The box SCR decreased superior translation by approximately 2 mm compared with the MCT at 0°, but translation remained greater compared with the intact	A box-shaped SCR using the native biceps tendon partially restores increased superior translation and peak subacromial contact pressure due to MCT. The technique may have a role in augmentation of an IMCT

				state in nearly every testing position. The in situ tenodesis had no effect on superior translation. Peak subacromial contact pressure was increased in the MCT at 0° and 20°. Abduction compared with the native state but not different between the native and box SCR at the same positions

ACR: Anterior cable reconstruction; IRCT: Irreparable rotator cuff tear; PR: Partial repair; BR: Biceps rerouting; BRSS: Biceps rerouting with side-to-side repair; psRCT: Irreparable posterosuperior rotator cuff tear; ghST: Glenohumeral superior translation; MAA: Maximum abduction angle; cDF: Cumulative deltoid force; sCP: Subacromial peak contact pressure; SCR: Superior capsular reconstruction; LHBT: Long head of biceps tendon; TFL: Tensor fasciae lata; MCT: Massive rotator cuff tear; IMCT: Irreparable and massive rotator cuff tear; ER: External rotation.

DISCUSSION

The main finding of this investigation was that LHBT transposition for MIRCTs was generally reported to reduce subacromial contact pressures and prevent superior humeral migration without limiting ROM. On clinical outcomes, compared to other surgical methods for MIRCTs, LHBT transposition resulted in significant improvement in ROM, AHD, and reducing retear rate.

In the included biomechanical study, Park *et al*[22] reported that SCR with LHBT transposition significantly reduced the humeral head displacement caused by massive rotator cuff tears and decreased subacromial contact pressure. Meanwhile, El-shaar *et al*[21] found that SCR with LHBT transposition achieved equivalent and potentially even greater biomechanical stability than SCR using a TFL autograft in preventing humeral head migration. Han *et al*[30] found that SCR for LHBT transposition with or without side-to-side repair both shifted the humeral head downward and was a further reduction in the contact surface area of the acromion. Besides the results of both techniques were comparable in terms of contact pressure and total rotational ROM. A biomechanical study by Han *et al*[29] found that compared with partial repair after MIRCTs, LHBT transposition with or without side-to-side repair both significantly reduced the humeral head migration distance at 0° and 20° of glenohumeral abduction and effectively reduced the subacromial contact pressure at 0° of glenohumeral abduction. Three different SCR with LHBT transposition techniques were compared in the study of Berthold *et al*[32]: V-shaped, box-shaped, and single-stranded. Each of the techniques significantly increased maximum abduction angle while significantly decreasing glenohumeral superior translation and maximum cumulative deltoid force compared with the irreparable posterosuperior rotator cuff tear. The V-shaped technique further showed a significantly increased maximum abduction angle and decreased maximum cumulative deltoid force when compared with the box-shaped and single-stranded techniques, as well as a significantly decreased glenohumeral superior translation compared with the box-shaped technique. Meanwhile, Denard *et al*[31] found that ROM was not impaired with box-shaped and single-limb LHBT transposition and that there was no difference in subacromial contact pressure compared to an intact rotator cuff.

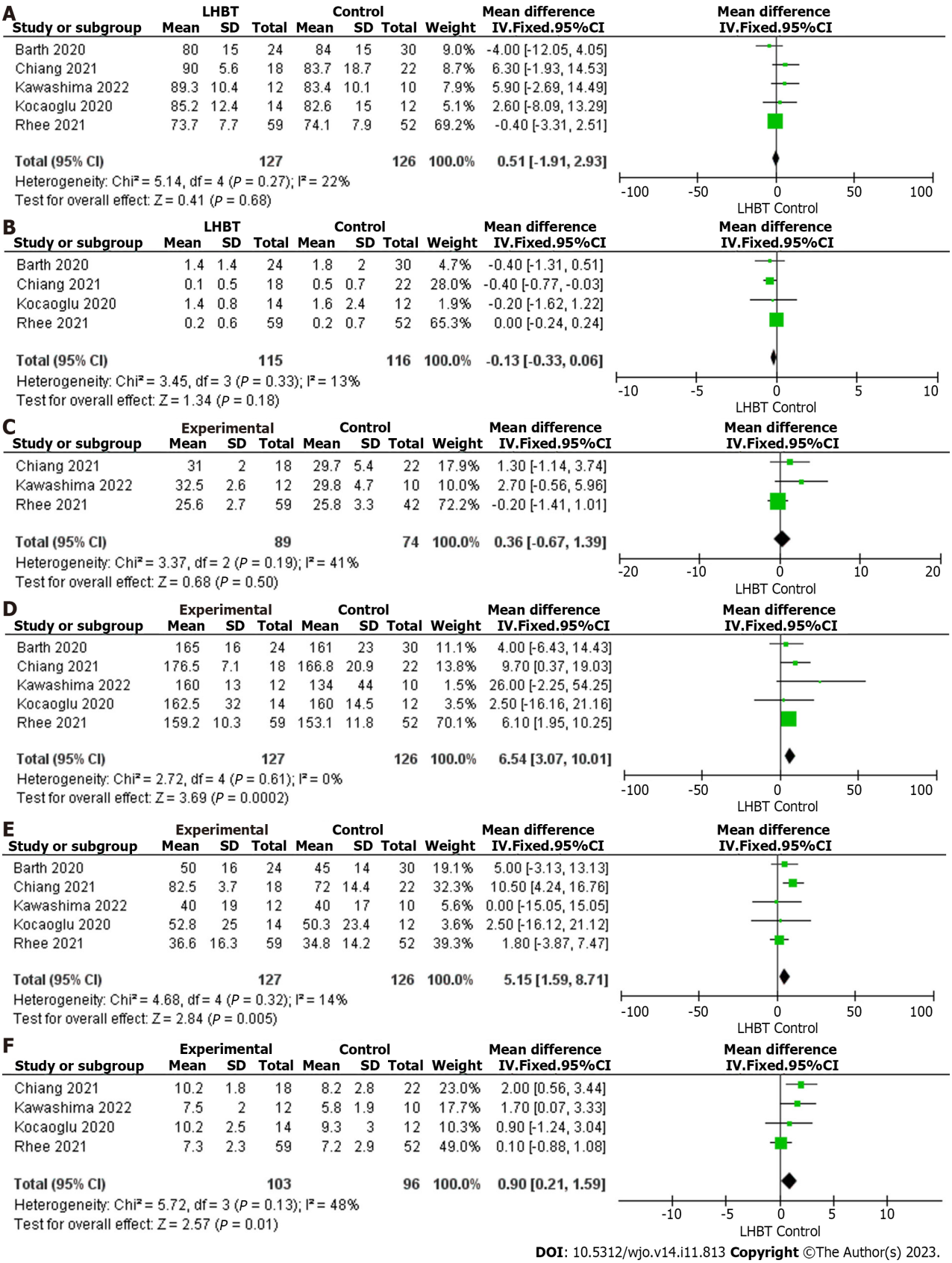
In the meta-analysis of the clinical study, compared to control group, LHBT transposition group improved FF, ER0, and AHD with a lower retear rate. No significant difference in ASES score, VAS score, and UCLA score was demonstrated between these two groups for MIRCTs. Two articles pioneered the treatment of MIRCTs with SCR using

Table 3 Overview of included clinical studies

Ref.	Country	Journal	Level of evidence, study type	Groups	No. of shoulder in group	Male:female sex	Age, yr	Follow-up, mo	Outcomes
Barth *et al*[37], 2020	France	*Am J Sports Med*	3, retrospective study	DR *vs* TOE with absorbable patch reinforcement *vs* SCR with LHBT autograft	28 *vs* 30 *vs* 24	15:13 *vs* 19:11 *vs* 16:8	63 ± 9 (48-83) *vs* 59 ± 7.6 (45-71) *vs* 60 ± 7 (47-81)	25 ± 2 (24-29) *vs* 27 ± 5 (24-36) *vs* 25 ± 2 (24-29)	ASES score, VAS score, constant score, range of motion, simple shoulder test, subjective shoulder value, muscle strength, retear rate
Kocaoglu *et al*[34], 2020	Turkey	*Orthop J Sports Med*	3, retrospective study	SCR with LHBT autograft *vs* SCR with a tensor fasciae lata autograft	14 *vs* 12	N/A	64.6 ± 8.4 *vs* 62.5 ± 6.5	28 *vs* 32	ASES score, VAS score, QuickDASH, range of motion, AHD, retear rate
Rhee *et al*[33], 2021	Korea	*Arthroscopy*	3, retrospective study	ARCR + BR *vs* ARCR	59 *vs* 52	32:27 *vs* 29:23	63.7 ± 6.5 *vs* 62.8 ± 6.9	15.1 ± 3.4 *vs* 25.1 ± 8.7	ASES score, VAS score, constant score, UCLA score, range of motion, muscle strength, AHD, retear rate
Chiang *et al*[36], 2021	China (Taiwan)	*Arthroscopy*	3, retrospective study	ARCR and SCR with LHBT autograft *vs* ARCR and tenotomy of LHBT performed at the insertion site	18 *vs* 22	7:11 *vs* 6:16	62.3 ± 7.5 *vs* 62.2 ± 6.1	26.6 ± 3.9 (24-38) *vs* 31.9 ± 6.4 (26-45)	ASES score, VAS score, UCLA score, rang of motion, AHD, retear rate
Kawashima *et al*[35], 2022	Japan	*Arthroscopy*	3, retrospective study	partial repair *vs* SCR with LHBT transposition	10 *vs* 12	6:4 *vs* 7:5	71.9 ± 7.5 *vs* 67.8 ± 2.0	37.2 (24-72) *vs* 24.8 (24-30)	ASES score, UCLA score, rang of motion, AHD, retear rate

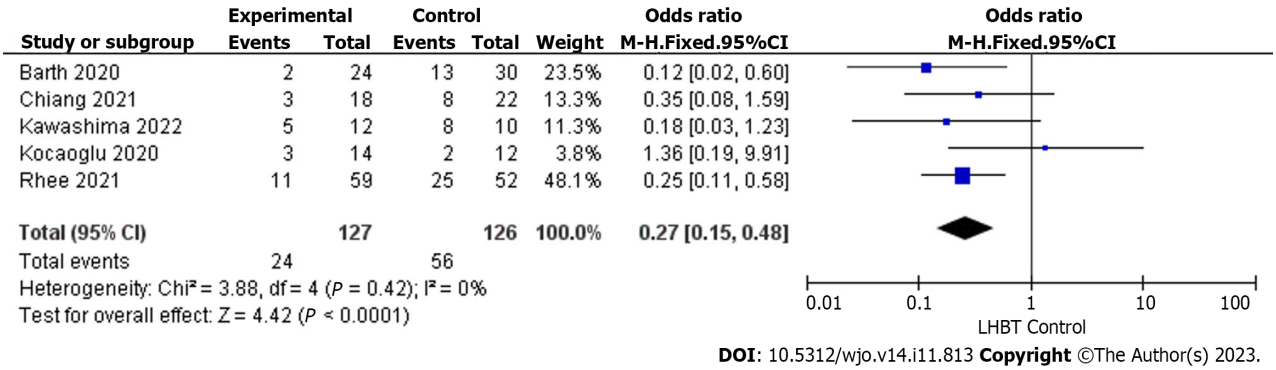
AHD: Acromiohumeral distance; ARCR: Arthroscopic rotator cuff repair; ASES: American Shoulder and Elbow Surgeons; DR: Double-row technique; LHBT: Long head of biceps tendon; N/A: Not available; SCR: Superior capsular reconstruction; TOE: Transosseous-equivalent technique; UCLA: University of California at Los Angles; VAS: Visual analogue scale.

autologous broad fascia as the repair material, and the postoperative follow-up found that the patients' function was significantly improved with satisfactory clinical outcomes[18,38]. However, the autologous broad fascia retrieval requires additional incisions, which not only increases the trauma but also makes the operation complicated and technically demanding. Besides, more anchors are used to fix the broad fascia, which leads to increased costs. Some authors have suggested replacing fascial autografts with human acellular dermal patch allografts to avoid any additional skin incisions and any donor site morbidity[39,40]. A recent study reported by Shin *et al*[41] showed satisfactory outcomes with SCR using acellular dermal allograft. However, a systematic review showed high retear rate on SCR using acellular dermal allograft compared with fascia lata[42]. The mechanical strength of acellular dermal materials remains controversial and expensive.



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Figure 2 Standard differences in means. A: Standard differences in means for American Shoulder and Elbow Surgeons score between long head of biceps tendon (LHBT) transposition group and control group; B: Standard differences in means for visual analogue scale score between LHBT transposition group and control group; C: Standard differences in means for University of California at Los Angles score between LHBT transposition group and control group; D: Standard differences in means for forward flexion between LHBT transposition group and control group; E: Standard differences in means for external rotation between LHBT transposition group and control group; F: Standard differences in means for acromiohumeral distance between LHBT transposition group and control group. CI: Confidence interval; LHBT: Long head of biceps tendon.



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Figure 3 Odds ratios for retear rate between long head of biceps tendon transposition group and control group. CI: Confidence interval; LHBT: Long head of biceps tendon.

SCR with LHBT transposition was proposed by Boutsiadis *et al*[19] first, and the LHBT without significant tears or severe degeneration was fully utilized in the operation, with the superior glenoid labral is preserved. LHBT was transferred laterally to the supraspinatus tendon footprint area for fixation. Finally, the distal LHBT is chosen to be cut or preserved according to its distal LHBT quality in order to simulate SCR, while the partially repaired rotator cuff can be bridged. The main advantage of this method is to borrow the LHBT to provide a tension-reducing scaffold to strengthen the anterior rotator cuff tissue mechanics and anterosuperior blocking effect to assist the massive rotator cuff repair and reduce the tension on the repaired rotator cuff tissue, thereby reducing the rate of postoperative rotator cuff retears and improving the AHD. This is consistent with the results of our meta-analysis.

Other advantages of SCR with LHBT transposition are that it not only avoids the trauma at the extraction site caused by taking the autologous broad fascia for SCR but also reduces the amount of anchor nails used, thus greatly reducing the cost and time of the procedure and decrease of infection. In addition, it is technically easier and more reproducible than SCR using fascial autografts or dermal allografts, which require a long learning curve. Finally, another possible advantage is the biological aspect of using a local autograft attached to the upper glenoid so that its vasculature may be preserved.

There are several potential limitations of this technique. The main condition is the availability of a relatively good quality LHBT, and SCR with other grafts should be considered when there is LHBT severe degeneration, LHBT rupture or partial tearing involving more than 50%, SLAP lesions > II, and some rare cases of anatomic variation or absence of the tendon[43]. However, in the case of chronic MIRCTs, they are often accompanied by LHBT damage. In addition, the LHBT is reportedly a pain generator in patients with rotator cuff tears, and the use of the LHBT as an autograft for SCR may, in theory, increase postoperative pain[37]. However, the results of clinical studies showed no difference in postoperative pain between the various compared techniques for either tenotomy or rerouting of the LHBT, suggesting that it can be safely used as an autograft[25,37].

This study had several limitations. First, the available studies or data about LHBT transposition used for MIRCTs were limited, only five studies with 127 patients in LHBT transposition group and 126 patients in control group. Second, there was insufficient high-quality comparative evidence, as the five included studies were all retrospective studies with a level of evidence 3, which may create recall or selection bias. Although the MINORS scores of these studies indicate good or fair quality evidence, they still fall short of rigorous randomized controlled trial studies. Third, the surgical approaches in the control group, although all of them are commonly used to treat MIRCTs, may have influenced the comparison of outcomes. Additional comparative trials, or even randomized controlled trials, are necessary in the future to determine which treatments are more advantageous in treating MIRCTs, and which modifications of the technique provide better outcomes. Moreover, prior investigations have revealed that distinct rehabilitation modalities and durations exhibit diverse prognostic implications for individuals undergoing arthroscopic repair of rotator cuff tears[44]. In this regard, forthcoming studies could potentially prioritize the evaluation of the influence of diverse rehabilitation approaches on the utilization of LHBT transposition as a therapeutic intervention for the management of MIRCTs. In addition, high-quality studies are necessary to evaluate the long-term outcomes of SCR with LHBT transposition, including postoperative pain, function and structural integrity. High-resolution ultrasound investigation may play an important role in this regard[45]. In a word, future high-quality research of SCR using LHBT transposition for MIRCTs is necessary.

CONCLUSION

This systematic review and meta-analysis demonstrated that SCR with LHBT transposition was a reliable and economical technique for treating MIRCTs, both in terms of biomechanical and clinical outcomes, with comparable clinical outcomes, improved ROM, AHD and reduced the retear rates compared to conventional SCR and other established techniques. To further evaluate the long-term effects of SCR with LHBT transposition, more high-quality randomized controlled studies are needed.

ARTICLE HIGHLIGHTS

Research background

Supracapsular reconstruction (SCR) combined with transposition of the biceps long head biceps tendon (LHBT) is an approach designed to meet the severe challenges posed by massive rotator cuff tears (MIRCT).

Research motivation

Although LHBT transposition has been adopted, its exact impact remains to be clearly elucidated.

Research objectives

There are gaps in our knowledge of the outcomes produced by this technique, and thus further research is needed to reveal its potential benefits and limitations.

Research methods

We conducted a methodical search of electronic databases to identify relevant literature based on inclusion and exclusion criteria. We first conducted a systematic review of the main findings and conclusions of the biomechanical studies. Subsequently, we conducted a comprehensive meta-analysis of the clinical outcomes of the included studies.

Research results

Biomechanical studies have reported that after performing LHBT transposition in MIRCT, there was a comprehensive improvement in subacromial contact pressure and a prevention of proximal humeral migration, without any resultant limitation in range of motion. The meta-analysis of LHBT transposition outcomes has encompassed five clinical studies demonstrated that, compared to other surgical methods for MIRCTs, LHBT transposition exhibited significant advantages in enhancing patients' ROM (forward flexion, mean difference [MD] = 6.54, 95% confidence interval [CI]: 3.00-8.08, external rotation [MD = 5.15, 95%CI: 1.59-8.17], acromiohumeral distance [AHD] [MD = 0.90, 95%CI: 0.21 to 1.59], and reducing the risk of retear [odds ratio = 0.27, 95%CI: 0.15-0.48]). There were no discernible differences between the two groups of patients in terms of American Shoulder and Elbow Surgeons scores, visual analogue scale scores, and University of California, Los Angeles scores.

Research conclusions

In summary, the utilization of LHBT transposition in SCR proved to be a dependable and cost-effective approach for addressing MIRCTs. This technique demonstrated favorable results not only in terms of biomechanical factors but also in clinical outcomes. It exhibited comparable efficacy to conventional SCR and other established techniques, while presenting notable improvements in ROM, AHD, and a reduced incidence of retear. Nevertheless, it is essential to emphasize the necessity for additional high-quality randomized controlled trials focusing on the long-term effects of SCR with LHBT transposition to further evaluate its efficacy.

Research perspectives

Future high-quality research of SCR using LHBT transposition for MIRCTs is necessary.

FOOTNOTES

Co-corresponding authors: Shi-Yi Chen and Xi-Liang Shang.

Author contributions: Wan RW and Luo ZW contributed equally to this study; Wan RW, Chen SY, and Shang XL participated in the study design, data analysis, and drafting of the critically revised the manuscript; Wan RW and Luo ZW were responsible for selecting articles for inclusion, and conducted the risk of bias assessment, and data extraction; Yang YM, Zhang HL, and Chen JN helped to revise the manuscript; Chen SY and Shang XL made invaluable contributions to conceptualizing the study and providing meticulous final review; All authors read and approved the manuscript.

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CASE REPORT

Surgical treatment of atlantoaxial dysplasia and scoliosis in spondyloepiphyseal dysplasia congenita: A case report

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Abstract

BACKGROUND

Spondyloepiphyseal dysplasia congenita (SEDC) is a rare autosomal dominant hereditary disease caused by COL2A1 mutations. SEDC primarily involves the skeletal system, with typical clinical manifestations, including short stature, hip dysplasia, and spinal deformity. Due to the low incidence of SEDC, there are only a few case reports regarding the surgical treatment of SEDC complicated with spinal deformities.

CASE SUMMARY

We report a case of a 16-year-old male patient with SEDC. He presented with typical short stature, atlantoaxial dysplasia, scoliosis, and hip dysplasia. Cervical magnetic resonance imaging showed spinal canal stenosis at the atlas level and cervical spinal cord compression with myelopathy. The scoliosis was a right thoracic curve with a Cobb angle of 65°. He underwent atlantoaxial reduction, decompression, and internal fixation from C1–C2 to relieve cervical myelopathy. Three months after cervical surgery, posterior correction surgery for scoliosis was performed from T3 to L4. Scoliosis was corrected from 66° to 8° and remained stable at 2-year follow-up.

CONCLUSION

This is the first case report of a patient with SEDC who successfully underwent surgery for atlantoaxial dysplasia and scoliosis. The study provides an important reference for the surgical treatment of SEDC complicated with spinal deformities.

Key Words: Spondyloepiphyseal dysplasia congenita; Surgical treatment; Atlantoaxial dysplasia; Scoliosis; Hip dysplasia; Case report

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Core Tip: This study describes the case of a 16-year-old male patient diagnosed with spondyloepiphyseal dysplasia congenita (SEDC) and treated with surgeries for multiple spinal deformities. SEDC is a rare genetic disorder, which mainly affects skeletal development, with an incidence of approximately 3/1000000. Due to the low incidence, there are very few reports on surgical treatment of skeletal deformities in patients with SEDC. We believe that our study makes a significant contribution to the literature because this is the first case report of a patient with SEDC who successfully underwent surgeries for atlantoaxial dysplasia and scoliosis.

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INTRODUCTION

Spondyloepiphyseal dysplasia congenita (SEDC) is a rare autosomal dominant genetic disorder with an incidence of approximately 3/1000000[1]. SEDC affects bone development, particularly of the spine and the long bones of the limbs [2]. SEDC is caused by mutations in the COL2A1 gene, which regulates the synthesis of type II collagen, a major component of cartilage and other types of connective tissues[3]. Mutations in COL2A1 disrupt the normal production and assembly of type II collagen, which lead to abnormal bone growth and development[3,4]. The symptoms of SEDC vary widely, including short stature, atlantoaxial dysplasia, abnormal curvature of the spine (scoliosis or kyphosis), hip dysplasia, joint pain, early onset arthritis, and vision disorders[5]. Some individuals with SEDC may also have cleft palate or other craniofacial abnormalities[5]. There is currently no cure for SEDC, but surgical treatment for skeletal deformities can help manage symptoms and improve quality of life[6]. Although a few cases of atlantoaxial and hip dysplasia have been reported, surgical treatment of SEDC with scoliosis is very rare[7-10]. Herein, we report the case of a patient with SEDC who successfully underwent surgery for atlantoaxial dysplasia and scoliosis.

CASE PRESENTATION

Chief complaints

A 16-year-old male patient presented with a 5-year history of progressive scoliosis.

History of present illness

At the age of 11, the patient was diagnosed with scoliosis and was treated with a brace for more than 12 h daily and had regular check-ups. However, his scoliosis continued to deteriorate.

History of past illness

The patient experienced difficulty walking and had challenges with physical activities since the age of 1 year. His growth and development were delayed compared to those of his peers. Radiography of the hip joints revealed bilateral hip dysplasia.

Personal and family history

The patient denied any family history of similar diseases or malignant tumors.

Physical examination

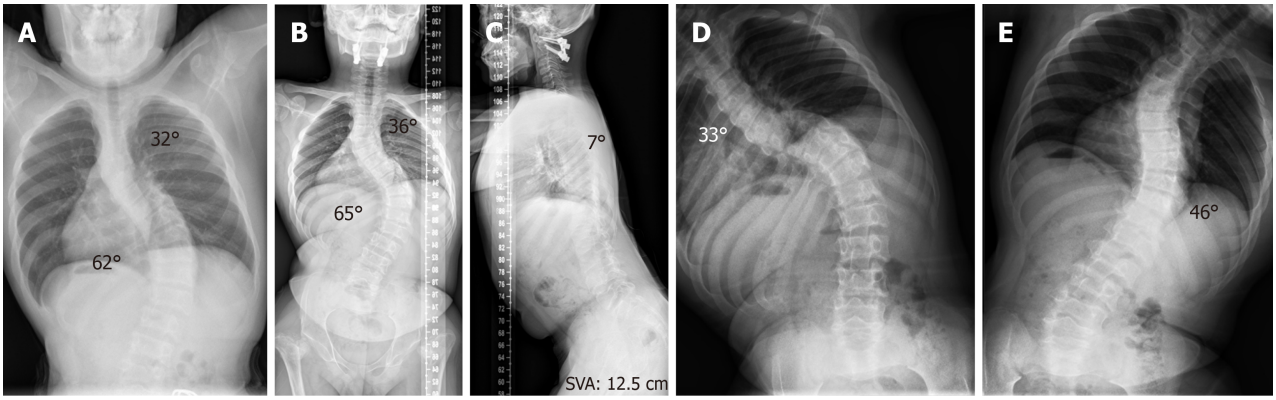
Physical examination revealed that the patient was 128 cm in height, weighed 46 kg, and was unable to ambulate steadily. There was a right-sided thoracic spine curvature, resulting in a "razorback" deformity. The patient exhibited decreased proximal muscle strength in both lower limbs (grade IV), and bilateral Hoffman signs and Babinski signs were positive.

Laboratory examinations

Ventilation function, electrocardiogram, echocardiogram, and other preoperative examination results were normal. Blood calcium, phosphorus, vitamin D, and alkaline phosphatase levels were normal for bone metabolism.

Imaging examinations

During the initial outpatient examination, the spine X-ray indicated a leftward proximal thoracic curve of 32° and a rightward main thoracic curve of 65° (Figure 1A). Three months following atlantoaxial decompression and fixation surgery, and prior to scoliosis correction, the spine X-rays revealed the proximal thoracic curve was 36°, the main thoracic curve was 65°, the thoracic kyphosis was 7°, and the sagittal vertical axis (SVA) was 12.5 cm (Figure 1B and C). On the bending X-rays, the Cobb angle of the proximal thoracic curve was 33°and the main thoracic curve was 46° (Figure 1D



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Figure 1 Preoperative X-ray data of the spine. A: The spine X-ray taken during the first outpatient clinic indicates a leftward proximal thoracic curve (PTC) of 32° and a rightward main thoracic curve (MTC) of 65°; B: Before scoliosis correction, the standing spine X-ray reveals the PTC is 36° and the MTC is 65°; C: The thoracic kyphosis is 7° and the sagittal vertical axis is 12.5 cm; D and E: On the bending X-rays, the Cobb angle of the PTC is 33°and the MTC is 46°.

and E). Computed tomography (CT) three-dimensional (3D) reconstruction of the spine showed flattening of the vertebral body and widespread narrowing of the intervertebral space (Figure 2A-C). 3D CT of the cervical spine showed dysplasia of the odontoid process of the axis and the anterior and posterior arches of the atlas (Figure 3A and B). Spinal CT showed shorter pedicle screw lengths in the thoracic and lumbar vertebrae (2.94–5.17 cm), but the cancellous bone of the pedicles was well developed. A hip X-ray revealed dysplasia of bilateral hip joints and severe damage to the femoral heads. No obvious abnormality was found on the X-ray of bilateral knee joints and the full-length of both lower limbs (Figure 3C-E). Magnetic resonance imaging (MRI) of the spine indicated stenosis of the cervical spinal canal in the atlantoaxial region and myelopathy of the cervical spine (Figure 4C). The spinal MRI did not reveal other intraspinal abnormalities. The appearance of the patient before scoliosis surgery is shown in Figure 2D and E.

FINAL DIAGNOSIS

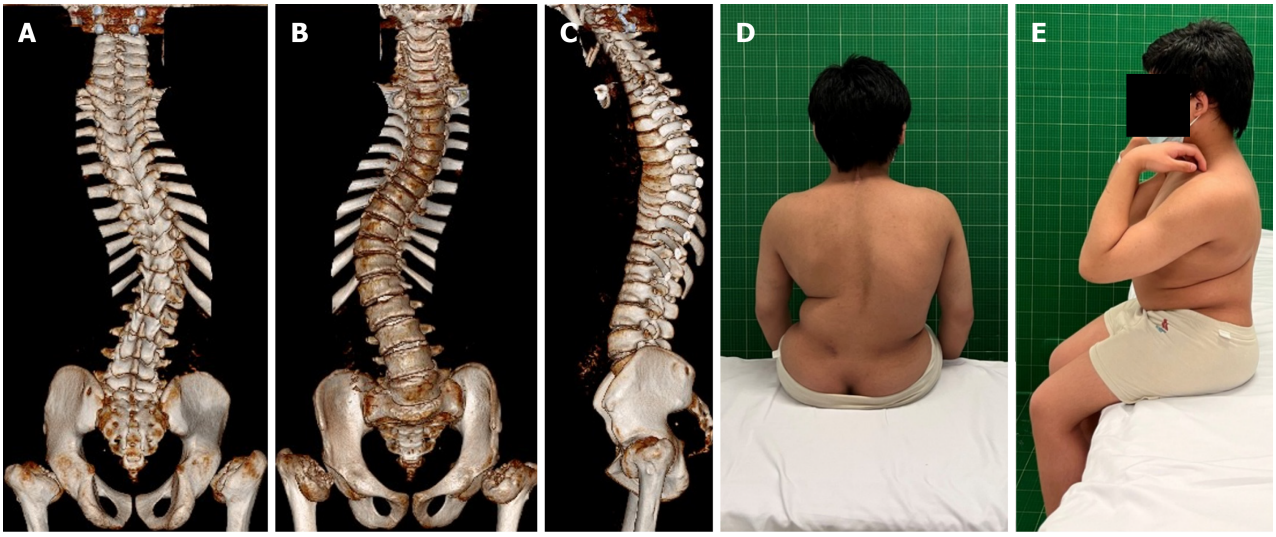
Combined with the patient's medical history and gene detection results (Figure 5), a diagnosis of SEDC was made.

TREATMENT

To avoid irreversible damage caused by cervical myelopathy, the patient was recommended to have atlantoaxial decompression and fixation surgery. Skull traction was implemented under anesthesia during the surgical procedure, and the atlantoaxial reduction was observed to be satisfactory. Consequently, one-stage posterior atlantoaxial reduction and fixation procedure was employed. During the procedure, lateral mass screws were placed on both sides of the atlas and pedicle screws were placed on both sides of the axis and fixed with connecting plates, and autogenous iliac cancellous bone were used for bone graft fusion. Three months after the operation, the patient underwent posterior spinal fusion, internal fixation, and bone graft fusion from T3 to L4 to treat his deteriorating scoliosis. During the surgery, Smith–Petersen osteotomies were performed within the fusion range to fully release the spine, and pedicle screws were inserted between T3 and L4. Autogenous combined with allogeneic bone particles were used for Moe bone grafting. Intraoperative blood loss was 450 mL, and the duration of surgery was 3.6 h. No abnormality was identified during intraoperative spinal cord monitoring.

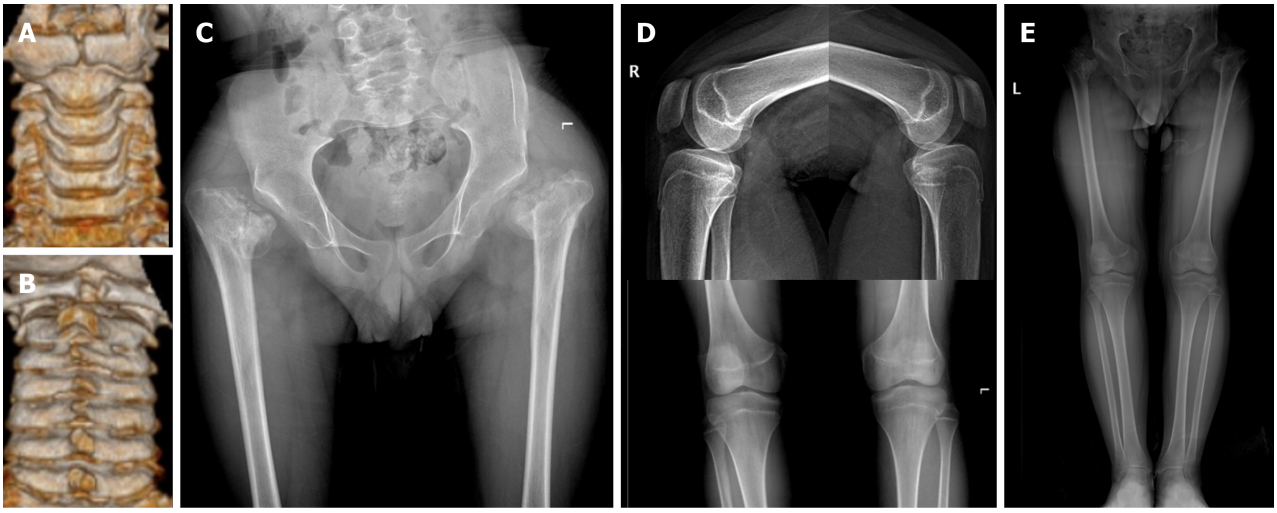
OUTCOME AND FOLLOW-UP

The patient was successfully extubated and recovered smoothly after both surgeries. After the atlantoaxial decompression and fixation surgery, the compression of the cervical spinal cord was significantly relieved, and the instability of the atlantoaxial joint was improved (Figure 4). Before the corrective surgery of scoliosis, the patient's muscle strength of bilateral proximal lower limbs was significantly improved to grade V. The Hoffman signs and Babinski signs were negative. One week after corrective surgery for scoliosis, the spinal X-ray revealed significant correction of scoliosis with the main thoracic curve corrected from 65° to 10°, thoracic kyphosis corrected from 7° to 26°, SVA corrected from 12.5 cm to 3.2 cm, and considerable improvement in the back's unevenness (Figure 6A-D). At the postoperative 2-year follow-up, the patient reported no symptoms of discomfort, such as back pain and weakness of the lower extremities, the atlantoaxial joint reduction remained effective and spinal correction retained its stability (Figure 6E-H).



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Figure 2 Preoperative computed tomography three-dimensional reconstruction of the spine and preoperative appearance. A-C: Computed tomography three-dimensional of the spine shows postoperative changes of atlantoaxial vertebrae, scoliosis, flattening of the vertebral bodies, and dysplasia of the femoral head; D: Views from the back show unevenness of the back and right deviation of the trunk; E: Lateral views before the operation.

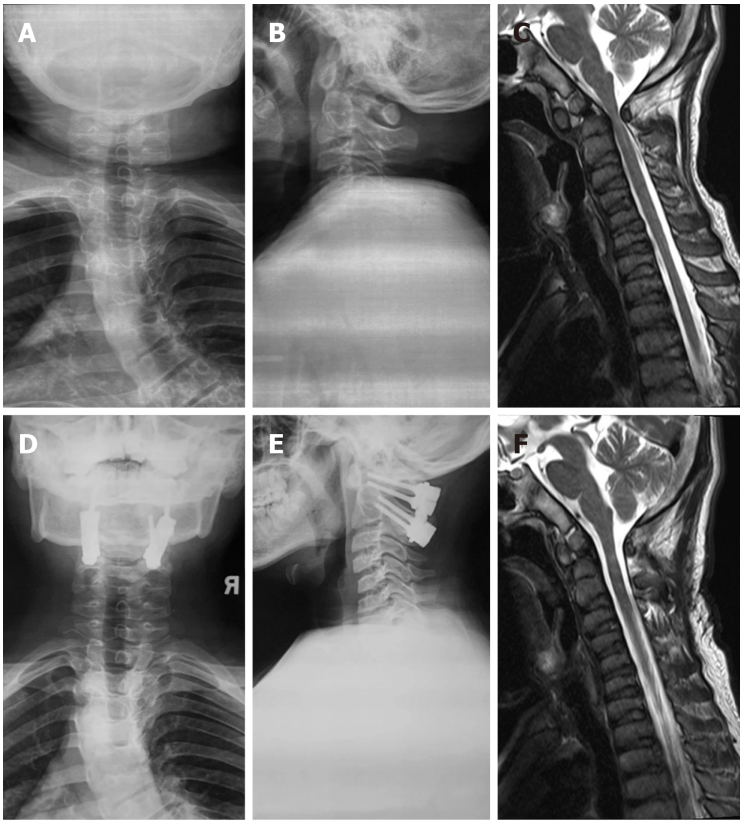


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Figure 3 Computed tomography three-dimensional reconstruction of the cervical spine and X-ray of the hip. A: The view from the front shows dysplasia of the anterior arch of the atlas and the odontoid process of axis; B: The view from the back shows dysplasia of the posterior arch of the atlas; C: A slight right inclination of the pelvis, dysplasia of bilateral hip joints, and severe damage to femoral heads are observed; D: No obvious abnormality is found in the X-ray of bilateral knee joints; E: X-ray of both lower limbs indicate that both lower limbs are equal in length.

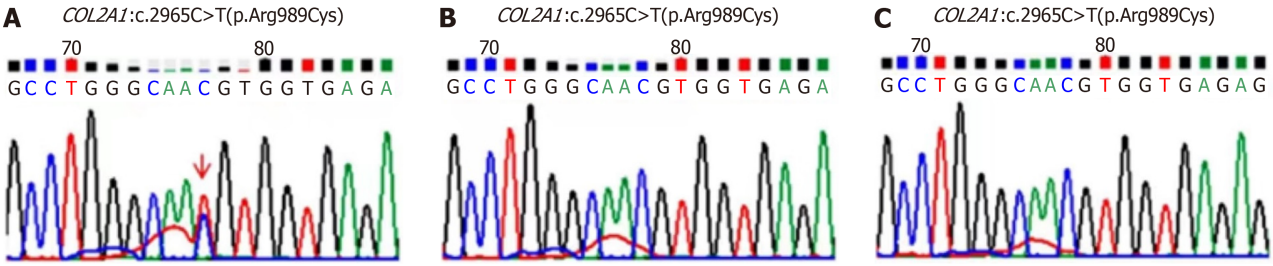
DISCUSSION

SEDC is a rare genetic disorder that affects skeletal growth and development. Diagnosis of SEDC involves a combination of clinical examinations, radiographic imaging, and genetic testing[1,11]. The radiographic findings typically include flattened vertebrae, shortened long bones, and hip dysplasia. Due to the low incidence of SEDC and its main clinical feature of short stature, it can be easily confused with relatively common skeletal dysplasia that also cause short stature, such as osteogenesis imperfecta, multiple epiphyseal dysplasia, and achondroplasia[12-14]. In addition, mutations in COL2A1 can cause various skeletal dysplasia, such as Kniest and Stickler dysplasia, which can also be easily confused with SEDC[15]. Therefore, it is sometimes difficult to distinguish SEDC from these diseases based only on clinical examination and imaging findings. However, genetic testing can confirm the diagnosis and identify the specific genetic mutation responsible for the disorder. Consequently, genetic testing has become an important tool for the diagnosis of SEDC. Barat-Houari *et al*[15] analyzed the phenotypes and genetic diagnoses of over 700 patients with type II collagenopathy and identified 415 different COL2A1 mutations. Our patient presented with skeletal dysplasia in infancy; however, owing to the lack of genetic testing at that time, the diagnosis was not confirmed until the patient was 16 years of age. His genetic testing revealed a COL2A1 heterozygous mutation c.2965C>T(p.Arg989Cys), which is the most



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Figure 4 Imaging data of atlantoaxial dysplasia before and after surgical treatment. A and B: Preoperative X-ray shows the widening of space between the anterior arch and odontoid process and dysplasia of the odontoid process; C: Preoperative MRI shows atlas-level spinal canal stenosis, spinal cord compression, and mild degeneration; D and E: Postoperative X-ray shows atlantoaxial fixation and fusion; F: The compression of the atlantoaxial spinal cord is relieved after the operation.

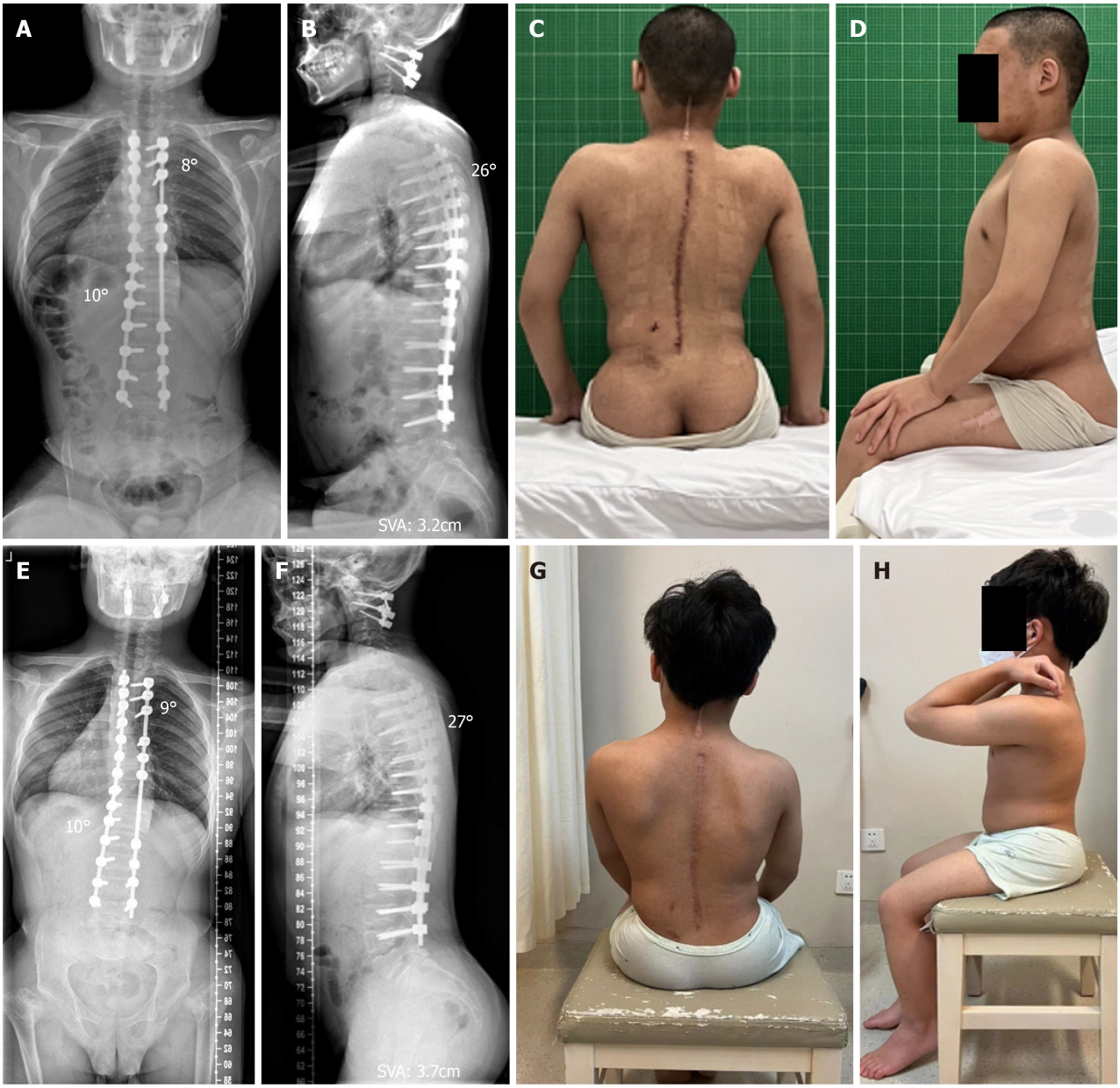


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Figure 5 Gene detection and Sanger sequencing in patients' pedigrees. A: The COL2A1 heterozygous mutation c.2965C>T(p.Arg989Cys) was found in the proband; B and C: The same pathogenic mutation was not found in the parents of the proband.

common mutation associated with SEDC[15]. The spectrum of gene mutations in SEDC will be further expanded and may guide the treatment of SEDC[16]. Genetic testing should be recommended for patients with clinical and radiological evidence suggestive of SEDC. Early diagnosis is crucial for providing appropriate follow-up treatment recommendations and genetic counselling for families affected by SEDC.

Currently, there are no specific therapeutic interventions for COL2A1 mutations, and treatments primarily focus on managing skeletal deformities. Surgical treatment for SEDC aims to correct deformities and prevent complications, such as joint pain, stiffness, and spinal cord compression. Treating hip dysplasia in SEDC can be challenging owing to the severe deformity and small volume of femoral heads, and often concomitant knee and spinal deformities. However, developmental dysplasia of the hip is an important factor that affects the walking ability of patients with SEDC. Shetty *et al*[17] performed bilateral valgus-extension osteotomy with hybrid external fixation in eight adolescent patients with SEDC who were followed up for 2 years and found significant improvements in the Harris hip score and postoperative mobility. Bayhan *et al*[10] reported that in children with SEDC, correcting the hip dysplasia by valgus hip osteotomy can maintain satisfactory walking function during 5 years of follow-up and improve hip mobility. Bisht *et al*[18] used CT to reconstruct the 3D structure of the hip joint and visualize the anatomical structure of the femoral head and neck, which was helpful for selecting implant sizes. Scheduled hip surgery can improve walking ability and delay the progression of



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Figure 6 Images and appearance at one week and two years after the operation. A: Spinal X-ray one week after operation showed that the Cobb angles of the proximal thoracic curve and main thoracic curve were 8° and 10°, respectively; B: The thoracic kyphosis was 26°, and the sagittal vertical axis (SVA) was 3.2 cm; C: Postoperative appearance from the back showed improvements in the unevenness of the back and balance of the trunk; D: Postoperative lateral appearance; E: Spinal X-ray two years after operation showed that the correction of scoliosis remained stable, with the Cobb angles of the proximal and main thoracic curves of 9° and 10°, respectively; F: The sagittal plane remained balanced with a SVA of 3.7 cm, and the thoracic kyphosis was 27°; G and H: The appearance of the back remained good.

hip joint osteoarthritis. However, our patient missed the opportunity for timely hip osteotomy surgery due to a lack of early diagnosis of SEDC. Even though the patient had severe bilateral hip joint damage, the presence of neurological damage due to atlantoaxial dysplasia makes it crucial to prioritize saving neurological function. Additionally, it was observed that the Cobb angle of scoliosis was still increasing three months after atlantoaxial decompression and fixation surgery. To avoid the potential need for more extensive surgery if scoliosis worsens, the decision was made to undergo scoliosis correction surgery before hip replacement surgery.

Among the various skeletal abnormalities associated with SEDC, atlantoaxial dysplasia is common and poses a serious threat to the patient's health. Liu *et al*[19] reported a case of SEDC complicated with atlantoaxial instability, spinal cord compression at the cranio-cervical junction, and quadriplegia. The patient underwent decompression of the cranio-cervical region and occipital-C4 fusion surgery, which improved neurological function after the operation. Serhan *et al*[20] performed upper cervical spine fusion with autogenous iliac crest bone grafting in 20 children clinically diagnosed with SEDC who were followed up for 8 years and reported that the instability of the upper cervical spine was significantly improved, and the bone graft fusion remained stable without any non-union. Miyoshi *et al*[9] analyzed seven patients with SEDC complicated with atlantoaxial subluxation who underwent reduction and fusion surgery and found that when

the diameter of the atlantoaxial spinal canal was less than 10 mm, atlantoaxial plate removal and occipital-cervical fusion were recommended. Al Kaissi *et al*[21] retrospectively analyzed 10 patients with SEDC and found that orthopedic treatment should begin with cervical spine evaluation to avoid severe neurological dysfunction or death. Multiple skeletal abnormalities were detected during the initial examination of our patient. However, atlantoaxial dysplasia exerted the greatest impact on the patient's quality of life. Therefore, atlantoaxial decompression and fixation surgery were recommended, resulting in improved muscle strength and the prevention of further spinal cord damage. From our perspective, surgery for atlantoaxial deformity should be performed promptly if atlantoaxial instability or cervical spinal cord compression is found.

Reports of successful scoliosis correction surgery in patients with SEDC are rare. Beighton *et al*[22] reported two cases of SEDC combined with scoliosis, both of which underwent posterior spinal fusion with Harrington instrumentation; however, the surgeries were unsuccessful. Winter *et al*[23] performed posterior spinal fusion with Harrington instrumentation in two patients with SEDC; during the follow-up period, one patient maintained good correction for 7 years, while the other experienced internal fixation failure due to pseudoarthrosis. Morita *et al*[7] used Luque rods to treat severe thoracolumbar kyphoscoliosis in a patient with SEDC. Although the correction was stable for 6 years postoperatively, scoliosis and kyphosis correction rates were only 10.5% and 25.9%, respectively. With the advancement of pedicle screws, posterior spinal fusion is believed to achieve a good corrective effect[24]. In this study, a high scoliosis correction rate of 84.6% was achieved through one-stage posterior spinal fusion, and there was no internal fixation failure or loss of correction during the 2-year follow-up. The high correction rate may be due to the use of a pedicle screw. In addition, the appropriate timing of treatment is also an important factor, as our patient's preoperative curve angle was 65°, which was smaller than in the five previously reported cases[7,22,23]. Furthermore, the preoperative spinal CT revealed that although the vertebral body in SEDC patients is small and flat, the cancellous bone of the pedicles developed well, suggesting that pedicle screw technology is suitable for scoliosis correction in SEDC. The selection of the upper and lower instrumented vertebrae (UIV and LIV) was also a crucial aspect of the pre-operative planning. Before surgery, the patient had balanced shoulders. The bending X-ray revealed that the proximal thoracic curve exceeded 25°, indicating the necessity for fusion[25]. Consequently, T3 was chosen as the UIV. As for the LIV, the center sacral vertical line (CSVL) passed between the pedicles of L4 in the bending X-ray. However, CSVL did not touch the pedicle of L3, so we opted to select L4 as the LIV. Our case suggests that a reasonable surgical plan, in combination with early treatment of scoliosis can achieve good results.

CONCLUSION

This is the first case report of a patient with SEDC who successfully underwent surgeries for atlantoaxial dysplasia and scoliosis. Early diagnosis of SEDC is important for providing appropriate treatment recommendations, and genetic testing is useful in confirming the diagnosis. Orthopedic evaluation of SEDC should begin with the cervical spine, as atlantoaxial dysplasia can be particularly detrimental. Early surgical intervention for hip dysplasia and scoliosis can result in favorable treatment outcomes. The use of pedicle screws may enhance the efficacy of scoliosis correction in patients with SEDC.

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FOOTNOTES

Author contributions: Cai HY collected data from medical records; Zhao JD reviewed the radiographs; Jiao Y wrote the manuscript; Huang XA provided intellectual support; Shen JX finalised the manuscript and was responsible for this; All authors reviewed the manuscript; Final approval of the manuscript has been obtained from all authors.

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CASE REPORT

Recurrent cyclops lesion after primary anterior cruciate ligament reconstruction using bone tendon bone allograft: A case report

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Abstract

BACKGROUND

Cyclops lesions are a known complication of anterior cruciate ligament (ACL) reconstruction, with symptomatic cyclops syndrome occurring in up to 11% of surgeries. Recurrent cyclops lesions have been rarely documented; this case study documents the successful treatment of a recurrent cyclops lesion.

CASE SUMMARY

A 28-year-old female presented following a non-contact injury to the right knee. Workup and clinical exam revealed an ACL tear, and arthroscopic reconstruction was performed. Two years later a cyclops lesion was discovered and removed *via* arthroscopic synovectomy. Seven months postoperatively, the patient presented with pain, stiffness, and difficulty achieving terminal extension. A smaller recurrent cyclops lesion was diagnosed, and a repeat synovectomy was performed. The patient recovered fully.

CONCLUSION

To the best of our knowledge, this is the first documented case of recurrent cyclops lesion after bone-patellar tendon-bone allograft ACL reconstruction presenting as cyclops syndrome.

Key Words: Anterior cruciate ligament; Cyclops lesion; Cyclops syndrome; Knee arthroscopy; Anterior cruciate ligament reconstruction; Case report

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Core Tip: A 28-year-old female presented following a noncontact injury to the right knee. Workup and clinical exam revealed an anterior cruciate ligament tear, and arthroscopic reconstruction was performed. Two years later a cyclops lesion was discovered and removed *via* arthroscopic synovectomy. Seven months postoperatively, the patient presented with pain, stiffness, and difficulty achieving terminal extension. A smaller recurrent cyclops lesion was diagnosed, and a repeat synovectomy was performed. The patient recovered fully.

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INTRODUCTION

The cyclops lesion is a known complication following anterior cruciate ligament (ACL) reconstruction[1]. Initially described by Jackson and Schaefer[2] in 1990, a nodule of fibrous tissue with central granulation forms on the anterior aspect of the ACL graft and encroaches upon the intercondylar space. When this lesion is associated with a loss of terminal extension accompanied by symptoms such as pain, stiffness, or clunking with full extension, it is referred to as cyclops syndrome[2]. The incidence of cyclops lesions following ACL reconstruction is 25%-47%; however, many of these cases are asymptomatic, do not require surgical intervention, and are not associated with inferior clinical outcomes[3,4]. The rate of symptomatic cyclops lesions presenting as cyclops syndrome is much lower, at 0%-11%[5-8].

When a patient presents with an extension deficit following ACL reconstruction, magnetic resonance imaging (MRI) is the standard of diagnosis for cyclops lesions[3,5,8,9]. Physical therapy (PT) alone is not sufficient to restore full range of motion, arthroscopy with lesion excision is recommended[3,5,8]. Surgical management generally results in long-term resolution of the extension deficit[8-11]. In rare cases the cyclops lesion can recur. Only one such case was documented over two decades ago as part of a larger study on MRI of cyclops lesions[5]. In this report, we present the investigation of a recurrent cyclops lesion in a patient who sustained an ACL tear which was reconstructed using a bone-patellar tendon-bone allograft and ultimately underwent successful resection and rehabilitation.

CASE PRESENTATION

Chief complaints

A 28-year-old female patient presented to the clinic with a sports-related noncontact injury to her right knee.

History of present illness

The patient experienced a noncontact injury to her right knee while playing soccer nine days prior to presentation. She reports difficulty ambulating and instability in the knee.

History of past illness

No prior knee injuries.

Personal and family history

Personal and family history was non-contributory.

Physical examination

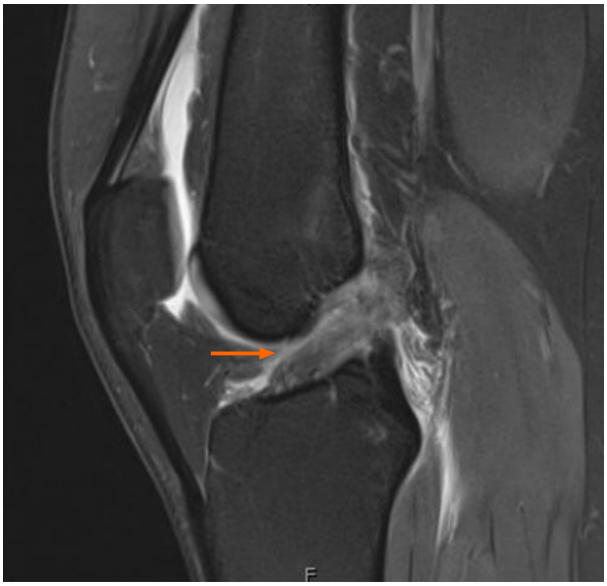
Examination revealed a painful right knee with effusion, tenderness along the lateral joint line, and positive Lachman test.

Imaging examinations

MRI demonstrated a complete tear of the ACL with associated bone contusions (Figure 1).

FINAL DIAGNOSIS

Recurrent cyclops lesion.



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Figure 1 Sagittal T2-weighted fast spin echo sequence magnetic resonance imaging (3 tesla magnet) revealed complete tear of the right anterior cruciate ligament (orange arrow).

TREATMENT

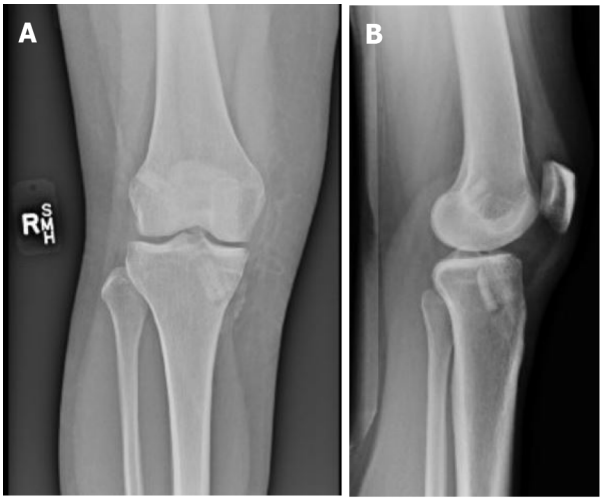
One week after initial presentation she was re-evaluated and arthroscopic ACL reconstruction was recommended, graft options were reviewed with the patient and a bone tendon bone allograft was selected as her graft of choice. She was provided a derotational brace, and referral to PT. Approximately 2.5 mo following the initial injury, reconstruction of the right ACL using bone-patellar tendon-bone allograft was performed. Body mass index (BMI) at the time of surgery was 29.9 kg/m^2. The femoral tunnel was prepared using an anteromedial portal technique utilizing a limited notchplasty. Bioabsorbable interference screws were used for both femoral and tibial fixation. The knee was placed in extension with a posterior drawer applied to the proximal tibia for final fixation. Figure 2 shows postoperative X-rays indicating appropriate tunnel placement. There were no complications and recovery and PT progressed as expected. She returned to all activities without restrictions.

Two years after the ACL repair, the patient sustained a repeat injury to her right knee, presenting about a month after this incident. The patient reported feeling a pop and medial-sided knee pain. Physical examination revealed swelling, medial joint line tenderness, and positive McMurray test. Radiographs were unremarkable. MRI demonstrated an intact ACL graft with a moderate-sized cyclops lesion estimated at a size of 16 mm × 17 mm × 11 mm (Figure 3). After 8 wk of PT, she still complained of stiffness and moderate pain with knee extension. Right knee arthroscopic synovectomy was recommended, and the patient proceeded with surgery approximately 1 mo later. BMI at the time of surgery was 26.7 kg/m^2.

Intraoperatively, there was an isolated cyclops lesion appreciated at the insertion of the ACL on the proximal tibia, which impinged in the intercondylar notch with terminal extension (Figure 4). A biter and mechanical shaver were used to remove the lesion. Both the ACL and posterior cruciate ligament (PCL) were noted to be intact. Femoral and tibial tunnels were found to be in appropriate position without evidence of notch impingement. Arthroscopic images were taken of the intact cyclops lesion, pre and post arthroscopic debridement. The patient was found to have a stable knee on examination under anesthesia. There were no surgical complications. Postoperatively PT was started immediately, emphasizing obtaining terminal extension with unrestricted passive and active motion. Knee Injury and Osteoarthritis Outcome Score (KOOS) was 76.33 6 wk following surgery.

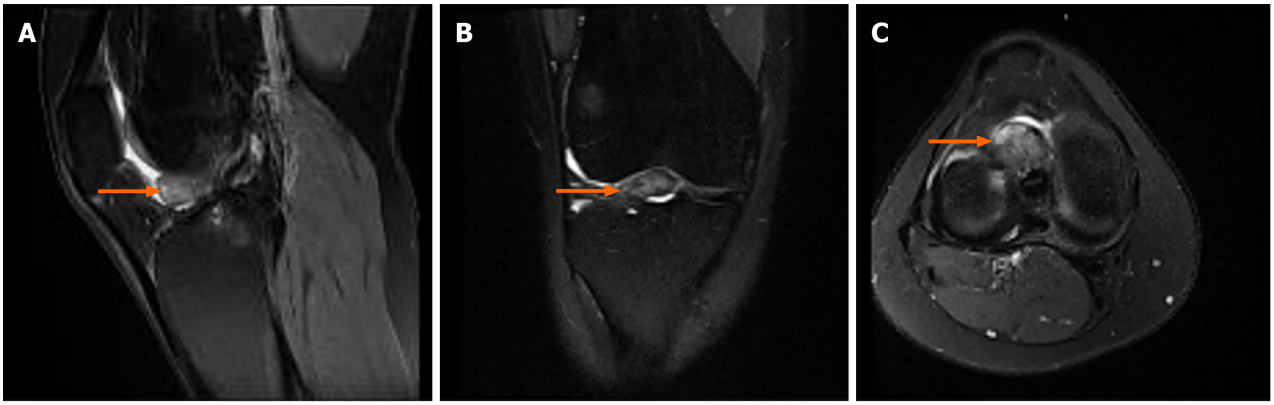
Seven months postoperatively, the patient presented with complaints of tightness and stiffness of her right knee, difficulty achieving terminal extension, and pain in the anteromedial aspect of her right tibia. An MRI was obtained, demonstrating intact ACL reconstruction with a smaller recurrent mass estimated at a size of 5 mm × 9 mm × 10 mm along the anterior margin of the distal ACL consistent with a recurrent cyclops lesion (Figure 5). Recurrent arthroscopic debridement was recommended after 8 wk of PT failed to improve her symptoms. Biopsy at the time of surgical intervention was also recommended to evaluate for recurrent synovial lesions such as pigmented villonodular synovitis. Two months later, the patient proceeded with a right arthroscopy and debridement of the right knee. BMI at the time of surgery was 27.1 kg/m^2. KOOS one week prior to surgery was 44.91.

Repeat arthroscopy demonstrated a recurrent cyclops lesion adjacent to the anterior aspect of the ACL reconstruction (Figure 6). The ACL and PCL were intact. The medial and lateral compartments showed no meniscus tears or arthritis. A straight biter and grasper were used to obtain biopsies of the cyclops lesion. A mechanical shaver was then used to remove the cyclops lesion in its entirety from the intercondylar notch. Full range of motion with terminal flexion and extension was verified. Arthroscopic images were taken, and the recurrent cyclops lesion was sent for biopsy. Surgery was completed with no complications.



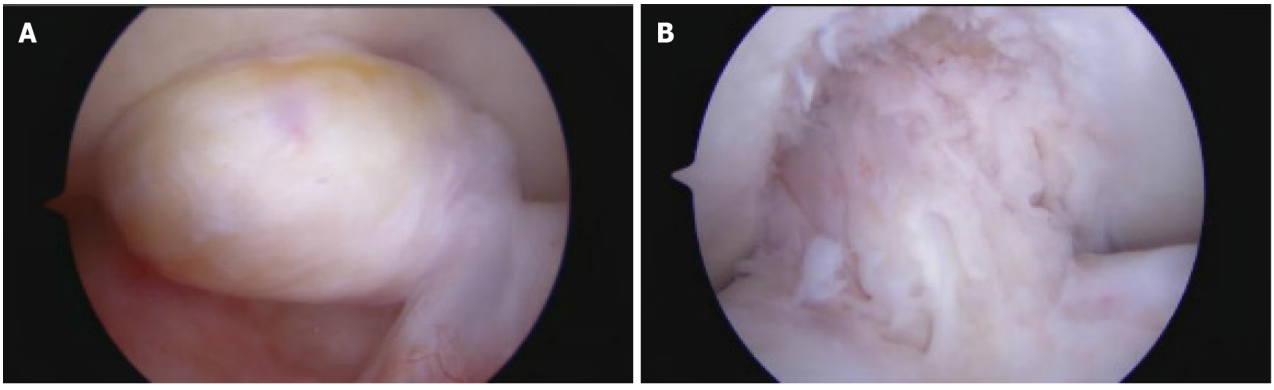
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Figure 2 Postoperative X-ray indicating the correct position of the femoral and tibial tunnels. A: Anteroposterior; B: Lateral.



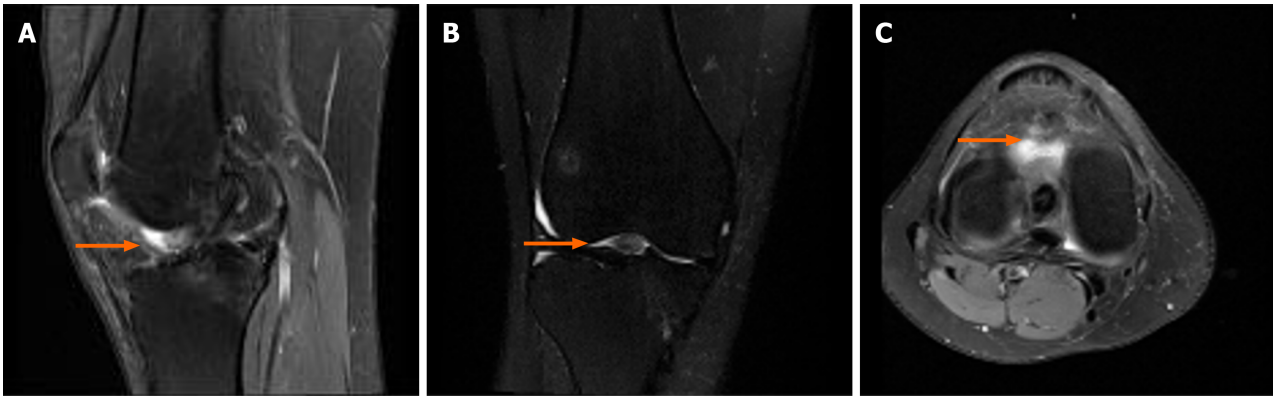
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Figure 3 Postoperative magnetic resonance imaging right knee. A: Magnetic resonance imaging films (3 tesla magnet) in sagittal proton-density fast spin echo with fat saturation (PD FSE FSAT) sequence (orange arrow); B: Coronal T2-weighted FSE FSAT sequence (orange arrow); C: Axial PD FSE FSAT sequence views taken after anterior cruciate ligament reconstruction with cyclops lesion measuring 16 mm × 17 mm × 11 mm (orange arrow).



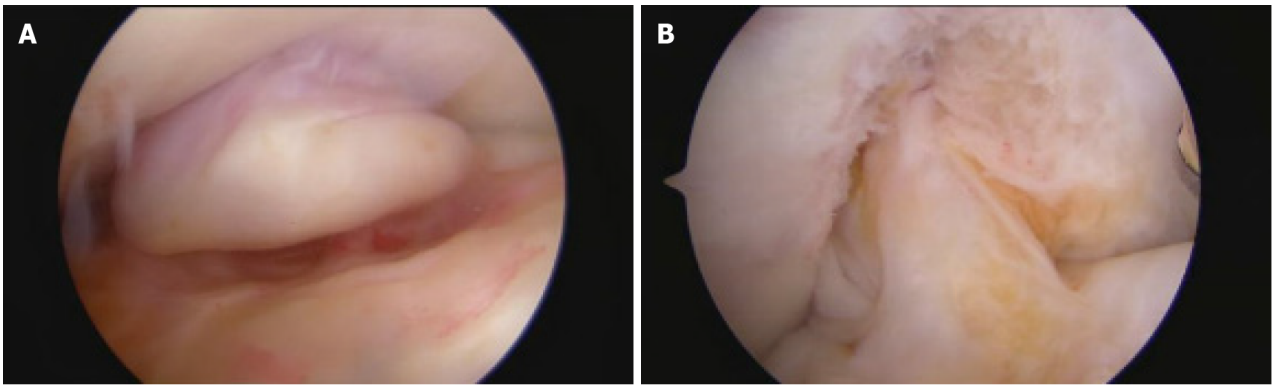
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Figure 4 Images taken during arthroscopic limited debridement of the right knee. A: Cyclops lesion at the proximal insertion of the anterior cruciate ligament; B: The intercondylar notch following removal of the lesion.



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Figure 5 Postoperative magnetic resonance imaging right knee. A: Magnetic resonance imaging films (3 tesla magnet) in sagittal proton-density fast spin echo with fat saturation (PD FSE FSAT) sequence (orange arrow); B: Coronal T2-weighted FSE FSAT sequence (orange arrow); C: Axial PD FSAT sequence views demonstrated a recurrent cyclops lesion of right anterior cruciate ligament graft with an estimated size of 5 mm × 9 mm × 10 mm (orange arrow).



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Figure 6 Images captured during repeat arthroscopy of the right knee. A: Recurrent cyclops lesion; B: The intercondylar notch following debridement.

Pathologic analysis determined the excised mass was composed of synovial tissue with fibrosis and reactive fibrocartilage, consistent with a recurrent cyclops lesion. At 6 wk postoperatively, the patient was progressing through PT and was able to achieve terminal extension. The patient attended PT for 8 wk. By the end of PT, right knee active range of motion (ROM) reached 0-140 degrees, symmetric with the contralateral knee. Upon completion of PT she was able to resume all activities without restrictions.

OUTCOME AND FOLLOW-UP

Nineteen months after arthroscopy for recurrent cyclops lesion, the patient retained full function of the knee with no recurrent stiffness, full active and passive ROM, and able to perform all normal daily and athletic activities without pain; she denies any local recurrence to date. KOOS was 100 and Lysholm score was 100% at final follow up.

DISCUSSION

The mechanism of development and risk factors for cyclops lesions are still under investigation, and the incidence of recurrent cyclops lesions is sparsely documented. The commonly proposed origin of cyclops lesions is development as a result of an inflammatory reaction to remnants of the ruptured ACL[1,6]. Studies have found preservation of ACL remnants was not associated with cyclops lesions or cyclops syndrome, and minimal debridement during ACL repair did not increase incidence of cyclops lesions[4,6,8]. Tomihara *et al*[12] recently found that bone-patellar-tendon-bone autograft, female sex, and increased BMI were significant risk factors for cyclops lesions and syndrome. Conversely, Facchetti *et al*[3] reported no association of cyclops lesion incidence with factors such as graft type or sex but did find a positive correlation with lower patient BMI. Based on direct contradictions in the literature, it is difficult to theorize which demographic or surgical factors may have influenced the repeated development of cyclops lesions in our patient. Additional factors that have been associated with the development of cyclops lesions following ACL reconstruction

include increased graft volume, double-bundle grafts, smaller femoral and tibial tunnel diameter and excessively anterior tibial tunnels, although none of these appear to be contributory in our patient[7,13,14].

It is suggested that early loss of extension following ACL reconstruction allows space for the cyclops lesion to form[4,6,15]. Gohil *et al*[4] found that multiple patients who experienced loss of extension 2 mo postoperatively did not demonstrate cyclops lesion on MRI, but they subsequently developed cyclops lesions with smaller extension deficits. At 3 and 6 wk postoperatively, Pinto *et al*[15] reported an extension deficit was associated with a significant increase in the incidence of cyclops lesions. The major risk factor for cyclops syndrome discovered by Delaloye *et al*[6] was an extension deficit at 3 and 6 wk following ACL reconstruction. The patient presented in our case progressed well through PT following both her ACL reconstruction and initial cyclops lesion excision and at no point in time did she have an extension deficit.

The only other known case of a recurrent cyclops lesion was reported by Bradley *et al*[5] in their investigation of the utility of MRI for diagnosis of cyclops lesions; four months following excision of the initial lesion, one patient demonstrated a recurrent cyclops lesion. The major difference between this case and our case lies in the presentation; the Bradley *et al*[5] lesion was discovered incidentally on postoperative MRI, whereas our patient returned 7 mo postoperatively with cyclops syndrome. Previous literature reports cyclops lesions are predominantly asymptomatic, do not confer poorer clinical outcomes, and do not show an association between lesion size and pain or other symptoms[3]. It is unclear to what extent our patient's cyclops lesions contributed to her clinical presentation. A key aspect may have been the trauma of her repeated valgus injuries, the first causing her ACL tear and the second about two years after the repair. Both recurrent cyclops lesions were successfully managed with repeat arthroscopy and excision[5].

CONCLUSION

While cyclops lesions following ACL reconstruction are a common complication, recurrent cyclops lesions are minimally documented. Here, we describe what is, to the best of our knowledge, the first known case of a recurrent cyclops lesion presenting as cyclops syndrome. Future studies should be aimed at reconciling which demographic and surgical factors contribute to the development of cyclops lesions and syndrome.

FOOTNOTES

Author contributions: Kelmer G was responsible for investigation, data curation and writing-original draft; Johnson AH was responsible for conceptualization, investigation, data curation, writing-review and editing; Turcotte JJ was responsible for writing-review and editing and supervision; Redziniak DE was responsible for conceptualization, writing-review and editing and supervision.

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ORIGINAL ARTICLE

Retrospective Study

Role of lateral soft tissues release in percutaneous hallux valgus correction: A medium term retrospective study

Fabio Zanchini, Ottorino Catani, Fabrizio Sergio, Alessia Boemio, Angelo Sieczak, Davide Piscopo, Salvatore Risitano, Gabriele Colò, Federico Fusini

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Abstract

BACKGROUND

In the field of minimally invasive surgery (MIS) for the treatment of hallux valgus (HV), different techniques have begun to emerge in the literature concerning the distal osteotomy of the first metatarsal bone, the synthesis or not of the metatarsal head, the possible association with lateral soft tissues release (LSTR) and osteotomy of the base of the first phalanx.

AIM
To evaluate the role of LSTR on percutaneous HV correction, evaluating functional and radiographical results.

METHODS
From January 2012 to May 2016 a total of 396 patients with mild to moderate symptomatic HV treated with the MIS technique were included in this retrospective study. The technique provides no internal fixation (WOS). Patients were divided into the LSTR group and no LSTR group (LSTR N). This surgical procedure (LSTR) was reserved for insufficient HV angle (HVA) correction during fluoroscopic control. Patients were evaluated at each follow-up by two other authors after appropriate training by senior authors (first practitioners). Clinical evaluation was performed before surgery, 6 mo after surgery, and 48 mo follow-up. American Orthopaedic Foot and Ankle Society (AOFAS) and visual analog scale (VAS) score was used to evaluate pain and function, and complications were recorded. In addition, the incidence of relapses and the degree of joint range of motion (ROM) with the association with the LSTR (capsule, adductor tendon, phalanx-sesamoid ligament, and the deep transverse metatarsal ligament) were evaluated. Radiological parameters included HVA and intermetatarsal angle (IMA). Patient satisfaction was assessed. Student *t*-test and Fisher exact test were used to assess statistical analysis.

RESULTS
From our study it is clear that no differences in term of HVA, VAS, IMA correction, rate of complications, and AOFAS score were found between groups, while a significant improvement of the same variables was found in each group between pre and postoperative values. A significant improvement in ROM at 6 mo (P = 0.018) and 48 mo (P = 0.02) of follow-up was found in LSTR N group. Complications were rare in both groups.

CONCLUSION
LSTR procedure on percutaneous HV correction seems to increase postoperative joint stiffness with a comparable incidence of relapse and a low incidence of complications.

Key Words: Hallux valgus; Percutaneous distal osteotomy; Lateral release; Minimally invasive surgery; Without ostheosynthesis; Range of motion

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Core Tip: Our study evaluated a court of 396 patients treated with percutaneous technique, pain particular attention to the influence of the lateral soft tissues release (LSTR) on postoperative joint range of motion (ROM) and hallux valgus recurrence. A significant difference in ROM was recorded in the group where the LSTR was carried out, while there was no superior incidence of relapse between groups. ROM was revealed better at follow-up in LSTR not performed group. We believe these data represent an essential element to understanding the etiopathogenesis of complications. This data also enhances the validity of minimally invasive surgery with no osteosynthesis technique.

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INTRODUCTION

Hallux valgus (HV) is a common and progressive deformity of the forefoot with a multifactorial etiology[1]. This pathology most frequently affects women between the ages of 40 and 60. This deformity occurs in younger patients when there is a pathology that causes an overload on the first ray[2]. HV is defined by a variable as angular deviation of the first ray greater than 15° with a progressive abduction and pronation of the first phalanx and adduction, pronation and elevation of the first metatarsal. In literature are described wide variety of bony procedures, including osteotomies at the level of the head, midshaft, and base of the first metatarsal, as well as arthrodesis of the first metatarsal-cuneiform joint. The surgical treatments can be associated or not with lateral soft tissues release (LSTR)[3-5]. HV's surgical management is made difficult not only by the complexity of pathology, but also by the absence of a surgical gold standard[6].

At present, minimally invasive surgery (MIS) is performed with minimal skin incisions (1-3 mm), under intraoperative X-ray guidance, and with or without internal fixation[7]. There is some confusion in the terminology used when referring to MIS or percutaneous surgery. The term percutaneous, which means made through the skin, should be utilized when there is no internal fixation (K-wire or screw), and MIS should be reserved for procedures with minimal incision but with osteosynthesis[8].

This percutaneous management combines different procedures according to the complexity of the deformity to be corrected[9-12]. These procedures have become popular among foot surgeons, most arising from the traditional open distal metatarsal osteotomy. The advantages of percutaneous procedure are: 1-d hospitalization, and decrease postoperative morbidity and shorter rehabilitation times, in addition patients better accept this technique[7,13].

The choice to perform the percutaneous technique for the correction of HV rather than open surgery is not commonly accepted among orthopedic surgeons, despite the fact that this technique has been widely used for several years and its equal efficacy, and sometimes its superiority, compared to the open technique has been widely demonstrated in the literature. The main debate is whether or not internal fixation should be used[14].

The alignment of the first ray by medial rotation of the first metatarsal head and distal metatarsal articular angle (DMAA) correction is obtained by Reverdin-Isham percutaneous osteotomy an intra-articular medial closing wedge osteotomy of the distal metatarsal, associated with an Akin osteotomy[15], both performed without osteosynthesis[10,13,16-18]. Reverdin-Isham is not a complete osteotomy, as the first metatarsal lateral cortex is preserved; the closing wedge ensures contact of the metatarsal head with the metaphysis. A special post-surgical corrective bandage makes internal fixation unnecessary. Due to early weight bearing, that technique allows the osteotomy to heal with the toe in its proper position[19].

MIS was introduced first in Spain and then in Europe by de Prado *et al*[18] and Lucas y Hernandez *et al*[20]. However, to our knowledge, no previous study has evaluated the long-term results of this technique. Thus, this prospective study aimed to evaluate the radiographic and clinical outcomes of patients with mild-to-severe HV treated by MIS with Reverdin-Isham and Akin percutaneous osteotomy following exostectomy and LSTR. The study aims to evaluate the role of LSTR on percutaneous HV correction, evaluating functional and radiographical results.

MATERIALS AND METHODS

Patients selection

From January 2012 to May 2016, 396 consecutive Caucasian patients with symptomatic HV from mild to moderate were enrolled in this study. All parties have been informed and have given their consent to the publication of the data. Of these patients, 79% (355) were women, and 10.35% (41) were men. The age ranged from 28 to 82 years (mean age 64 years). The surgical procedures were performed by two surgeons Fabio Zanchini, MD, PhD, Professor and Ottorino Catani, the supporters of MIS in southern Italy, who followed the patients in the outpatient evaluation and diagnosed the study participants. The surgical technique, the inclusion and exclusion criteria, the postoperative course, and the rehabilitation protocol were the same for both groups. Patients were evaluated at each follow-up by two other authors after appropriate training by senior authors (first practitioners). Standard follow-up was each week for the first 42 d, then at 3, 6, 9, and 12 mo, and then yearly for at least 4 years.

The inclusion criteria were: Patients with mild to moderate painful HV after at least 6 mo of conservative treatment without acceptable results. Mild to moderate bunions have been included. This criterion was defined by the evaluation of the value of the intermetatarsal angle (IMA), described as mild (IMA from 10° to 13°), moderate (IMA from 14° to 20°), and severe (IMA > 20°). Patients with concurrent deformities in the lesser toe and metatarsalgia that required an accessory surgical time of finger correction and Distal Minimally Invasive Metatarsal Osteotomy (DMMO) of the II-III-IV metatarsal were also included. The presence of a previous correction of HV on the contralateral side or bilateral deformities were not considered an exclusion criterion. Patients who underwent previous HV correction surgery on the same side, with hallux rigidus, flat foot with joint laxity, rheumatoid arthritis, or other inflammatory conditions were excluded. Patients with diabetes, peripheral neuropathy, psychiatric and infectious diseases were excluded.

All procedures were performed under regional anesthesia with a sciatic blockage at the level of popliteal fossa using a nerve stimulator to inject 10 mL of mepivacaine hydrochloride at 1.5%, with ultrasound guidance. Of the 396 patients enrolled in the study, all subjects received the same surgical treatment, postoperative protocol and rehabilitation. From them, 209 (53%) underwent additional LSTR, defined as the transverse section of the adductor hallucis and lateral hemicapsulotomy. This surgical procedure was reserved for insufficient HV angle (HVA) correction during fluoroscopic control. The other 187 patients (47%) did not require additional surgical time.

Radiographic evaluation

Radiographic examination in anteroposterior and lateral weight-bearing projection was performed in all patients in the preoperative, immediate postoperative, and during 6 wk, 3, 6, and 9 mo follow-up, and then yearly. Each time, the following parameters were evaluated: HVA (normal value < 15°) and IMA (normal value < 10°). In addition, bone callus formation and the vanishing of transparency lines were screened to exclude consolidation delay or pseudoarthrosis. The lack of consolidation was defined as the persistence of the transparency lines and lack of bone callus formation after 9 mo from surgery. HVA values in the last follow-up > 15° were considered HV relapse.

Clinical evaluation

All patients were clinically evaluated with the same protocol in the preoperative and subsequent follow-up stages. The American Orthopaedic Foot and Ankle Society (AOFAS) scale was performed preoperatively, at 6 mo, and the last follow-up (4 years) for a maximum of 100 points divided into the following categories: Toe alignment (max 15 points), functional ability (max 45 points), and pain (max 40 points). Particular emphasis was given to the range of motion (ROM) evaluation by analyzing the global extension and flection of the metatarsophalangeal joint (MTPJ) and considering > 100° of motion the normal value, as described by Shereff *et al*[21] with the ideal value of 110°. The ROM evaluation was

performed preoperatively, at 6 mo, and then at the last follow-up.

Statistical analysis

Continuous data were reported as mean and standard deviation, while categorical data were reported as rate. The statistical analysis was performed using the student *t*-test, using appropriate software Sigmaplot (Systat software Inc., San Jose, A, United States). Data of AOFAS, visual analog scale (VAS), and ROM were compared between groups where LSTR was performed (LSTR Y) and LSTR not performed (LSTR N) through a 2-tailed Student *t*-test. At the same time, the rate of non-union, metatarsalgia, and complications were evaluated between groups with Fisher exact test. The *P*-value was set at $P < 0.05$.

Surgical technique

All patients were treated with the same surgical technique, with percutaneous correction of HV (ICD-9-CM 727.1; ICD-10 M20.1), except for the group of LSTR, where latera release of soft tissue was performed. Both group wee trated with WOS technique (Figure 1). In this technique, the percutaneous osteotomy with a 2.0 mm × 12.0 mm Shannon burr (cat. 256018, FH Orthopedics SAS, Heimsbrunn, France) were performed extracapsulary in the subcapital region, perpendicular to longitudinal axis. The head can be translated up to 90% of first ray shaft diameter to recentering the sesamoids. In case of high DMAA with a curved proximal phalanx, Akin osteotomy was performed with 2.0 mm × 12.0 mm Shannon Burr. The lateral release, when performed, was obtained using a Beaver 64 scalpel (Rüttgers, Solingen, Germany). The incision is made on the most lateral part of the dorsal aspect of the MTPJ of the great toe, lateral to the extensor tendons and the scapel blade is inserted parallel to the extensor tendons. The blade is introduced deeply, entering the joint between the proximal phalangeal and metatarsal articular surfaces, until it is noted to be rubbing on the cartilage. The scapel blade is then advanced deeper until it reaches the inferolateral aspect of the base of proximal phalanx of the great toe, which is the point of insertion of the adductor tendon of the great toe. The blade is rotated 90° to orient the cutting edge laterally, and it is moved laterally. At the same time the great toe is moved medially, tensing the adductor to facilitate section of the tendon, which can be confirmed on fluoroscopy. Lateral metatarsophalangeal capsulotomy is then performed, preserving the dorsal half to avoid excessive destabilization of the joint[22].

Postoperative care

All patients followed the same postoperative protocol and were followed in the same way standardized by the two surgeons. There were no changes in postoperative protocol between groups. Weightbearing was allowed 3 h after surgery with a flat sole and rigid shoe. The bandage was maintained for 5 wk (Figure 2A), with replacement every 7-14 d. Upon removal of the bandage, patients were instructed to wear an interdigital silicone separator for two months as a night bracer. Upon removal of the bandage was prescribed the same rehabilitation protocol to all patients (10 sessions of assisted mobilizations of the I M-F, step rehabilitation, active exercises, *etc*.).

RESULTS

Forty-one male patients and 355 females were included in the study. Two-hundred-nine patients were included in the LSTR Y group, while 187 patients were included in the LSTR N group, with a mean age of 64 ± 16.02 years and 63.85 ± 16.85 years, respectively. Results of preoperative, 6 mo, and last follow-up values of HVA, IMA, ROM, AOFAS, and VAS were reported in Table 1, while the clinical feature is reported as the last case (Figure 2B). Group comparison showed no difference in the preoperative value of HVA ($P = 0.523$), IMA ($P = 0.686$), ROM ($P = 0.596$), AOFAS ($P = 0.882$), and VAS ($P = 0.924$).

A significant difference was found in ROM between groups at 6 mo ($P = 0.018423$) and the last follow-up ($P = 0.02$). No differences were found in terms of HVA at 6 mo ($P = 0.593197$), and last follow-up ($P = 0.929243$) and IMA at 6 mo ($P = 0.750608$) and last follow-up ($P = 0.649461$), AOFAS at 6 mo ($P = 0.841372$) and last follow-up ($P = 0.737018$) and VAS at 6 mo ($P = 0.263118$) and the last follow-up ($P = 0.413075$). The rate of non-union showed no significant differences between groups ($P = 0.4541$); the same was found for metatarsalgia ($P = 0.5502$).

Complications and management

No thromboembolic complications, no cases of hallux varus due to hypercorrection, and no cases of avascular necrosis were reported. No nerve injury was observed in any of the patients. Complications were observed in 37 patients (about 9%); 21 in the LSTR Y group and 16 in the LSTR N group. The reported complications showed no significant differences in the two groups ($P = 0.73$).

Four patients developed a superficial infection at the medial access to exostosis, all resolved by general and local antibiotic therapy for 4 wk. One patient developed a deep infection which was also resolved by specific antibiotic administration after isolation of the bacterium. Seven patients submitted a consolidation delay. They were treated with pulsed electromagnetic fields (2 applications per day for 30 d) and administration of clodronic acid. Four reached healing and the complete regression of the symptomatology (pain and swelling of the MTPJ) after 12 mo from surgery. Two patients developed asymptomatic pseudoarthrosis: 1 required reintervention due to pain persistence. After 6 mo, the consolidation was achieved, with regression of the symptoms but subsequent development of joint stiffness.

In 9 patients, the medial margin of the cortical created impingement with soft tissues; two patients refused reintervention, while in 7 patients, the problem was solved with percutaneous removal of the bone prominence. Eleven patients reported HV recurrence with a mild HVA value lower than the preoperative values; in 5 patients, exostosis relapsed.

Table 1 The main clinical and radiological features of patients included in the study preoperatively, at 6 mo, and at the last follow-up

	Preop		6 mo		Last follow-up	
	Soft tissue release	No soft tissue release	Soft tissue release	No soft tissue release	Soft tissue release	No soft tissue release
HVA	22.4 ± 5.26	22.74 ± 5.5	11.11 ± 2.01	11.22 ± 1.86	12.06 ± 1.39	12.07 ± 1.32
IMA	12.6 ± 1	12.61 ± 0.98	8.14 ± 1.36	8.18 ± 1.33	8.930 ± 1.35	8.99 ± 1.34
ROM	101.94 ± 9.64	102.46 ± 9.9	104.47 ± 7.9	106.28 ± 7.24	104.70 ± 6.07	105.96 ± 6.4
AOFAS	68.08 ± 8.51	67.95 ± 8.17	88.95 ± 8	88.79 ± 8	90.58 ± 6.3	90.37 ± 6.41
VAS	4.41 ± 1.12	4.42 ± 1.14	1.28 ± 1.01	1.39 ± 0.99	0.93 ± 0.76	0.99 ± 0.74

HVA: Hallux valgus angle; IMA: Intermetatarsal angle; ROM: Range of motion; AOFAS: American Orthopaedic Foot and Ankle Society; VAS: Visual analog scale.



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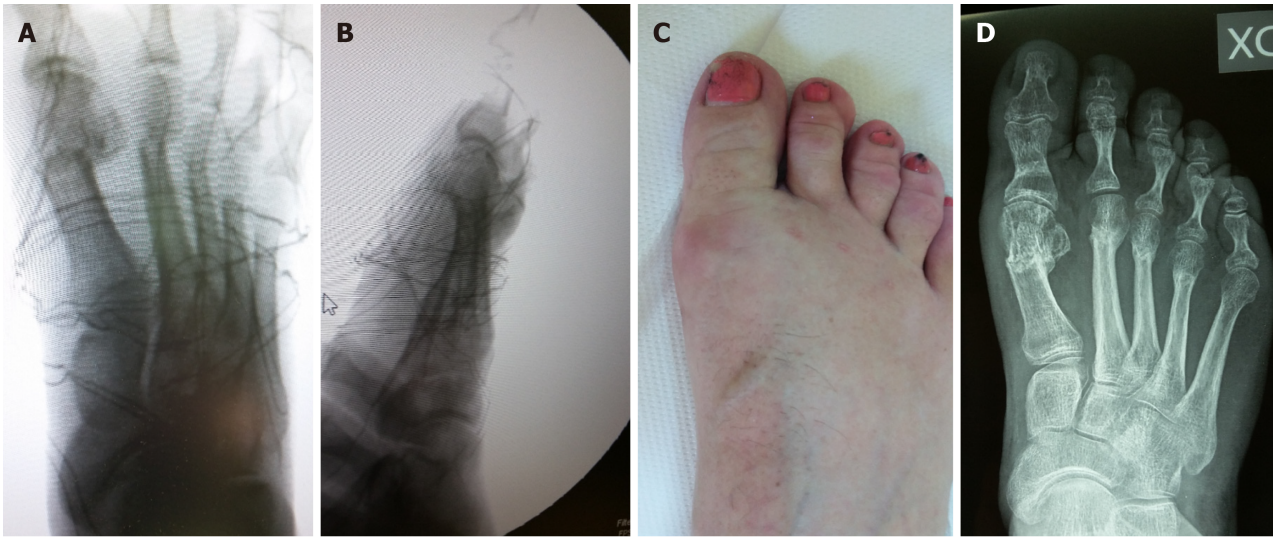
Figure 1 Preoperative clinical and radiological features of a 42 years female patient with hallux valgus. A: Preoperative clinical; B: Radiological features.

There was no significant prevalence between treatment groups (P = 0.7628). Four of these patients underwent re-intervention and then declared satisfied with the result. In 8 patients, medial exostosis relapsed. Insufficient debris removal and/or exostectomy were found in all these patients. Seven of them underwent a subsequent reintervention with percutaneous exostectomy. Nineteen patients reported severe stiffness at 6 mo follow-up, with no differences between groups (P = 0.4817). A significant improvement in joint stiffness was reached in 8 patients who performed intense physiotherapy. After the revision of the preoperative X-ray, mild signs of joint degeneration were already highlighted in 85% of patients with residual joint stiffness. Eleven patients reported transfer metatarsalgia: 7 to medium-term follow-up and 4 to long-term follow-up. Four of these patients were treated with plantar orthoses with no more pain. Seven patients requested a re-intervention of percutaneous dorsalization osteotomy (DMMO) of the II-III-IV metatarsal head with symptomatology resolution. Two of them subsequently developed metatarsalgia II-V which was treated with orthoses.

DISCUSSION

Studies concerning percutaneous or MIS for treating HV have increased exponentially in recent years[23-25]. Growing scientific evidence demonstrates the percutaneous MIS technique's effectiveness in treating mild to moderate bunions. Compared with open techniques, the results overlap with fewer complications and greater patient satisfaction[26,27].

Our study evaluated a court of 396 patients treated with WOS technique as described by Lucattelli *et al*[22], pain particular attention to the influence of the LSTR on postoperative joint ROM and HV recurrence. A significant difference in ROM was recorded in the group where the LSTR was carried out, while there was no superior incidence of relapse between groups. Moreover, it must be noted that the starting ROM influences the postoperative ROM after surgery.



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Figure 2 Postoperative fluoroscopic picture of the patient treated with percutaneous hallux valgus correction without fixation (bandages) and follow-up. A: Postoperative fluoroscopic picture of the patient treated with percutaneous hallux valgus correction without fixation (bandages); B: Clinical and postoperative X-rays of the previous patients at 6 mo of follow-up.

According to the conclusions of the metanalysis of Izzo *et al*[28], we found no difference in AOFAS and recurrence rate between procedures, but ROM was revealed better at follow-up in LSTR N group, which was not directly investigated in the meta-analysis.

We believe these data represent an essential element to understanding the etiopathogenesis of complications. LSTR did not produce significant differences between the two groups regarding the increased incidence of relapses. This data also enhances the validity of MIS with no osteosynthesis technique. Being a step-by-step procedure, it allows us to reserve the LSTR as the last surgical gesture and carry it out exclusively when, from the intraoperative evaluation, sufficient metatarsal-phalangeal joint congruence has not been obtained[29].

The osteotomy practiced with a burr provided more significant shortening and joint decompression than the one performed with a blade[22,30]. We always associate Akin's osteotomy while keeping the medial cortical intact to balance the physiological loss of correction in post-op[31]. In agreement with Coughlin, the proper correction of DMMA allows the restoration of the balance of muscle forces at the level of the first ray in order to avoid adhesions and soft tissue retraction[1,32]. Our study reported better IMA correction than Reverdin and comparable results to Bauer *et al*[17] and Isham[19].

Our results demonstrated the reliability, durability, and lower incidence of complications of the technique than open techniques for HV correction[4,33]; we have recorded an incidence of complications of 9%, similar to other studies where the surgery was performed without fixation other than bandages[22,34-36] and fewer complications than studies with other MIS techniques[12,24].

According to Tournemine *et al*[37], we believe that the low incidence of this complication is due to our setting to practice DMMO in patients with particularly short metatarsals and patients with slightly and occasionally reported metatarsalgia[38,39]. Joint stiffness (global ROM < 95°) was recorded in 5.88% of patients treated without LSTR and 3.83% treated with LSTR, for a global rate of 4.8%. Some results could be justified by the lack of debris removal from the joint after exostectomy and partly by the lack of recognition of an initial hallux rigidus[40-42].

From the analysis of immediate postoperative radiography, we learned that the accurate removal of debris is a fundamental element, and two factors play a decisive role. The first is the image quality of the brightness amplifier during the intervention and the projection of the radiogram, which can be misinterpreted; and the second is the direct removal with the rasp towards the capsule to extract the fragments that often remain strictly attached to the capsule and are not easily removable even with saline solution irrigation[43]. To avoid the recurrence of exostoses we also recommend extending the exostectomy up to 2-3 mm beyond the profile of the medial cortex[25].

We reported a low percentage of pseudoarthrosis compared to those described in other different MIS techniques. In our view, it is one of the advantages of our technique. The removal of the exostosis makes it necessary for the axis correction with a lower head translation, which ensures more stability. Moreover, the osteotomy is performed intra-capsular and safely regarding bone consolidation[44,45]. The Bosch and SERI techniques needed a greater translation of the head, which is not modular. The infection rate is similar to other percutaneous studies, and it is lower than other studies analyzing treatment with K wire at a rate ranging from 0.8% to 8%[12,13,24,46].

As for most literature, no avascular necrosis was reported[47,48]. While even if rare, it was reported that an incidence of avascular necrosis ranges from 0.8% to 3.5%[49]. Low burr speed and continuous irrigation with saline solution are fundamental elements to avoid avascular necrosis and scrupulous respect for the osteotomy level[30]. We believe that the low incidence of transfer metatarsalgia is linked to our practice of DMMO (II-III-IV) in patients who report mild and occasional metatarsalgia, in particular in those in which a metatarsal formula with index minus is evidenced[30,50,51].

AOFAS score increased in both groups at 6 mo and last follow-up with increase in functional abilities and decrease in pain.

The study has several limitations; some are intrinsic to the study's retrospective nature, while others are intrinsic with the study design. The lack of randomization, priori sample size calculation, the lack of blindness, and the decision to perform soft tissue lateral release or not are the study's most critical limitations. The results of this study should be useful to surgeons treating these conditions. However, due to the lack of prospective studies in the literature regarding the LSTR procedure, we hope that our work will be a starting point for future prospective studies regarding this technique. We hope, in particular, that the aspect of joint stiffness will be deepened.

CONCLUSION

The percutaneous correction of HV is a reliable and safe procedure that significantly improves the AOFAS score and radiological angles, with a low risk of recurrence for the LSTR group. LSTR does not seem to affect pathology relapse, while the adequate correction of HVA remains the crucial factor. Early weight-bearing, minimal invasiveness, and the lack of internal fixation represent this technique's advantages. LSTR seems to increase postoperative joint stiffness with a comparable incidence of relapse and a low incidence of complications. This data also enhances the validity of MIS with no osteosynthesis technique. Being a step-by-step procedure, it allows us to reserve the LSTR as the last surgical gesture and carry it out exclusively when, from the intraoperative evaluation, sufficient metatarsal-phalangeal joint congruence has not been obtained.

ARTICLE HIGHLIGHTS

Research background

Several minimally invasive surgical techniques for the correction of hallux valgus (HV) have emerged in the literature. These techniques concern the distal osteotomy of the first metatarsal, the use or not of internal fixation, osteotomy of the base of the first phalanx (Akin osteotomy). All these techniques can be associated with the lateral release of soft tissues.

Research motivation

The lack of copious prospective studies regarding lateral soft tissues release (LSTR) procedure.

Research objectives

The object of this study is to evaluate the role of LSTR on percutaneous HV correction, evaluating functional and radiographical results.

Research methods

From January 2012 to May 2016, a total of 396 patients with mild to moderate symptomatic HV treated with the MIS technique were included in this retrospective study. The technique provides no internal fixation. Patients were divided into the LSTR group (LSTR Y) and no LSTR group (LSTR N). This surgical procedure (LSTR) was reserved for insufficient HV angle (HVA) correction during fluoroscopic control. Patients were evaluated at each follow-up by two other authors after appropriate training by senior authors (first practitioners).

Research results

We found a statistically significant difference in range of motion between the two groups (LSTR-N and LSTR-Y) at 6 mo ($P = 0.018423$) and the last follow-up ($P = 0.02$). There are no significant differences between groups for the other parameters assessed (HVA, intermetatarsal angle, American Orthopaedic Foot and Ankle Society, visual analog scale).

Research conclusions

LSTR does not seem to affect pathology relapse, while the adequate correction of HVA remains the crucial factor. LSTR seems to increase postoperative joint stiffness with a comparable incidence of relapse and a low incidence of complications.

Research perspectives

Because of the lack of copious prospective studies regarding LSTR procedure, we feel a more thorough literature review is presented with both prospective and retrospective analyses. The results of this study should be useful to surgeons treating this condition and can be used in the design of future investigations into the joint stiffness.

FOOTNOTES

Author contributions: Zanchini F, Catani O, and Sergio F designed the research study and performed the research; Boemio A, Sieczak A,

and Piscopo D analyzed the data and wrote the manuscript; Colò G and Fusini F share co-last authorship, and they revised the text of the manuscript; and all authors have read and approve the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Comitato Etico dell'Istituto Clinica Ortopedica AOU Luigi Vanvitelli, Campania.

Informed consent statement: This is to certify that signature of a consent form for the study was waived by our Institutional Review Board for the current study because of its retrospective nature and part of our service evaluation assessment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at boemioale@gmail.com Participants gave informed consent for data sharing.

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Comparison of clinical outcomes between total hip replacement and total knee replacement

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Abstract

BACKGROUND

Total hip replacements (THR) and total knee replacements (TKR) are effective treatments for severe osteoarthritis (OA). Some studies suggest clinical outcomes following THR are superior to TKR, the reason for which remains unknown. This study compares clinical outcomes between THR and TKR.

AIM

To compare the clinic outcomes of THR anad TKR using a comprehensive range of patient reported outcome measures (PROMs).

METHODS

A prospective longitudinal observational study of patients with OA undergoing THR and TKR were evaluated using a comprehensive range of generic and joint specific PROMs pre- and post-operatively.

RESULTS

A total of 131 patients were included in the study which comprised the THR group (68 patients) and the TKR group (63 patients). Both groups demonstrated significant post-operative improvements in all PROM scores ($P < 0.001$). There were no significant differences in post-operative PROM scores between the two groups: Hip and Knee Osteoarthritis Outcome scores ($P = 0.140$), Western Ontario and McMaster Universities Osteoarthritis Index pain ($P = 0.297$) stiffness ($P = 0.309$) and function ($P = 0.945$), Oxford Hip and Knee Score ($P = 0.076$), EuroQol-5D index ($P = 0.386$) and Short-Form 12-item survey physical component score ($P = 0.106$). Subgroup analyses showed no significant difference ($P > 0.05$) between cruciate retaining and posterior stabilised prostheses in the TKR group and no significant difference ($P > 0.05$) between cemented and uncemented fixation in the

THR group. Obese patients had poorer outcomes following TKR but did not significantly influence the outcome following THR.

CONCLUSION

Contrary to some literature, THR and TKR are equally efficacious in alleviating the pain and disability of OA when assessed using a comprehensive range of PROMs. The varying knee prosthesis types and hip fixation techniques did not significantly influence clinical outcome. Obesity had a greater influence on the outcome following TKR than that of THR.

Key Words: Obesity; Osteoarthritis; Patient reported outcome measures; Total hip arthroplasty; Total knee arthroplasty

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Core Tip: Previous literature has suggested that the when comparing outcomes of total hip and knee replacements, on symptoms, function, and quality of life, as assessed by patient reported outcome measure (PROM) scores, total hip replacement have superior benefits to total knee replacements. This study has demonstrated, when a comprehensive range of PROM scores are used, both procedures are equivocally and very effective for the treatment of severe osteoarthritis. Sub-analysis in the study has confirmed that whilst obese patients have poorer outcomes, they can still greatly benefit from surgical intervention.

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INTRODUCTION

Osteoarthritis (OA) is a heterogenous disorder of joints which is characterised by degradation and loss of articular cartilage, osteophyte formation, subchondral remodelling and synovial inflammation which leads to symptoms of joint stiffness, instability, swelling, weakness and, most commonly, pain[1]. Globally, an estimated 240 million people globally suffer from the chronic sequelae of OA and is a leading cause of global disability[2,3]. Risk factors for OA include female gender[4], obesity[5], increasing age[6], and soft tissue trauma including meniscal tears[7]. As the United Kingdom population ages and becomes increasingly obese, rates of OA prevalence have increased from 8.2% to 10.7% in the past 20 years[4]. Over 90000 primary total knee replacements (TKR) and over 95000 primary total hip replacements (THR) were performed in 2019 in the United Kingdom[8].

First line conservative treatment of OA includes analgesia, physiotherapy, activity modification, viscosupplementation, orthotics, steroid injections, topical gels, *etc*[9]. When symptoms are refractory to a consented period of non-operative treatment, surgical intervention is indicated in patients considered anaesthetically fit to undergo the procedure[10]. TKR and THR are the most common surgical procedures for the management of end-stage OA[8]. The major aims of joint arthroplasties are to improve symptoms of pain and functionality whilst improving the biomechanical and kinematic milieu of the joint[11].

Primary TKRs involve replacing the articular surface of the femur and tibia using either a cruciate retaining (CR) or posterior stabilized (PS) prosthesis. Primary THRs involve reaming the articular surface of the acetabulum and also removing the head and proximal neck of the femur and implanting cup and stem prosthetic components into the acetabulum and femur respectively, using either a cemented or uncemented technique[12,13]. Alternatively, a hybrid approach of a cemented femoral stem and an uncemented acetabular component can be utilised.

Lower limb joint arthroplasty also aims to improve the individual's quality of life (QoL). Patient reported outcome measures (PROMs) are validated instruments which assess the symptoms, function and wellbeing of patients from their own perspective[14]. These offer a more detailed analysis than overall satisfaction rates. Published satisfaction rates following TKR average 81%[15] and range from 75% to 92%[16] whereas slightly higher rates, 86% to 95%, are reported following total hip arthroplasty[17]. A few studies have compared TKR and THR using PROMs to identify which is associated with the greatest improvement in clinical outcomes[18-20]. These studies suggest THRs are associated with superior outcomes however they are limited by a lack of variety of PROM instruments.

Wylde *et al*[18] compared the midterm clinical outcomes for TKR and THR procedures between 5 and 8 years post-operatively using the Oxford Knee Scores (OKS) and Oxford Hip Scores (OHS) respectively for 1725 patients. This showed clinical outcomes following THR were statistically superior to those following TKR. However, the use of only a single PROM score, despite the vast cohort size, provides a weak comparison of the two surgical procedures. Equipoise remains over the clinical outcomes following TKR and THR in this cohort when using additional PROM instruments, particularly joint-specific PROMs that do not consider comorbidities.

Current literature provides clear justification comparing TKR and THR using a more extensive selection of PROM instruments than previous studies which will help to identify if results remain similar under a more scrutinous comparison. Previous research has suggested that an increased body mass index (BMI) is associated with worse post-operative functional scores and increased complications following TKR than patients of normal BMI[21]. Similarly, clinical outcomes following THRs were worse for obese and morbidly obese patients than those who were non-obese[22]. Furthermore, increasing levels of obesity have been shown to increase total stress and stress distribution in hip implants [23]. The impact of obesity using PROMs following TKR and THR also requires further investigation. The aim of this study was to quantitatively evaluate patients with OA of the hip and knee before and after joint replacement surgery using validated PROMs and to compare the clinical outcomes between THR and TKR.

MATERIALS AND METHODS

This was a prospective longitudinal observational study of adult patients with advanced hip and knee OA, that was refractory to initial conservative treatment, who underwent elective primary THR and primary TKR, respectively, by a single consultant orthopaedic surgeon between August 2015 and March 2019. All patients included in this study completed PROM forms at their initial outpatient clinic consultation and also 12 mo following their surgery at their final post-operative follow-up clinic appointment. This study was exempt from institutional review board and ethics committee approval as it was a pragmatic study evaluating the existing clinical practice of the senior author. This observational study constituted part of the second author's Masters dissertation.

All TKR's were implanted *via* a standard medial para-patellar approach using Palacos + Gentamycin PMMA cement (Heraus Medical Gmbh, Hanau, Germany). The TKR prosthesis used for the TKR group was Genesis II (Smith & Nephew Inc., Memphis, Tennessee, United States) for both the CR and PS implants and all patients also had patella resurfacing (round resurfacing onlay patella). All THR's were implanted *via* standard posterior approach using Palacos + Gentamycin PMMA cement (Heraus Medical Gmbh, Hanau, Germany) for the cemented hip components. The cemented THR prosthesis used was the cemented Exeter V40 femoral stem (Stryker Corp., Michigan, United States) and the cemented Exeter X3 RimFit acetabular cup (Stryker Corp., Michigan, United States). The uncemented THR prosthesis used was the uncemented anthology femoral stem (Smith & Nephew Inc., Memphis, Tennessee, United States) and the uncemented R3 acetabular cup (Smith & Nephew Inc., Memphis, Tennessee, United States). The hybrid THR used the cemented Exeter V40 femoral stem along with the uncemented R3 acetabular cup. Generic PROM scores for all patients included: (1) EuroQol-5D index (EQ-5D)[24-27]; (2) Short Form 12-item Survey (SF-12)[28]; and (3) Self-assessment Co-Morbidity Questionnaire (SCQ)[29]. Knee specific PROM scores for TKR patients included: (1) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[30,31]; (2) Knee Osteoarthritis Outcome Score (KOOS)[32,33]; and (3) OKS [34,35]. Hip specific PROM scores for THR patients included: (1) WOMAC[30,31]; (2) Hip Osteoarthritis Outcome Score (HOOS)[36,37]; and (3) OHS[35,38].

All data was scored and analysed according to the instructions in the original publications for each PROM, and any missing data was handled in line with the current literature. The OKS and the OHS were calculated using the updated standardised scoring system; 0 to 48 as described by Murray *et al*[35].

Statistical analysis

An a priori power calculation for this study was derived from previously published literature of the WOMAC score[39] with a minimal clinically important change of 10 and a standard deviation of 15. The sample sizes were based on a conventional type I error of 5% and a type II error rate of 10% (*i.e.*, 90% power). The calculation revealed that a sample size of approximately 49 subjects per group was required for a clinically relevant between group mean difference. Plotted histograms with fitted curve lines, box-plots, normal Q-Q plots and the Shapiro-Wilk statistic were used to test normality of data distribution. Almost all the continuous variables in the study displayed a skewed distribution and therefore the relevant non-parametric statistical tests were used for the data analysis. The Mann-Whitney *U* test was used for the between group statistical analyses and the Wilcoxon Signed Rank test was used for the within group analyses. The Kruskal-Wallis *H* test was used for the three-group hip prosthesis data analysis and the BMI analysis. The level of statistical significance was set at $P < 0.05$. Statistical analysis was performed using SPSS for Windows version 26.0 (IBM Corp., Armonk, New York). The power calculation was performed using Minitab statistical software version 18 (Minitab LLC, State College, Pennsylvania).

RESULTS

Patient demographics

A total of 131 patients were included in the study which constituted the TKR group ($n = 63$) and the THR group ($n = 68$). Table 1 shows their demographics, which overall, where very similar between the two groups. On average both groups were approximately 70 years old, overweight to obese, predominantly female and had undergone unilateral joint replacements. Both groups had similar American Society of Anaesthesiologist Physical Classification System classifications and SCQ scores.

Table 1 Patient demographics

	Total knee replacement (*n* = 63)	Total hip replacement (*n* = 68)
Age (yr), mean ± SD	72.1 ± 8.3	68.7 ± 9.4
Gender (male:female)	22:41	27:41
Laterality (left:right:bilateral)	27:34:2	27:41:0
Height (m), mean ± SD	1.62 ± 0.09	1.66 ± 0.10
Weight (kg), mean ± SD	80.2 ± 15.1	82.6 ± 16.7
BMI (kg/m^2), mean ± SD	30.4 ± 4.2	30.0 ± 5.5
ASA median (range)	2 (1-3)	2 (1-3)
SCQ median (range)	4 (0-15)	5 (0-18)

BMI: Body mass index; ASA: American Society of Anaesthesiologist Physical Classification System; SCQ: Self-Assessed Co-Morbidity Questionnaire.

TKR vs THR

Tables 2 and 3 (within-group analyses) show that all PROM scores significantly improved post-operatively as compared to their pre-operative results for both TKR and THR, respectively, with the only exception being the SF-12 MCS sub-score for THR (Table 3). Table 4 (between-group analysis) show no statistically significant differences in any of the PROM analyses between the two groups pre-operatively (with the only exception being KOOS/HOOS sports and recreation) or post-operatively.

TKR prostheses type

Of the 63 TKR patients, 36 had CR TKRs and 27 had PS TKRs. When comparing CR to PS TKRs there were no statistically significant differences in PROM scores between the two implants, neither pre-operatively nor post-operatively as shown in Table 5.

THR prosthesis type

Of the 68 THR patients, 36 had cemented THRs, 28 had uncemented THRs, 4 had hybrid THRs. The comparisons of pre-operative and post-operative PROM score are shown in Table 6. As the sample size of the hybrid group was small, no upper bound interquartile range value was produced during statistical analysis, thus only the lower quartile value is given. The different types of fixations showed no statistically significant differences pre-operatively or postoperatively. The difference in HOOS symptoms score did generate a *P*-value of 0.046 however given the borderline statistical significance and being the only identified difference between any of the THR subgroups, it is likely to reflect a type I statistical error.

Obesity

Comparisons of pre-operative and post-operative PROM scores of the TKR group and the THR group by BMI classification are shown in Tables 7 and 8 respectively. In the TKR group (Table 7) there were no significant differences between BMI classifications pre-operatively. However, higher BMI classifications (more obese patients) scored significantly worse following TKR in the KOOS Pain (P = 0.046), KOOS QoL (P = 0.032) and WOMAC pain (P = 0.045) sub-scores. Overall, there were no statistically significant differences pre- or post-operatively in the THR group (Table 8) pertaining to BMI classifications with the only exception being patients with a higher BMI had poorer OHS pre-operatively, however this was of borderline statistical significance (P = 0.046).

DISCUSSION

This study showed that both primary THR and primary TKR significantly improved patient reported outcomes following surgery in patients with advanced hip and knee OA. Overall, there was no significant difference in PROM scores post-operatively between the two procedures and are therefore considered to be equally efficacious in this regard. A large effect size, and of strong statistical significance was seen as found in recent United Kingdom studies[40].

The TKR group and THR group had similar baseline demographics in terms of age and gender as well as general health pertaining to anthropometric measures and prevalence of medical comorbidities, thereby allowing for a valid direct comparison of their PROM scores. The between-group pre-operative comparison of outcome scores showed no significant differences, reflecting the impact of pain, function, and QoL of severe hip and knee OA can be equally debilitating. The post-operative scores also showed no significant differences between the two groups suggesting that two procedures are equally effective at improving pain, function, and QoL. This is contrary to the findings of other studies[18-20] whereby THR outcomes have been shown to be superior to TKR outcomes. Bachmeier *et al*[19] found superior WOMAC and Medical Outcomes Study Short Form-36 (MOS SF-36) scores in the THR group. The conclusion of that

Table 2 Comparison of pre-operative and post-operative patient reported outcome measure scores: Total knee replacement

	Pre-operative (*n* = 63), median (IQR)	Post-operative (*n* = 63), median (IQR)	*P* value[1]	*Z* value
KOOS pain	36 (25-44)	92 (77 – 98)	< 0.001[a]	-6.617
KOOS symptoms	36 (21-46)	89 (82 – 93)	< 0.001[a]	-6.842
KOOS ADL	38 (31-44)	88 (78-97)	< 0.001[a]	-6.902
KOOS Sport/Rec	5 (0-25)	70 (50-86)	< 0.001[a]	-4.571
KOOS QoL	13 (6-25)	75 (56-93)	< 0.001[a]	-6.457
Overall KOOS	28.9 (18.2-37.9)	80.7 (64.5-89.4)	< 0.001[a]	-5.160
WOMAC pain	40 (30-50)	90 (80-100)	< 0.001[a]	-6.575
WOMAC stiffness	25 (25-37.5)	75 (63-100)	< 0.001[a]	-6.708
WOMAC function	38.2 (30.9-44.1)	91.2 (77.9-97.1)	< 0.001[a]	-6.625
Oxford knee score	15 (11-19)	40 (33-43)	< 0.001[a]	-6.618
EQ-5D index	0.345 (0.211-0.548)	0.821 (0.703-1)	< 0.001[a]	-6.237
EQ-5D VAS	65 (50-80)	83 (71-95)	< 0.001[a]	-5.323
SF-12 PCS	27.6 (23.2-32.1)	43.8 (33.0-50.4)	< 0.001[a]	-5.333
SF-12 MCS	47.0 (39.3-56.5)	58.6 (51.5-61.3)	< 0.001[a]	-3.832

[1]Wilcoxon Signed Rank test.

[a]Statistically significant $P < 0.05$.

IQR: Interquartile range; KOOS: Knee Osteoarthritis Outcome Score; ADL: Activities of daily living; Sport/Rec: Sports and recreation; QoL: Quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D: EuroQol-5D index; VAS: Visual Analogue Scale; SF-12: Short form 12 item survey; PCS: Physical component summary; MCS: Mental component summary.

study is limited, as it had approximately 50% dropout rate at 12 mo, the use of only a small range of PROM scores and was conducted 22 years ago where much has changed in the field of arthroplasty surgery. Choi *et al*[20] also found superior clinical outcomes for THR at 2 years using WOMAC and SF-12 scores. That study was limited by its unequal demographics between the two cohorts as the TKR group were older, more overweight and contained a much higher proportion of females. Additionally, only one disease specific (WOMAC) and one generic (SF-12) PROM score was assessed. The WOMAC score uses generic joint-related questions to compare clinical outcomes but are not joint specific [30]. The MOS SF-36 and SF-12 are generic health PROM scores, therefore co-factors such as medical comorbidities[41] may confound the overall end results as unhealthier patients will have worse scores irrespective of the clinical outcomes of their osteoarthritic joints post-operatively. Additionally, the THR group in one study were significantly older, more overweight and had a higher proportion of females, than the TKR group[20]. Wylde *et al*[18] compared only the Oxford Hip and Knee Scores but were able to demonstrate greater improvements in the THR group at 5-8 years despite a response rate of 72%.

This study explored the differences in PROM scores between CR and PS TKR implants. These procedures have their respective advantages and can impact post-operative clinical outcomes differently. The implant utilised is dependent upon patient eligibility as well as surgeon training and experience[42]. In principle, a CR TKR retains the posterior cruciate ligament (PCL) which preserves the femoral rollback mechanism thereby improving stability and proprioception which provides a more natural gait than a PS prosthesis[43,44]. PS TKRs involve replacing the PCL by inserting an articulating femoral cam and tibial spine mechanism[45] which is considered to be more mechanically stable with improved knee flexion[46]. CR TKR may be contra-indicated in the presence of a degenerated, deficient or chronically ruptured PCL, a PCL with poor elasticity, significant coronal and sagittal knee malalignment or in patients with a history of knee trauma where soft tissue balancing may prove difficult[42]. This study demonstrated there are no significant differences in post-operative PROM scores between the two implants. This confirms previous findings of no differences in PROMS between these types of knee arthroplasty[47,48].

THR techniques involve cemented, uncemented or a hybrid approach. Each has benefits depending on patient eligibility. Cementing is associated with improved overall survival and all-cause revision rates compared to uncemented and hybrid fixations[49] and has less complications in elderly patients with low bone density[50]. However, uncemented fixation may have superior survivorship than cemented fixations in younger patients, and overall, uncemented fixation is slightly more commonly practiced than cemented in England and Wales[51]. Uncemented fixation removes the risk of cement fragmentation and subsequent implant loosening requiring revision, and importantly prevents the possibility of bone cement implantation syndrome which can cause cardiovascular collapse and can be fatal[52]. Hybrid THR avoids the complication of acetabular cement fragmentation whilst retaining the aforementioned advantages of a cemented femoral stem[53]. There is little evidence demonstrating superior overall outcomes of hybrid THRs to other fixations[54].

Table 3 Comparison of pre-operative and post-operative patient reported outcome measure scores: Total hip replacement

	Pre-operative (*n* = 68), median (IQR)	Post-operative (*n* = 68), median (IQR)	*P* value[1]	*Z* value
HOOS pain	33 (25-40)	92 (77-98)	< 0.001[a]	-4.868
HOOS symptoms	38 (30-49)	89 (82-93)	< 0.001[a]	-4.909
HOOS ADL	37 (26-43)	88 (78-97)	< 0.001[a]	-4.841
HOOS Sport/Rec	19 (6-31)	70 (50-86)	< 0.001[a]	-4.788
HOOS QoL	19 (6-31)	75 (56-93)	< 0.001[a]	-4.663
Overall HOOS	28.9 (18.2-37.9)	80.7 (64.5-89.4)	< 0.001[a]	-4.681
WOMAC pain	40 (30-49)	95 (85-100)	< 0.001[a]	-4.932
WOMAC stiffness	25 (25-50)	88 (75-100)	< 0.001[a]	-4.760
WOMAC function	36.8 (28.3-44.1)	91.9 (75.7-98.5)	< 0.001[a]	-4.864
Oxford hip score	14 (10-20)	42 (35-47)	< 0.001[a]	-4.912
EQ-5D index	0.335 (0.169-0.533)	0.857 (0.643-1)	< 0.001[a]	-4.918
EQ-5D VAS	65 (50-80)	90 (79-95)	< 0.001[a]	-4.357
SF-12 PCS	24.8 (21.7-29.3)	50.6 (36.5-55.0)	< 0.001[a]	-4.623
SF-12 MCS	49.6 (39.9-58.3)	57.8 (55.4-59.8)	0.076	-1.776

[1]Wilcoxon Signed Rank test.

[a]Statistically significant $P < 0.05$.

IQR: Interquartile range; KOOS: Knee Osteoarthritis Outcome Score; ADL: Activities of daily living; Sport/Rec: Sports and recreation; QoL: Quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D: EuroQol-5D index; VAS: Visual Analogue Scale; SF-12: Short form 12 item survey; PCS: Physical component summary; MCS: Mental component summary.

This study showed none of the implantation techniques demonstrated superior or inferior PROM scores as compared to each other. This is contrary to some previous evidence that uncemented THRs have better EQ-5D scores and pain relief [55,56].

This study has demonstrated hip and knee arthroplasty remain highly effective treatments for severe OA and greatly improve pain, function, and QoL regardless of the surgical method used. Results suggest that all prostheses for TKR and fixations for THR in this study, considering patient eligibility, remain as effective options for treating hip and knee OA to provide good clinical outcomes.

Obesity was associated with higher pain and poorer QoL following TKR as shown by the KOOS and WOMAC scores respectively in the present study. Obesity has previously been associated with a higher rate of post-operative complications including pain, superficial wound infections, deep joint infections, deep vein thrombosis, mechanical failure and dislocations as well as worse clinical outcomes such as more chronic pain, more disability and a higher risk of revision[57-59]. This study confirmed these findings as demonstrated by worse post-operative scores in KOOS pain, KOOS QoL, and WOMAC pain instruments for overweight and obese patients following TKR.

Si *et al*[21] found poorer post-operative clinical outcomes following TKR in obese patients using the Knee Society Score only, and Deakin *et al*[22] demonstrated obesity to be associated with worse clinical outcomes following both TKR and THR using the OKS and OHS respectively. These studies found significant differences between those considered: Not obese (BMI < 30), obese (BMI 30-40) and morbidly obese (> 40). In the present study, weight categories of normal (BMI < 25), overweight (BMI 25-30), obese (BMI > 30) and morbidly obese (BMI > 40) were used, thereby not conflating 'normal' and 'overweight' patients. Obese patients with hip OA had worse symptoms pre-operatively according to only one instrument (OHS) however this difference was not significant post-operatively. Conversely, in the TKR group, worse post-operative outcomes where demonstrated in obese patients for KOOS pain, KOOS QoL and WOMAC pain subscores.

For obese patients, pre-operative weight loss is routinely advocated as part of their conservative management. Overall, this study demonstrates good outcomes, as shown by improvements across multiple PROM scores, can be achieved in obese patients. Patients that are categorised as overweight or obese should not be denied arthroplasty based on BMI alone as obese patients obtained improved clinical outcomes and alleviation of their OA symptoms, however, caution should be exercised in the morbidly obese category of patients. The loss of functionality, associated with OA, may be a factor in patients being unable to lose weight through regular exercise. However, weight loss is primarily driven by diet, much more so than exercise, although the two combined approaches yield the best results. Therefore, it reasonable to consider total joint replacement if similar outcomes to patients of normal BMI are attainable. Furthermore, the previous studies measure one disease specific PROM each, the present study adds a more extensive insight into the impact of obesity on post-operative outcomes.

Table 4 Comparison of pre-operative and post-operative patient reported outcome measure scores: Total knee replacement *vs* total hip replacement

		TKR (*n* = 63), median (IQR)	THR (*n* = 68), median (IQR)	*P* value[1]	*Z* value	*U* value
KOOS/HOOS pain	Pre-operative	36 (25-44)	33 (25-40)	0.597	-0.528	1755
	Post-operative	92 (77-98)	95 (84-100)	0.208	-0.370	1206
KOOS/HOOS symptoms	Pre-operative	36 (21-46)	38 (30-49)	0.415	-0.415	1729
	Post-operative	89 (82-93)	90 (80-100)	0.629	-0.483	1189
KOOS/HOOS ADL	Pre-operative	38 (31-44)	37 (26-43)	0.298	-1.040	1656
	Post-operative	88 (78-97)	91 (76-98)	0.711	-0.370	1206
KOOS/HOOS Sport/Rec	Pre-operative	5 (0-25)	19 (6-31)	0.030[a]	-2.164	1001
	Post-operative	70 (50-86)	75 (56-100)	0.158	-0.141	738
KOOS/HOOS QoL	Pre-operative	13 (6-25)	19 (6-31)	0.106	-1.616	1519
	Post-operative	75 (56-93)	84 (58-94)	0.499	-0.676	1030
KOOS/HOOS overall	Pre-operative	28.9 (18.2-37.9)	28.0 (21.0-37.6)	0.833	-0.211	1267
	Post-operative	80.7 (64.5-89.4)	88.8 (72.9-95.5)	0.140	-1.476	713
WOMAC pain	Pre-operative	40 (30-50)	40 (30-49)	0.984	-0.02	1886
	Post-operative	90 (80-100)	95 (85-100)	0.297	-1.04	1020
WOMAC stiffness	Pre-operative	25 (25-37.5)	25 (25-50)	0.583	-0.55	1786
	Post-operative	75 (63-100)	88 (75-100)	0.309	-1.02	1114
WOMAC function	Pre-operative	38.2 (30.9-44.1)	36.8 (28.3-44.1)	0.639	-0.47	1798
	Post-operative	91.2 (77.9-97.1)	91.9 (75.7-98.5)	0.945	-0.07	1151
OKS/OHS	Pre-operative	15 (11-19)	14 (10-20)	0.859	-0.177	1826
	Post-operative	40 (33-43)	42 (35-47)	0.076	-1.775	932
EQ-5D index	Pre-operative	0.345 (0.211-0.548)	0.335 (0.169-0.533)	0.719	-0.36	1761
	Post-operative	0.821 (0.703-1)	0.857 (0.643-1)	0.386	-0.87	988
EQ-5D VAS	Pre-operative	65 (50-80)	65 (50-80)	0.308	-1.02	1579
	Post-operative	83 (71-95)	90 (79-95)	0.374	-0.89	1019
SF-12 PCS	Pre-operative	27.6 (23.2-32.1)	24.8 (21.7-29.3)	0.073	-1.79	1308
	Post-operative	43.8 (33.0-50.4)	50.6 (36.5-55.0)	0.106	-1.62	690
SF-12 MCS	Pre-operative	47.0 (39.3-56.5)	49.6 (39.9-58.3)	0.777	-0.28	1574
	Post-operative	58.6 (51.5-61.3)	57.8 (55.4-59.8)	0.438	-0.78	784

[1]Mann-Whitney *U* test.

[a]Statistically significant $P < 0.05$.

IQR: Interquartile range; TKR: Total knee replacement; THR: Total hip replacement; KOOS: Knee Osteoarthritis Outcome Score; HOOS: Hip Osteoarthritis Outcome Score; ADL: Activities of daily living; Sport/Rec: Sports and recreation; QoL: Quality of life; OKS: Oxford Knee Score; OHS: Oxford Hip Score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D: EuroQol-5D index; VAS: Visual Analogue Scale; SF-12: Short form 12 item survey; PCS: Physical component summary; MCS: Mental component summary.

A strength of this study is its comparison of multiple disease specific PROMs and (KOOS, HOOS, WOMAC, OKS and OHS) as well as generic PROMs (EQ-5D scores and SF-12). The use of this variety of scores can provide a more holistic and detailed assessment of clinical outcomes than that available in the current literature. Appropriate power calculations prove this study is adequately powered and less likely to produce a type-II statistical error. An additional strength of this study is that the hip and knee OA cohorts had similar demographics and severity of OA disease, allowing for direct comparison of improvements between the two arthroplasty procedures.

There are some potential limitations of this study. The relative impact of arthroplasty on hip and knee OA were compared directly using HOOS and KOOS in Table 4, despite them being separate instruments. Whilst different, they are comprised of the same metrics and sub-scores which enable direct comparisons. This method has previously been used

Table 5 Comparison of pre-operative and post-operative total knee replacement patient reported outcome measure scores: Cruciate retaining *vs* posterior stabilised implants

		Cruciate retaining (*n* = 36), median (IQR)	Posterior stabilised (*n* = 27), median (IQR)	*P* value[1]	*Z* value	*U* value
KOOS pain	Pre-operative	36 (23-44)	36 (25-42)	0.568	-0.57	445.0
	Post-operative	89 (69-100)	94 (83-97)	0.271	-1.10	348.5
KOOS symptoms	Pre-operative	36 (26-53)	32 (21-43)	0.181	-1.34	390.0
	Post-operative	86 (80-89)	89 (86-93)	0.074	-1.79	358.5
KOOS ADL	Pre-operative	39 (31-46)	38 (29-44)	0.950	-0.06	481.5
	Post-operative	88 (75-96)	94 (82-97)	0.292	-1.05	410.5
KOOS Sport/Rec	Pre-operative	5 (0-29)	5 (0-25)	0.721	-0.36	277.0
	Post-operative	70 (50-85)	70 (60-95)	0.671	-0.43	237.5
KOOS QoL	Pre-operative	6 (2-25)	13 (6-27)	0.408	-0.83	411.0
	Post-operative	75 (56-81)	75 (61-94)	0.557	-0.59	354.5
Overall KOOS	Pre-operative	29. 8 (20.8-36.5)	27.2 (16.8-38.5)	0.880	-0.15	286.5
	Post-operative	81.3 (64.0-88.8)	80.7 (75.3-90.8)	0.730	-0.35	232.0
WOMAC pain	Pre-operative	40 (30-50)	35 (30-50)	0.867	-0.17	474.0
	Post-operative	90 (75-100)	95 (85-100)	0.376	-0.88	363.0
WOMAC stiffness	Pre-operative	25 (25-47)	25 (25-38)	0.930	-0.09	480.0
	Post-operative	75 (63-88)	75 (75-100)	0.112	-1.59	374.5
WOMAC function	Pre-operative	39.0 (30.9-45.2)	38.2 (29.4-44.1)	0.851	-0.19	472.5
	Post-operative	88.2 (73.5-97.1)	94.1 (82.4-97.0)	0.286	-1.07	350.5
Oxford knee score	Pre-operative	14 (11-21)	15 (12-18)	0.760	-0.31	451.0
	Post-operative	41 (33-43)	40 (34-44)	0.794	-0.26	408.0
EQ-5D index	Pre-operative	0.322 (0.217-0.530)	0.392 (0.181-0.568)	0.747	-0.32	428.0
	Post-operative	0.795 (0.679-1)	0.829 (0.714-1)	0.885	-0.15	368.5
EQ-5D VAS	Pre-operative	65 (50-80)	80 (53-83)	0.180	-1.34	348.5
	Post-operative	85 (79-95)	80 (70-86)	0.151	-1.44	346.5
SF-12 PCS	Pre-operative	28.1 (23.2-31.6)	25.7 (23.4-32.5)	0.653	-0.45	379.5
	Post-operative	43.8 (34.9-52.2)	44.6 (28.3-50.9)	0.572	-0.57	248.5
SF-12 MCS	Pre-operative	44.0 (38.7-53.9)	49.7 (41.6-57.1)	0.294	-1.05	341.5
	Post-operative	57.5 (49.9-60.6)	59.4 (51.4-61.6)	0.306	-1.02	227.0

[1]Mann-Whitney *U* test.

IQR: Interquartile range; KOOS: Knee Osteoarthritis Outcome Score; ADL: Activities of daily living; Sport/Rec: Sports and recreation; QoL: Quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D: EuroQol-5D index; VAS: Visual Analogue Scale; SF-12: Short Form 12 item survey; PCS: Physical component summary; MCS: Mental component summary.

[18] for comparing OHS against OKS, as was the case in the present study too. PROMS provide clinicians and researchers with a tool to translate a qualitative description of patient's symptoms into quantitative measures that can be used to tailor an individual's management or assess and compare treatment methods in broader populations. However, PROM questionnaires are subject to missing data and errors due to patient factors such as willingness to complete all the questionnaires and comprehension of the wording of the individual items within each instrument. Inherently, studies using PROMs carry the potential for bias from these factors. Missing data was handled using established methods accordingly[30,60]. This study was conducted using data from a single surgeon at a single centre which may limit the generalisability of the findings but had the advantage of ensuring uniform procedures so that all other factors of the patient's care remained consistent. Longer term follow-up of clinical outcomes after surgery would also be advantageous to evaluate if the parity of results persisted in the long-term too.

Table 6 Comparison of pre-operative and post-operative total hip replacement patient reported outcome measure scores: Cemented, uncemented and hybrid fixations

		Cemented (*n* = 36), median (IQR)	Uncemented (*n* = 28), median (IQR)	Hybrid (*n* = 4), median (IQR)	*P* value[1]	*H* value
HOOS pain	Pre-operative	35 (22.4-44.6)	31 (25-38)	40 (33-X)	0.512	1.338
	Post-operative	95 (70-100)	98 (93-100)	89 (83- X)	0.332	2.205
HOOS symptoms	Pre-operative	40 (30-50)	35 (29-45)	35 (15-X)	0.544	1.216
	Post-operative	85 (75-90)	95 (85-100)	73 (65-X)	0.046[a]	6.614
HOOS ADL	Pre-operative	37 (25-43)	35 (28-44)	40 (35-X)	0.808	0.425
	Post-operative	91 (68-96)	98 (84-100)	80 (66-X)	0.176	3.479
HOOS Sport/Rec	Pre-operative	16 (5-27)	25 (6-43)	25 (19-X)	0.611	0.986
	Post-operative	75 (48-95)	94 (75-100)	59 (50-X)	0.111	4.405
HOOS QoL	Pre-operative	19 (6-31)	19 (13-38)	31 (25-X)	0.401	1.827
	Post-operative	75 (50-94)	88 (69-100)	56 (50-X)	0.259	2.703
Overall HOOS	Pre-operative	26.1 (19.7-40.0)	29.7 (21.5-40.3)	35.9 (25.3-X)	0.812	0.418
	Post-operative	88.4 (64.8-92.2)	95.0 (79.0-98.8)	71.4 (65.2-X)	0.130	4.086
WOMAC pain	Pre-operative	45 (25-55)	35 (30-40)	40 (35-X)	0.497	1.398
	Post-operative	95 (65-100)	95 (90-100)	90 (80-X)	0.764	0.538
WOMAC stiffness	Pre-operative	25 (25-50)	25 (25-38)	25 (25-X)	0.964	0.074
	Post-operative	88 (75-88)	88 (75-100)	69 (63-X)	0.170	3.540
WOMAC function	Pre-operative	39.7 (26.5-50.0)	34.6 (29.0-44.1)	39.7 (35.3-X)	0.790	0.472
	Post-operative	91.2 (67.7-95.6)	98.5 (83.8-100)	80.1 (66.2-X)	0.190	3.317
Oxford hip score	Pre-operative	14 (10-19)	14 (11-22)	19 (17-X)	0.238	2.872
	Post-operative	41 (33-46)	44 (39-47)	38 (34-X)	0.347	2.118
EQ-5D index	Pre-operative	0.375 (0.155-0.533)	0.314 (0.217-0.535)	0.604 (0.482-X)	0.128	4.106
	Post-operative	0.836 (0.592-1)	1 (0.747-1)	0.790 (0.580-X)	0.529	1.274
EQ-5D VAS	Pre-operative	65 (50-80)	65 (39-80)	60 (60-X)	0.938	0.127
	Post-operative	90 (70-95)	90 (80-98)	80 (65-X)	0.779	0.499
SF-12 PCS	Pre-operative	25.0 (21.1-27.3)	25.3 (21.9-31.1)	24.7 (20.4-X)	0.597	1.030
	Post-operative	50.6 (32.3-54.8)	53.4 (43.3-55.8)	42.9 (36.4-X)	0.447	1.610
SF-12 MCS	Pre-operative	49.5 (41.1-58.2)	50.6 (38.7-58.6)	50.7 (34.4-X)	0.980	0.040
	Post-operative	56.6 (53.7-59.8)	59.2 (57.3-60.8)	47.1 (36.1-X)	0.128	4.104

[1]Kruskal Wallis *H* test.

[a]Statistically significant $P < 0.05$.

IQR: Interquartile range; HOOS: Hip Osteoarthritis Outcome Score; ADL: Activities of daily living; Sport/Rec: Sports and recreation; QoL: Quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D: EuroQol-5D index; VAS: Visual Analogue Scale; SF-12: Short Form 12 item survey; PCS: Physical component summary; MCS: Mental component summary.

CONCLUSION

THR and TKR are greatly effective at improving pain, function, and QoL in patients with severe OA. The clinical outcome of both procedures was found to be equally efficacious in this regard post-operatively. No significant difference was found in the outcome between CR and PS TKR implants, nor was a significant difference found between cemented and uncemented THRs. Obesity had a greater influence on the outcome following TKR than that of THR.

Table 7 Pre-operative and post-operative impact of body mass index category on patient reported outcome measure scores: Total knee replacements

		Normal (*n* = 8), median (IQR)	Overweight (*n* = 24), median (IQR)	Obese (*n* = 31), median (IQR)	*P* value[1]	*H* value
KOOS pain	Pre-operative	41 (22-51)	38 (26-49)	33 (22-42)	0.230	2.936
	Post-operative	97 (95-100)	92 (73-97)	88 (72-98)	0.046[a]	6.160
KOOS symptoms	Pre-operative	32 (23-62)	38 (21-56)	32 (22-43)	0.701	0.712
	Post-operative	91 (86-95)	89 (86-93)	86 (79-93)	0.129	4.098
KOOS ADL	Pre-operative	40 (25-53)	38 (34-45)	40 (26-43)	0.466	1.527
	Post-operative	96 (89-99)	91 (78-97)	87 (76-96)	0.214	3.079
KOOS Sport/Rec	Pre-operative	5 (0-63)	8 (0-25)	5 (0-20)	0.621	0.952
	Post-operative	75 (60-100)	73 (51-84)	65 (45-88)	0.582	1.083
KOOS QoL	Pre-operative	19 (0-44)	19 (6-31)	6 (6-19)	0.302	2.394
	Post-operative	91 (75-99)	75 (63-100)	63 (47-81)	0.032[a]	6.881
Overall KOOS	Pre-operative	36.5 (12.1-51.1)	32.2 (20.8-43.8)	26.6 (16.7-33.7)	0.354	2.075
	Post-operative	87 (80-97)	81.3 (67.2-92.0)	79.9 (64.1-84.8)	0.208	3.139
WOMAC pain	Pre-operative	45 (25-54)	40 (30-50)	35 (25-50)	0.332	2.206
	Post-operative	100 (95-100)	90 (75-99)	90 (79-100)	0.045[a]	6.186
WOMAC stiffness	Pre-operative	38 (6-59)	25 (25-47)	25 (25-38)	0.704	0.702
	Post-operative	100 (75-100)	75 (63-100)	75 (63-88)	0.084	4.960
WOMAC function	Pre-operative	39.7 (25.0-53.3)	38.2 (34.1-45.2)	39.7 (26.5-44.1)	0.521	1.302
	Post-operative	97.1 (93.0-100)	91.2 (78.3-97.1)	86.0 (75.7-97.1)	0.125	4.154
Oxford knee score	Pre-operative	17 (11-23)	15 (11-19)	14 (11-19)	0.566	1.137
	Post-operative	39 (38-40)	42 (33-45)	39 (33-43)	0.559	1.165
EQ-5D index	Pre-operative	0.502 (0.107-0.630)	0.304 (0.215-0.479)	0.356 (0.206-0.535)	0.606	1.002
	Post-operative	0.837 (0.821-1)	0.837 (0.735-1)	0.767 (0.633-0.939)	0.260	2.696
EQ-5D VAS	Pre-operative	80 (65-80)	80 (50-90)	60 (50-70)	0.139	3.940
	Post-operative	80 (74-85)	85 (70-95)	85 (70-90)	0.652	0.856
SF-12 PCS	Pre-operative	29.6 (24.8-36.4)	28.2 (23.9-37.8)	27.2 (21.6-29.9)	0.257	2.714
	Post-operative	49.0 (44.0-51.7)	46.9 (30.1-53.3)	38.5 (32.5-49.6)	0.379	1.942
SF-12 MCS	Pre-operative	48.2 (38.1-54.6)	50.1 (40.0-59.6)	45.0 (38.6-54.1)	0.692	0.737
	Post-operative	58.6 (53.4-60.6)	59.3 (44.2-62.3)	57.8 (51.2-60.5)	0.897	0.208

[1]Kruskal Wallis *H* test.
[a]Statistically significant $P < 0.05$.
KOOS: Knee Osteoarthritis Outcome Score; ADL: Activities of daily livin; Sport/Rec: Sports and recreation; QoL: Quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D: EuroQol-5D index; VAS: Visual Analogue Scale; SF-12: Short Form 12 item survey; PCS: Physical component summary; MCS: Mental component summary.

Table 8 Pre-operative and post-operative impact of body mass index category on patient reported outcome measure scores: Total hip replacements

		Normal (*n* = 14), median (IQR)	Overweight (*n* = 16), median (IQR)	Obese (*n* = 34), median (IQR)	Morbidly obese (*n* = 4), median (IQR)	*P* value[1]	*H* value
HOOS pain	Pre-operative	38 (23-43)	35 (29-44)	30 (25-39)	22.5 (15-X)	0.405	2.917
	Post-operative	99 (65-100)	99 (86-100)	93 (73-97)	97 (97-97)	0.310	3.582

HOOS symptoms	Pre-operative	40 (28-53)	38 (25-53)	40 (30-49)	35 (25-X)	0.720	1.339
	Post-operative	90 (63-100)	98 (69-100)	85 (78-90)	85 (85-85)	0.718	1.349
HOOS ADL	Pre-operative	39 (23-48)	38 (32-42)	33 (27-43)	18 (18-X)	0.277	3.860
	Post-operative	92 (67-99)	98 (73-100)	84 (63-96)	94 (94-94)	0.294	3.712
HOOS Sport/Rec	Pre-operative	28 (20-31)	25 (19-44)	6 (0-25)	13 (6-X)	0.088	6.536
	Post-operative	88 (75-100)	91 (55-100)	63 (34-91)	75 (75-75)	0.252	4.090
HOOS QoL	Pre-operative	25 (6-41)	25 (19-31)	19 (13-25)	13 (0-X)	0.486	2.443
	Post-operative	88 (58-100)	81 (53-98)	69 (38-90)	94 (94-94)	0.376	3.106
Overall HOOS	Pre-operative	35.9 (29.9-41.7)	36.0 (24.8-38.5)	25.7 (20.7-33.3)	25.0 (12.8-X)	0.267	3.950
	Post-operative	91.2 (88.8-100)	95.1 (68.3-98.6)	79.0 (60.4-90.0)	89.0 (89.0-89.0)	0.256	4.047
WOMAC pain	Pre-operative	40 (33-63)	38 (31-53)	38 (30-45)	25 (15-X)	0.445	2.673
	Post-operative	100 (68.8-100)	100 (85-100)	90 (75-98)	95 (95-95)	0.332	3.417
WOMAC stiffness	Pre-operative	38 (19-50)	38 (25-50)	25 (25-38)	25 (13-X)	0.377	3.099
	Post-operative	94 (56-100)	94 (66-100)	75 (75-88)	75 (75-75)	0.483	2.459
WOMAC function	Pre-operative	39.7 (30.1-54.4)	39.7 (32.0-43.8)	33.1 (26.8-44.1)	17.6 (17.6-X)	0.267	3.951
	Post-operative	91.9 (69.1-99.3)	98.5 (73.2-99.6)	83.8 (63.2-95.6)	94.1 (94.1-94.1)	0.313	3.562
Oxford hip score	Pre-operative	23 (12-29)	18 (13-22)	13 (10-19)	7 (5-X)	0.046[a]	8.001
	Post-operative	44 (35-47.75)	44 (36-48)	39 (31-45)	47 (47-47)	0.275	3.882
EQ-5D index	Pre-operative	0.527 (0.059-0.699)	0.481 (0.235-0.568)	0.289 (0.210-0.420)	0.169 (-0.199-X)	0.305	3.624
	Post-operative	1 (0.659-1)	1 (0.685-1)	0.750 (0.639-0.892)	1 (1-1)	0.158	5.198
EQ-5D VAS	Pre-operative	60 (40-80)	80 (60-85)	65 (40-74)	65 (40-X)	0.250	4.105
	Post-operative	93 (60-100)	94 (71-100)	80 (75-84)	90 (90-90)	0.106	6.114
SF-12 PCS	Pre-operative	31.8 (19.7-37.1)	26.8 (22.5-37.9)	24.1 (21.4-27.6)	25.0 (21.7-X)	0.370	3.144
	Post-operative	54.8 (40.5-56.0)	49.3 (36.4-55.3)	43.9 (28.0-54.8)	49.3 (49.3-49.3)	0.590	1.914
SF-12 MCS	Pre-operative	59.5 (51.2-63.1)	53.5 (39.9-61.7)	47.4 (40.1-52.7)	32.3 (16.7-X)	0.075	6.919
	Post-operative	57.5 (55.9-59.8	59.8 (55.7-60.8)	57.7 (50.2-59.8)	60.8 (60.8-60.8)	0.334	3.396

[1]Kruskal Wallis *H* test.

[a]Statistically significant $P < 0.05$.

IQR: Interquartile range; HOOS: Hip Osteoarthritis Outcome Score; ADL: Activities of daily living; Sport/Rec: Sports and recreation; QoL: Quality of life; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; EQ-5D: EuroQol-5D index; VAS: Visual Analogue Scale; SF-12: Short Form 12 item survey; PCS: Physical component summary; MCS: Mental component summary.

ARTICLE HIGHLIGHTS

Research background

Patient report outcome measures (PROMs) quantitatively assess patient's symptoms, function and quality of life (QoL). It is known severe osteoarthritis (OA) can be alleviated by joint replacement. To what extent these procedures improve symptoms, function, and QoL can vary depending on the joint, type of procedure, and patient co-factors. Additionally, it is important to maintain a contemporary assessment of the impacts of current surgical practice. The significance of this study is it is the first study of its type to assess the impact of total hip replacements (THR) and total knee replacements (TKR) using a large range of PROMS, in a modern cohort, which also provides sub-analysis on the impact of implant type and obesity.

Research motivation

Previous literature on the impact of THR and TKR is either out-of-date or very narrow in it's scope. As an orthopedic surgeon, it is important to predict the impact of these procedures, in order to tailor management for each patient. Therefore, knowing the impact of modern arthroplasty on symptoms, function, and QoL should be explored and available in the literature. Additionally, factors such as obesity can significantly deter surgeons from offering surgery to patients due to known peri-operative risks without fully appreciating the long term benefits patients can achieve. It is therefore our motivation to explore if THR and TKR can offer good outcomes to patients and begin to explore which

patient, implant and operative factors can lead to the best outcomes or pose particular risks. Future research can use the approach of this study identify which of the factors should be considered when counseling patients with severe OA.

Research objectives

The primary objective of this study was to explore patient reported outcome measures in patients before and after total hip and knee replacement procedures. This was achieved with a sufficiently powered study to detect statistical and clinic significance, and comparison of the two groups was also achieved. Future research can monitor the impact of these procedures as surgical technology continues to improve. Additionally, further research can proceed determine which other factors impact patient outcomes following joint arthroplasty.

Research methods

This study is a pragmatic clinic study of real time clinical practice. The PROMs used in this study are routinely collected in clinical practice and some contribute to data collected by the United Kingdom National Joint Registry. The range of PROMs, although used in a different context, have been utilised in the MD thesis of the senior author. These studies shared similar methodologies to the studies cited. The value of using a range PROMs could be incorporated into national joint registries to allow for research which is highly powered and diverse in its assessment of outcomes.

Research results

This study contributes to the modern literature by demonstrating that hip and knee arthroplasty are equally effective at treating the symptoms of severe OA, and equally successful at improving patient function and QoL. This study reflects more recent clinical practice, more comparable clinical cohorts and a broader range of PROMS than the current literature offers. These results can be built upon to establish which other factors impact patient outcomes following joint arthroplasty.

Research conclusions

This study proposes the theory that hip and knee OA can be equally symptomatic in severity, and limiting in QoL and function to patients. Furthermore, arthoplasty is equally effecting at improving these outcomes, regardless of the method used (cruciate retaining *vs* posterior stabilized, cemented *vs* uncemented). This study compares established outcome measures for established surgical procedures. Whilst no new or novel methodology is proposed, a comprehensive assessment has been demonstrated for the first time in the literature.

Research perspectives

Broadly speaking, research should aim to establish which patient, operative and implant factors can be optimised in order to produce the best outcomes, and mitigate risk, for patient undergoing joint arthroplasty for OA.

FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Importance of computed tomography in posterior malleolar fractures: Added information to preoperative X-ray studies

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Abstract

BACKGROUND

Ankle fractures are common lesions of the lower limbs. Approximately 40% of ankle fractures affect the posterior malleolus (PM). Historically, PM osteosynthesis was recommended when PM size in X-ray images was greater than 25% of the joint. Currently, computed tomography (CT) has been gaining traction in the preoperative evaluation of ankle fractures.

AIM

To elucidate the similarity in dimensions and to correlate PM size in X-ray images with the articular surface of the affected tibial plafond in the axial view on CT (AXCT) of a PM fracture.

METHODS

Eighty-one patients (mean age: 39.4 ± 13.5 years) were evaluated (54.3% were male). Two independent examiners measured PM size in profile X-ray images (PMXR) and sagittal CT (SAGCT) slices. The correlation of the measurements between the examiners and the difference in the PM fragment sizes between the two images were compared. Next, the PM size in PMXR was compared with the surface of the tibial plafond involved in the fracture in AXCT according to the Haraguchi classification.

RESULTS

The correlation rates between the examiners were 0.93 and 0.94 for PMXR and

SAGCT, respectively ($P < 0.001$). Fragments were 2.12% larger in SAGCT than in PMXR ($P = 0.018$). In PMXR, there were 56 cases < 25% and 25 cases ≥ 25%. When PMXR was < 25%, AXCT corresponded to 10.13% of the tibial plafond. When PMXR was ≥ 25%, AXCT was 24.52% ($P < 0.001$). According to the Haraguchi classification, fracture types I and II had similar PMXR measurements that were greater than those of type III. When analyzing AXCT, a significant difference was found between the three types, with II > I > III ($P < 0.001$).

CONCLUSION

PM fractures show different sizes using X-ray or CT images. CT showed a larger PM in the sagittal plane and allowed the visualization of the real dimensions of the tibial plafond surface.

Key Words: Ankle fracture; Posterior malleolar fracture; Computed tomography; X-ray; Posterior malleolus fracture; Trimalleolar facture

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Core Tip: The study showed fractures of the posterior malleolus (PM) were different sizes on X-ray and computed tomography (CT) images. It is possible to see that some PM patterns considered small on radiographs affected a significant joint area when CT scans were performed. CT scans also showed that the actual size of the PM fragment was larger than that seen on radiographs.

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INTRODUCTION

Ankle malleolar fractures are the most common fractures among those involving load-bearing joints[1]. Approximately 40% of ankle fractures are trimalleolar fractures[2], which affect the posterior edge of the tibia in addition to the lateral and medial malleoli, more specifically the portion known as Volkmann's triangle or posterior malleolus (PM)[3]. Fractures involving the PM cause more incongruity, joint instability, and worse results than unimalleolar or bimalleolar fractures of the ankle[4-7].

Since the article by Nelson and Jensen[7] in 1940, the internal fixation of the PM has been recommended in ankle fractures, considering a size of one-third of the fragment relative to the articular surface of the tibia in lateral X-ray images. Other authors have stipulated a value of 25% of the articular surface as the determinant for the fixation of the posterior fragment to thereby restore ankle congruity[8-10]. PM fixation is currently controversial[11-14], and variable clinical results have been obtained in the treatment of trimalleolar fractures[15]. The classic recommendation to fix PM fractures with a radiological size ≥ 25% theoretically improves articular congruence and reduces the risk of post-traumatic arthritis[16,17]. On the other hand, some authors report fixing PM fractures of various sizes, including small fragments (< 25%), under the justification of providing more stability to the ankle joint and better functional results[18,19].

When diagnosing a PM in lateral ankle X-ray images, its visualization is frequently impaired by overlapping bone images, plaster immobilizations, or external fixators[20]. Moreover, measuring the size of a posterior fracture can be difficult, resulting in the underestimation of the size of the PM, which leads to an inaccurate interpretation, which in turn interferes with the treatment[20-22]. Thus, computed tomography (CT) is increasingly recommended in the treatment of ankle fractures, especially when the PM is affected[14,23]. CT allows a better interpretation of all joint fragments, particularly regarding PM morphology and size, and it also aids in preoperative planning[24,25]. Different PM fracture patterns are observed in CT studies, depending on the size of the bone fragment, its anatomical location, bone impaction, and the fragment's relationship with other malleoli and the syndesmosis[15,23]. Specific PM classifications have been created, with associated recommendations for the best treatment for each type of fracture[2,26-28].

However, there is no clear relationship between the size of the PM in X-ray images and its actual size in CT slices or between the articular surface of the affected tibia and the fracture. Thus, the aim of the present study was to analyze PM size in X-ray and CT studies and to relate the size of the fragment obtained from X-ray images to the articular area of the tibial plafond.

MATERIALS AND METHODS

Over a 5-year period from 2016 to 2021, 370 patients diagnosed with an ankle fracture were treated at our hospital (a level 1 trauma center). Of these fractures, 144 involved the PM. The study included patients aged 18 years or older with an

ankle fracture or fracture-dislocation involving the PM [AO Foundation/Orthopedic Trauma Association (AO/OTA) classification 44-A3, 44-B3, and 44-C1/2]. Cases of tibial plafond fractures, cases of ankle fractures associated with other hindfoot fractures, and cases with incomplete data in the medical records, such as absence of appropriate X-ray and CT images, were excluded. A total of 81 patients met the study's inclusion criteria. The study was approved by our Institutional Ethics Committee. The fractures were categorized according to the AO/OTA classification, and the Haraguchi CT classification was used specifically for the PM[26].

The Enterprise Imaging XERO Viewer software (Agfa HealthCare, Mortsel, Belgium) version 8.1.2 was used to select and analyze X-ray images, and the RadiAnt DICOM Viewer software (Medixant, Poznań, Poland) version 2.3 was used to analyze CT images. The PM fragments were measured on lateral X-ray images (PMXR) by two independent examiners (herein named X and Y), based on the relationship between fracture size and total articular surface (Figure 1). In sagittal CT (SAGCT) slices, the image with the largest PM was selected, and the latter was measured by the two examiners (X and Y). Similarly, to PMXR, PM size in SAGCT was measured using the proportion between the size of the fracture fragment and the total length of the joint (Figure 2). A second CT image was used in the axial plane to determine the size of the affected articular area in the tibial plafond. A point 5 mm above the highest point of the tibial articular surface was marked on the sagittal plane, and the corresponding axial (AXCT) slice was selected. The total tibial and PM areas were measured using the RadiAnt DICOM Viewer 2.3 software, and the fragment size relative to the total tibial plafond area on the AXCT was calculated (Figure 3).

Fractures were categorized into two groups based on the PMXR measurement: (1) PM < 25% of the joint; and (2) PM ≥ 25% of the joint. This cutoff value was used due to the consensus in the literature. Based on these groups, PM size was compared between PMXR and SAGCT, and the mean value of the examiners' measurements was considered. A second evaluation was performed to determine the difference in PM size based on a classification of the fractures into smaller PMXR intervals, namely < 15%, 15%–19.9%, 20%–24.9%, 25%–29.9%, and ≥ 30% of the articular surface. For AXCT, the size of the affected articular surface was measured in both groups (A and B), and the size of the PM and the involvement of the articular surface were compared in the respective morphological categories using the classification proposed by Haraguchi *et al*[26].

The statistical analysis was performed using the SPSS Statistics software for Mac (IBM Corporation, Armonk, NY, United States), version 23, considering the mean of the values obtained by the examiners in PMXR and SAGCT. Data normality was tested for the quantitative variables using the Kolmogorov–Smirnov test. Interobserver reliability was assessed using the Kappa method for the qualitative variables and Pearson's correlation for the quantitative variables. For direct comparison between X-ray and CT, the paired-sample *t*-test or the Wilcoxon, Mann–Whitney, and Kruskal–Wallis tests were used, depending on data normality, type of variable, and number of groups. The significance level was $P < 0.05$, with a 95% confidence interval.

RESULTS

A total of 81 patients participated in the study, of whom 44 were male (54.3%) and 37 were female (45.6%), with a mean age of 39.4 years (± 13.5). One ankle fracture (1.2%) was type A in the AO/OTA classification, 51 (62.9%) were type B, and 29 (35.8%) were type C. It was observed that the PM presented more than one fracture line in 22 cases (27.2%), which is described in the literature as a chondral or intercalary fragment at the center of the fracture, between the metaphysis and the posterior tibial cortex[29,30] (Table 1).

The PMXR sizes measured by examiners X and Y were 21.15% and 20.46%, respectively, with a mean of 20.81% and Pearson's correlation index of 0.93 ($P < 0.001$). With regard to SAGCT, the values obtained were 23.45% and 22.39%, with a mean of 22.92% and Pearson's index of 0.94 ($P < 0.001$). This interobserver correlation was excellent both for PMXR and SAGCT (Table 2). Thus, regardless of the measured image, a good interobserver evaluation was obtained with the proposed measurement method. A significant difference was found in mean size between the images, with PM size in SAGCT being 2.12% (95% confidence interval: 0.3–3.8) greater than in X-ray images ($P = 0.018$).

When the sample was divided into two groups according to PMXR size, groups A (< 25%) and B (≥ 25%) had 56 and 25 patients, or 69.13% and 30.86% of the sample, respectively. When analyzing the AXCT of all fractures, the PM affected a mean 14.57% of the tibial plafond, but there was a difference between the groups, with 10.13% and 24.52% of the tibial plafond affected in group A (< 25%) and in group B (≥ 25%), respectively, ($P < 0.001$) (Table 3). The subdivision into the < 15.0%, 15.0%–19.9%, 20.0%–24.9%, 25.0%–29.9%, and ≥ 30.0% intervals and their respective AXCTs (Table 3) was performed to evaluate the gradual increase in the affected articular surface according to PMXR size. There were differences among all the evaluated subgroups, namely a gradual surface increase with the increase in PMXR; only the 20.0%–24.9% interval showed no statistical significance relative to the previous subgroup.

According to the Haraguchi classification, 29 fractures (35.8%) were type I, 33 (40.7%) were type II, and 19 (23.4%) were type III. In group A there were 21, 16, and 19 type I, type II, and type III fractures, respectively, whereas in group B there were 8 and 17 type I and type II fractures, respectively. The analysis of PM size in the X-ray images showed that type I and type II fractures had similar PMXR size (21.6% and 24.8%) and that both were larger than type III (small shell-shaped) fractures ($P < 0.001$).

In the overall evaluation of the articular surface, differences were found in AXCT among all Haraguchi CT categories, with PM fragments with mean values of 12.24%, 22.80%, and 3.84% of the tibial plafond surface, respectively, resulting in II > I > III ($P < 0.001$) (Table 4 and Figure 4). Differences in the articular surface of the tibial plafond (AXCT) for the Haraguchi subtypes were found in both groups, with $P < 0.001$ in group A and $P = 0.002$ in group B (Table 5 and Figure 5).

Table 1 Demographic and lesion characteristics, *n* = 81

Characteristic	Subcategory	*n* (%)
Age[a]		39.48 (± 13.59)
Sex	Male	44 (54.32)
	Female	37 (45.67)
Diagnosis	Fracture	42 (51.85)
	Fracture + dislocation	39 (48.14)
AO/OTA 44	A	1 (1.23)
	B	51 (62.96)
	C	29 (35.80)
Haraguchi	1	29 (35.80)
	2	33 (40.74)
	3	19 (23.45)
Intermediate fragment	Yes	22 (27.16)
	No	59 (72.83)

[a]Mean (standard deviation). AO/OTA: AO Foundation/Orthopedic Trauma Association.

Table 2 Interobserver reliability of posterior malleolus size measurements

	Examiner X	Examiner Y	Pearson's	*P* value
X-ray measurement				
Absolute size of the tibia	5.28 (± 0.83)	5.09 (± 0.82)	0.88	< 0.001
Absolute size of the PM	1.43 (± 0.75)	1.32 (± 0.69)	0.92	< 0.001
MP size (PMXR)[a]	21.15 (± 10.20)	20.46 (± 9.66)	0.93	< 0.001
Mean PM size[a]	20.81 (± 9.70)		-	-
CT measurement				
Absolute size of the tibia	3.23 (± 0.65)	3.13 (± 0.62)	0.95	< 0.001
Absolute size of the PM	0.97 (± 0.38)	0.88 (± 0.37)	0.89	< 0.001
PM size (SAGCT)	23.45 (± 9.51)	22.39 (± 9.96)	0.94	< 0.001
Mean PM size	22.92 (± 9.60)			
Interobserver agreement				
PM < 25% in X-ray images	56	58	0.88	< 0.001
PM ≥ 25% in X-ray images[b]	25	23		
PM < 25% in CT[b]	51	56	0.76	< 0.001
PM ≥ 25% in CT[b]	30	25		

[a]Percentage.
[b]Cases (absolute frequency). CT: Computed tomography; PM: Posterior malleolus; PMXR: Profile X-ray images of the posterior malleolus; SAGCT: Sagittal computed tomography images of the posterior malleolus.

DISCUSSION

Historically, X-ray has been the most widely used imaging technique in the diagnosis of malleolar fractures and consequently of PM fractures. The indication for PM fixation is mostly associated with its size relative to the joint, although no consensus has emerged to date on the smallest articular fragment size that requires surgery[8,30,31].

Table 3 Analysis of the articular surface of the ankle affected by the posterior malleolar fracture in axial computed tomography slices

Grouping according to PMXR < 25% and ≥ 25% (cases)	All cases	Group A, < 25%	Group B, ≥ 25%	*P* value	
	14.57% (81) (± 9.84)	10.13% (56) (± 6.71)	24.52% (25) (± 8.40)	< 0.001	
Subdivision of PMXR, %	< 14.9	15.0-19.9	20.0-24.9	25.0-29.9	≥ 30.0
Affected articular surface % (cases)	7.65 (26) (± 6.92)	11.03[a] (18) (± 5.57)	14.31 (11) (± 6.34)	20.79[a] (14) (± 4.19)	27.87[a] (12) (± 10.78)

[a]Statistically significant ($P < 0.05$) when compared to the previous group. PMXR: Profile X-ray images of the posterior malleolus.

Table 4 Relationship between the size of the posterior malleolus and the affected articular surface according to the Haraguchi classification

Classification	Haraguchi			
	I	II	III	*P* value
Cases (%)	29 (35.8)	33 (40.7)	19 (23.4)	N/A
X-ray				
PM size % (PMXR)	21.66[a] (± 9.91)	24.84[a] (± 9.03)	12.45 (± 4.17)	< 0.001
CT				
Articular surface of the tibial plafond % (AXCT)	12.24 (± 5.47)	22.80 (± 8.28)	3.84 (± 2.78)	< 0.001

[a]There was a statistically significant difference only when compared to Haraguchi III. There was no significant difference between Haraguchi I and II; there was a statistically significant difference when all categories were compared. The $P < 0.001$ value was found when comparing the three groups and indicates a significant statistical difference. AXCT: Axial computed tomography slice of the posterior malleolus; CT: Computed tomography; N/A: Not applicable; PM: Posterior malleolus; PMXR: Profile X-ray images of the posterior malleolus.

Table 5 Articular surface of the posterior malleolus in axial computed tomography slices according to the Haraguchi classification

Haraguchi (*n*)	Size of the posterior malleolus, by X-ray	
	< 25%, *n* = 56	≥ 25%, *n* = 25
I (29)	10.84% (± 3.74)[a]	15.29% (± 7.62)[b]
II (33)	17.99% (± 5.79)[a]	27.33% (± 7.81)[b]
III (19)	3.84% (± 2.78)[a]	-

[a]$P < 0.001$.
[b]$P = 0.002$.

The fact that there are different forms of measuring PM size should be considered. In addition, factors, such as image quality, immobilizations, and fixations, can interfere with PM measurement[20]. Several X-ray parameters have been studied to interpret ankle fractures, and PM size has good interexaminer reproducibility[21]. There is controversy regarding the best way of measuring PM size in lateral X-ray images; moreover, interobserver agreement shows variable results[22]. Currently, many authors consider CT essential for an adequate understanding of PM fractures due to the limitations of X-ray images and because CT aids in surgical planning by providing information on PM size and morphology and on its relationship with other malleoli and with the syndesmosis[20-22,32,33].

In the present study, considering only the X-ray images, the interobserver correlation for PM size was 0.93 ($P < 0.001$), which is excellent and higher than that obtained by Meijer *et al*[22] in an analysis with a larger number of examiners. This result suggests that good quality preoperative X-rays are fundamental for the adequate interpretation of the PM findings. A correlation of 0.94 ($P < 0.001$) was also achieved in the measurement performed in sagittal CT, which showed that an accurate measurement of the PM can be achieved using a simple method, regardless of the complementary exam that is used.



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Figure 1 Measurement of the size of a posterior malleolus fracture fragment in a profile X-ray image. The proportion between the fracture and the total articular surface, *i.e.* the a/(a + b) ratio, was evaluated.

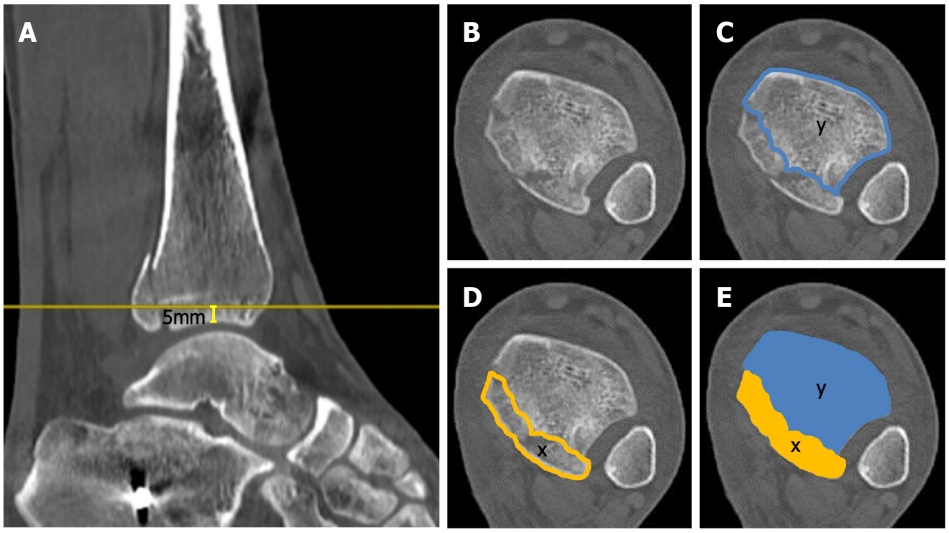


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Figure 2 Measurement of a posterior malleolus fracture fragment in a sagittal tomography slice R. Similarly to what was completed for X-ray images, the proportion between the fracture and the total articular surface, *i.e.* the a/(a + b) ratio, was evaluated.

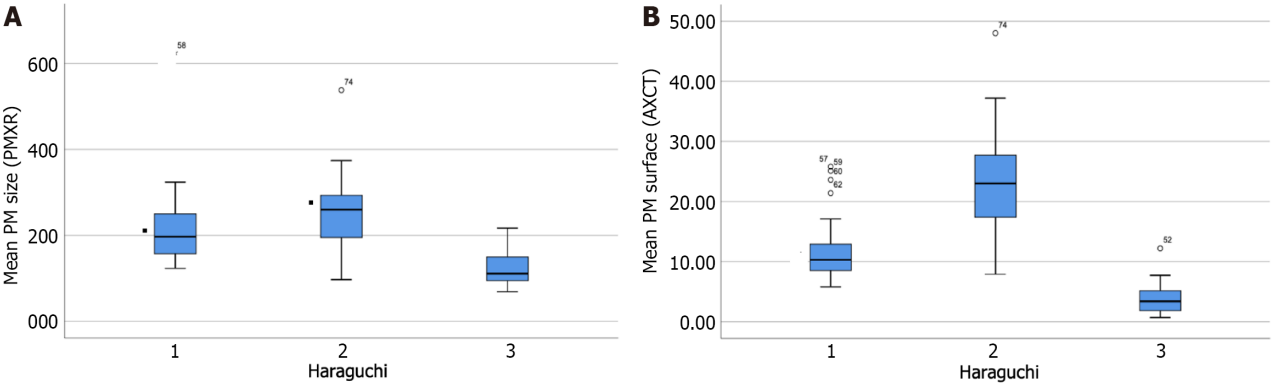
Most patients (56; 69.1%) had PM < 25% in PMXR. Therefore, if only the PM size was considered, the choice would be not to fix that fragment[13,16,34]. Stringfellow *et al*[35] compared X-ray and CT images and found that CT slices showed a larger PM than X-ray images in 92% of the cases. This result is similar to that obtained in the present study, in which the mean PM was found to be 2.12% larger (P = 0.018) in CT images. Thus, considering only the 25% cutoff value in PMXR as an indication for PM fixation, patients with fractures considered to be borderline, with PMXR values close to 25%, would probably fail to have the posterior fragment treated adequately if the diagnosis were based solely on X-ray images. For this reason, in recent decades, several authors started recommending the fixation of fragments < 25% because they feared that X-ray images could underestimate PM size when compared to CT[10,21].

Another concern is that X-ray images may not be adequate for the visualization of small osteochondral fragments and articular surface impaction[23,29,30,36]. The present case series supports this concern, as an osteochondral or intermediate fragment was found in 27.1% of CT images. Similarly, Büchler *et al*[21] reported that 23% of osteochondral



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Figure 3 Axial computed tomography scan posterior malleolus measure. A: The sagittal plane; B: The corresponding axial slice was selected 5 mm above the highest point of the tibial articular surface; C: In the axial image, the tibial articular surface; D: The area corresponding to the posterior malleolus fracture was measured; E: Thus, the x/(x + y) ratio was used to obtain the percentage of the tibial plafond surface (axial view) involved in the posterior malleolus.



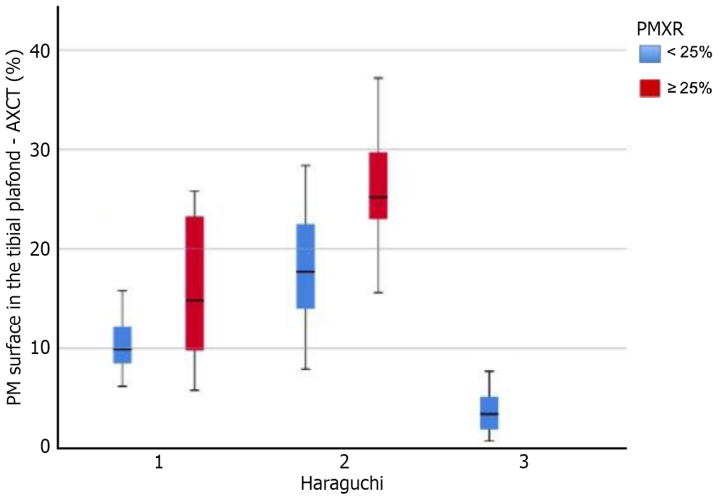
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Figure 4 Comparative size of posterior malleolus on X-rays and axial computed tomography scan according to the Haraguchi classification. A: The percent size of the posterior malleolus measured in profile X-ray images according to Haraguchi classification; B: The percent size of the posterior malleolus measured in axial tomography images according to the Haraguchi classification. A statistically significant difference was found only when compared to Haraguchi 3. No difference was found between Haraguchi 1 and 2 ($P < 0.001$). PMXR: Posterior malleolus size in profile X-ray images; AXCT: Axial computed tomography slice of the posterior malleolus.

fractures were not identified in X-ray images but were present in sagittal CT slices, thus suggesting that X-ray images have low sensitivity for diagnosing intermediate PM fragments, which could be a further hindrance for articular reduction[21,23,30].

By correlating X-ray images with axial CT slices, it is possible to determine the size of the articular surface affected by the PM fragment. In an initial evaluation considering groups < 25% and ≥ 25%, a significant difference in the percentage of affected articular surface was found: 10.13% *vs* 24.52% ($P < 0.001$). Previous studies have proposed random predetermined PM size intervals to evaluate the clinical results, articular congruity, and post-traumatic arthritis[35]. Similarly, by determining smaller PM intervals for X-ray images (< 15.0%, 15.0%-19.9%, 20.0%-24.9%, 25.0%-29.9%, and ≥ 30.0%), it was possible to evaluate the gradual increase in the percentage of affected articular surface in each interval relative to the previous interval. It should be noted that fragments in intervals 15.0%-19.9% and 20.0%-24.9% may have a similar articular surface. These results indicate that fragments considered small in X-ray images represent a relatively larger articular surface.

When the fractures were grouped according to their CT classification, type I and type II fractures had a similar size in X-ray images and could only be differentiated from type III (small shell) fractures; however, axial CT showed the difference between the articular surfaces of each CT type, as shown by the descriptive study of Haraguchi *et al*[26]. All the different CT types of fractures also showed differences in the size of the axial surface between groups A and B. We emphasize that the articular surfaces of the tibial plafond in type II fractures in group A and type I fractures in group B were of similar size (Figure 5). This means that although type II fragments in group A were deemed small in X-ray



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Figure 5 The distribution of the percent area of the tibial plafond of the posterior malleolus fracture according to the various Haraguchi classification types. Blue: Group A; Red: Group B; PMXR: Posterior malleolus size in profile X-ray images; AXCT: Axial computed tomography slice of the posterior malleolus; PM: Posterior malleolus.

images (< 25%), the articular involvement was similar to that of a large fragment, such as one from group B. This information can only be obtained from the CT evaluation. Thus, the exclusive use of X-ray images for preoperative planning is associated with the risk of PMs with a larger area than expected being treated inadequately, which can interfere with the patient's postoperative results.

The present study achieved a relevant sample, considering other studies on the same subject[26-28], and the study variables showed excellent correlation and interobserver agreement according to Landis and Koch[37], who demonstrated the applicability of the measuring method. However, the present study also had some limitations. The distribution of PM fractures among the three CT categories was satisfactory. However, there was a significant sample loss, and the distribution was based solely on 2D CT images, when some studies also used 3D images to evaluate PM[22, 33]. Finally, the present findings add new information to the topic of articular involvement in PM fractures, which will hopefully aid the analysis of the clinical results of patients with PM fractures in future studies.

CONCLUSION

The size of PM fractures varies when evaluated by X-ray and CT. CT studies show a larger PM in the sagittal plane compared to PMXR images, and they also allow the identification of the presence of intermediate or chondral fracture fragments. Preoperative CT makes it possible to determine the real size of the articular surface of the tibial plafond, which can be underestimated if only X-ray is used.

ARTICLE HIGHLIGHTS

Research background

For many decades when a posterior malleolus (PM) fracture was diagnosed, the size of the fragment on radiographs was always taken into consideration at the time of treatment. Therefore, fixation of the PM was recommended when greater than 25% of the tibial joint surface was involved.

Research motivation

This study aimed to see the real size of the PM fragment in ankle fractures and determine whether an X-ray image would be sufficient to show the real size of the fracture. It is also unknown if there is any correlation between PM size on X-rays and computed tomography (CT) scans.

Research objectives

To compare the PM size of the X-rays with the sagittal CT scans to see if they are similar and to evaluate the PM size compared with the axial CT scan and the articular surface of the tibial plafond involved in the ankle fracture.

Research methods

Two foot and ankle specialists compared measurements of PM size on radiographs with CT scans. The PM size on the

sagittal images and the joint surface area of the tibial plafond on the axial images were compared.

Research results

We found that PM fragments were 2.12% larger in sagittal CT than in X-rays. When analyzing axial CT scans, a significant difference was found between the three types of Haraguchi fractures.

Research conclusions

PM fractures showed different sizes using X-ray or CT images. CT showed a larger PM in the sagittal plane and allowed the visualization of the real dimensions of the tibial plafond surface.

Research perspectives

This study showed that CT is better to understand the size of the PM. Even small PM fractures on X-rays can affect a large portion of the articular surface. It would be recommended not to underestimate small PM fractures and always perform preoperative CT evaluation.

FOOTNOTES

Author contributions: De Marchi Neto N, Christian RW and Severino NR contributed to conceptualization; De Marchi Neto N and Nesello PFT contributed to methodology; De Marchi Neto N and Nesello PFT contributed to formal analysis and investigation; De Marchi Neto N and Nesello PFT contributed original draft preparation and figures; Bergamasco JMP and Costa MT contributed reviewing and editing; Christian RW and Severino NR contributed to supervision.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Efficacy and safety of thermobalancing therapy with Dr Allen's Device for chronic low back pain: A randomised controlled trial

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Abstract

BACKGROUND

Lumbar disc herniation and non-specific low back pain are common conditions that seriously affect patients' health-related quality of life (HRQoL). Although empirical evidence has demonstrated that novel Thermobalancing therapy and Dr Allen's Device can relieve chronic low back pain, there have been no randomised controlled trials for these indications.

AIM

To evaluate the efficacy of Dr Allen's Device in lumbar disc herniation (LDH) and non-specific low back pain (NSLBP).

METHODS

A randomised clinical trial was conducted investigating 55 patients with chronic low back pain due to LDH (n = 28) or NSLBP (n = 27), out of which 15 were randomly assigned to the control group and 40 were assigned to the treatment

group. The intervention was treatment with Dr Allen's Device for 3 mo. Changes in HRQoL were assessed using the Numerical Pain Rating Scale and the Japanese Orthopedic Association Back Pain Questionnaire.

RESULTS

Thermobalancing therapy with Dr Allen's Device showed a significant reduction in pain in the treatment group ($P < 0.001$), with no recorded adverse effects. Both pain assessment scales showed a significant improvement in patients' perception of pain indicating improvement in HRQoL.

CONCLUSION

The out-of-hospital use of Thermobalancing therapy with Dr Allen's Device for Low Back Treatment relieves chronic low back pain significantly and without adverse effects, improves the level of activity and HRQoL among patients with LDH and NSLBP. This study demonstrates the importance of this safe first-line therapy that can be used for effective at-home management of chronic low back pain.

Key Words: Chronic low back pain; Lumbar disc herniation; Non-specific low back pain; Thermobalancing therapy; Dr Allen's Device; Numerical pain rating scale

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Core Tip: This prospective randomised controlled trial assessed the efficacy and safety of novel Thermobalancing therapy and wearable Dr Allen's Device for chronic low back pain. Patients with non-specific low back pain and lumbar disc herniation were assessed by the Numerical Pain Rating Scale, and the Japanese Orthopedic Association Back Pain Evaluation Questionnaire. Research results showed a significant reduction in pain and the improvement in patients' health-related quality of life in the treatment group. No adverse effects were observed. Therefore, Thermobalancing therapy with Dr Allen's Device can be recommended for the at-home management of chronic low back pain.

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INTRODUCTION

Non-specific low back pain (NSLBP) is the leading cause of disability worldwide[1]. Of the numerous causes of low back pain, lumbar disc herniation (LDH) is a major contributor accounting for around 9% of chronic low back pain (CLBP) in the population[2]. The main symptom of LDH and NSLBP is chronic pain in the lower spine area that can impact the quality of life and heavily burden individuals, their families, and society[3].

Common treatments for NSLBP and LDH include pain management with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids and anticonvulsants, steroid injections, and spinal surgeries. Oral medications for pain control can be effective but they only provide short term symptomatic relief and are not without adverse effects. NSAIDs, acetaminophen and anticonvulsants can cause serious side effects and can lead to health problems, such as gastrointestinal complications and cardiovascular events[4,5]. Opioid use in people with chronic pain can cause constipation, nausea, itching, dizziness and can even result in opioid dependence. Opioid overdose is becoming a major public health problem[6,7]. Epidural "around the spinal cord" steroid injections aimed at relieving low back pain can lead to irreversible complications and should therefore be used as the last resort[8]. Lower back surgeries may provide pain relief more rapidly than conservative therapy but carry more risk and the outcomes at one year are similar using both these modalities. Moreover, surgery can still be an option after conservative therapy[9].

The above adverse effects of the available treatment options for low back pain limit their use and highlight the need for a conservative, safe and effective mode of treatment.

Over the last decade, Thermobalancing therapy and non-invasive Dr Allen's Devices were used in patients for effective and safe out-of-hospital management of chronic diseases affecting different organs. This novel treatment was patented as "Therapeutic device and method"[10].

The use of Thermobalancing therapy with Dr Allen's Device as a monotherapy in men over 55 years of age with benign prostatic hyperplasia (BPH) showed improvement of clinical symptoms, including lower urinary tract symptoms[11,12]. Evidence also suggests that Thermobalancing therapy is effective in the treatment of chronic prostatitis/chronic pelvic pain syndrome[13] and kidney stone disease (KSD) without renal colic[14].

Although empirical evidence has also demonstrated that this novel treatment option can relieve chronic low back pain in cases of lumbar disc herniation and non-specific causes, there have been no randomised control trials for these indications.

This is the first clinical study that attempts to demonstrate the effectiveness and safety of Dr Allen's Device for Low Back Treatment in patients with chronic low back pain due to LDH or NSLBP, as well as the ability of this therapy to improve health-related quality of life (HRQoL).

MATERIALS AND METHODS

Study design and participants

Our study was a prospective, randomised, interventional, parallel group study conducted to demonstrate the efficacy of Dr Allen's Device for low back treatment in the management of chronic low back pain. The trial was registered at the Iranian Registry of Clinical Trials. The study was conducted in accordance with the Declaration of Helsinki. It was approved by the Ethics Review Committee.

Patients aged 18-60 years having low back pain for at least 12 wk were recruited at a hospital and an outpatient clinic for the trial after initial radiological evaluation. For every patient with LDH, one patient with NSLBP was recruited to maintain a 1:1 ratio of the conditions. Participants were excluded if they had severe co-morbidities, such as cancer, heart failure or infection.

A total of 55 male and female patients with low back pain met the eligibility criteria and were recruited for the study. The patients were then randomised into treatment and control groups. This resulted in two groups: A treatment group of 40 patients with chronic low back pain, consisting of 20 patients with NSLBP and 20 patients with LDH, and a control group of 15 patients consisting of 7 patients with NSLBP and 8 patients with LDH. Randomisation was performed using simple randomisation procedures and computer-generated random numbers. No blinding was done due to the nature of the intervention.

Patient satisfaction was considered an adequate representation of treatment efficacy and was assessed at the beginning of the study and after treatment using two well-established self-administered questionnaires: Numerical Pain Rating Scale (NPRS)[15] and The Japanese Orthopedic Association Back Pain Evaluation Questionnaire (JOABPEQ)[16]. The NPRS scores were obtained at the beginning of the study and after 1 and 3 mo of using Dr Allen's Device for low back treatment, and the JOABPEQ scores were obtained at the beginning and end of therapy.

Randomisation

A total of 55 patients with chronic low back pain were recruited for the clinical trial after receiving a detailed explanation of the clinical trial and the possible benefits of thermobalancing therapy, and after giving informed consent. They were divided into two groups, those with LDH and those with NSLBP, based on their aetiology identified by radiological imaging. The ratio of patients in these groups was 1:1 as an equal number of patients with LDH (n = 28) and NSLBP (n = 27) were recruited. Although NSLBP is more common on average in the general population, the type of pain in LDH tends to be more severe, and such patients present more frequently to the hospital compared to patients with NSLBP.

Each group (LDH, NSLBP) was randomised separately using a 3:1 ratio for ethical reasons as the control group was not going to receive the intervention. It was decided that a larger treatment group would allow for a better understanding of adverse effects if any. Patients with LDH were randomised into a treatment group of 20 patients and a control group of 8 patients and patients with NSLBP were randomised into a treatment group of 20 patients and a control group of 7 patients. The final treatment group consisted of 40 patients and the control group consisted of 15 patients.

Intervention

The intervention was Thermobalancing therapy with Dr Allen's Device for Low Back Pain Treatment used as a monotherapy for a 3-mo period. The patients in the treatment group used Dr Allen's Device for low back pain treatment as a monotherapy for 3 mo. Patients in the control group did not receive any intervention.

Dr Allen's Device for Low Back Pain Treatment

Dr Allen's Device is a Class I medical device and registered with the British Medicines and Healthcare Products Regulatory Agency (MHRA). Thermobalancing therapy with Dr Allen's Device can be used as an out-of-hospital treatment by patients at home. Dr Allen's Device applies a thermoelement, made from a special wax-based material, topically to the skin or worn over close-fitting underwear over the affected organs. In people with lower back pain, the thermoelement is applied to the back over the sore area (Figure 1). This thermoelement accumulates the naturally emitted body heat, warms up, directs heat to the region of pain, and maintains the optimal level of heat in the region of pain over time. Wearing and using Dr Allen's Device for Low Back Pain Treatment is comfortable.

Outcomes

The NPRS and the JOABPEQ were used to assess the effectiveness of treatment. The NPRS is an 11-point pain rating scale that can be used to estimate the degree of pain experienced by the patient. The scale ranges from 0 (no pain) to 10 (worst imaginable pain)[17]. A study about the responsiveness of NPRS has found that a 2-point improvement represents meaningful change[18].

The JOABPEQ has 25 questions which evaluate 5 functional domains with scores ranging from 0-100. According to a study, a 20 point improvement in the functional domains of JOABPEQ represents meaningful change[19].

In our study, the change in the NPRS score and the functional domains of JOABPEQ assessed before the intervention and during the follow up period was considered as the primary endpoint.



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Figure 1 Dr Allen's Device for Low Back Pain Treatment applied to the affected lower back area.

Sample size estimation

Sample size was calculated using G*Power software. A total of 54 participants (40 participants in treatment group and 14 participants in control group) were required to conduct a two tailed study with a type I error of 5% and a power of 80%. We had 15 patients in the control group.

Statistical analysis

The collected data was organised in Microsoft Excel and statistical analysis of the results was performed using the Data Analysis module of Microsoft Excel 2010. Paired sample t-tests were used for the comparison of parametric data. The non-parametric data was assessed using the Mann-Whitney U test. A P value < 0.05 was considered statistically significant.

RESULTS

A total of 55 patients with chronic low back pain either due to NSLBP (n = 27) or LDH (n = 28) identified by radiological assessment participated in the study. After randomisation, the treatment group consisted of 40 patients, 20 with LDH and 20 with NSLBP, and the control group consisted of 15 patients, 8 with LDH and 7 with NSLBP, as shown in the patient allocation flow diagram (Figure 2).

Mean age of the patients was 41.07 ± 8.05 years. The overall male to female ratio was 29:26. Correlation analysis between demographic variables and the NPRS and JOABPEQ scores and patient characteristics are detailed in Table 1. Pearson's product-moment correlation was used for continuous variables and point-biserial correlation was used for dichotomous variables.

For initial evaluation, patients were presented with the NPRS scale and the JOABPEQ. Instructions about how to answer the questions were provided and the clinicians ensured that the patients understood the questions adequately in order to obtain the most accurate responses. Details of low back pain intensity experienced by the patients was obtained using the NPRS scale as answers to four questions, namely, "How would you rate your pain RIGHT NOW", "USUAL level of pain during the last week", "BEST level of pain during the last week" and "WORST level of pain during the last week". The patients scored the intensity of their pain from 0 to 10.

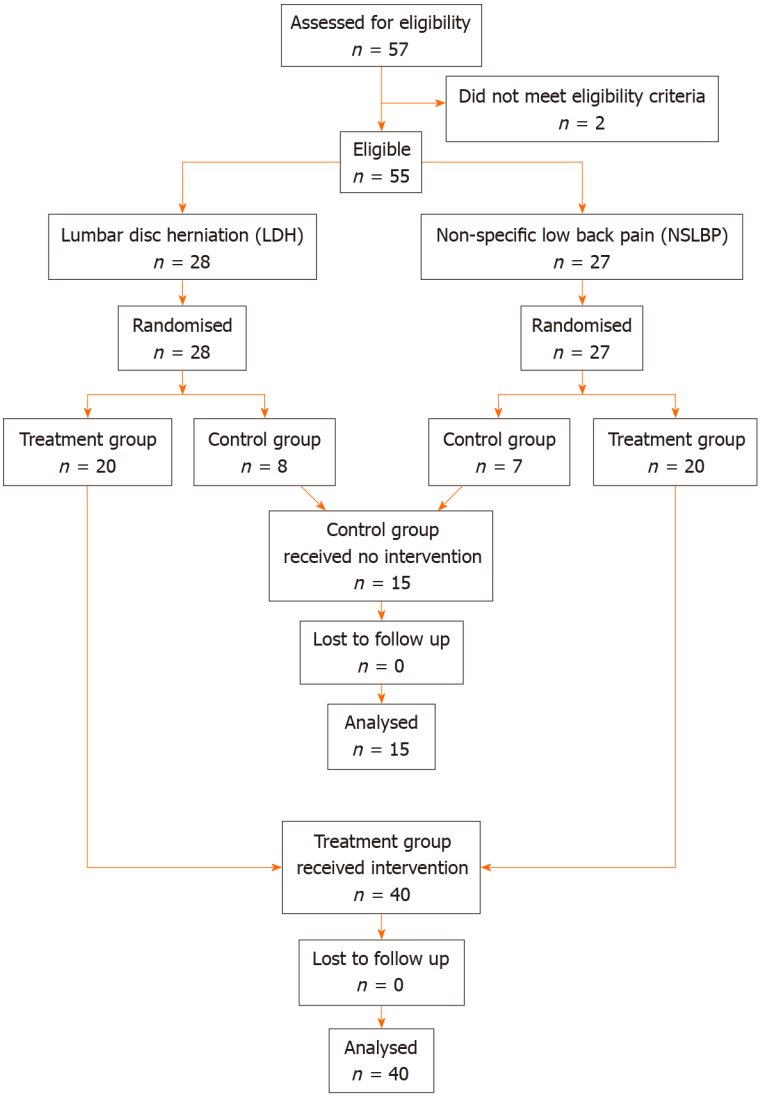
The JOABPEQ questionnaire required answers to 25 separate questions which were then evaluated to scores ranging from 0 to 100 for five different functional domains.

The NPRS scale was presented to the patients again at the end of one month, and the NPRS scale and the JOABPEQ were presented to the patients again at the end of three months of treatment and their responses were compared with the initial assessment.

A 2-point improvement in the different parameters of the NPRS scale was considered significant. Out of the 40 patients in the treatment group, 82.5%, 77.5%, 75% and 75% showed significant improvement in the "How would you rate your pain RIGHT NOW", "USUAL level of pain during the last week", "BEST level of pain during the last week" and the "WORST level of pain during the last week" scores respectively. A total of 7 patients had unchanged scores and 2 patients experienced increased pain intensity.

In the control group, none of the patients showed any significant improvement. Out of the 15 patients in the control group, 26.67%, 40%, 40% and 13.3% showed significant increase in the "How would you rate your pain RIGHT NOW", "USUAL level of pain during the last week", "BEST level of pain during the last week" and "WORST level of pain during the last week" scores indicating increase in pain intensity. Scores remained unchanged in 12 patients.

On statistical analysis, the comparison of the mean initial and final pain scores in the treatment group was found to be statistically significant across all the parameters of the NPRS scale, while no statistically significant change was observed in the control group. The comparison is presented in Figure 3 and in Table 2.



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Figure 2 Patient allocation flow diagram.

The scores of the five domains of JOABPEQ evaluated at the beginning of the study were compared with those evaluated at the end of 3 months. In the treatment group, all 40 patients showed an improvement indicated by an increase in 20 points in the low back pain domain. A 72.5% improvement was observed in the lumbar function domain and 10% of the patients showed worsening. Walking ability was improved in 75% of the patients and worsened in 10% of the patients. Social life function was improved in 75% of the patients of the treatment group and worsened in 5%. Mental health was improved in 77.5% of patients, with no patients showing worsening.

In the control group, a very small proportion of patients, i.e., 13.3%, 6.7%, 20% and 6.7% of the 15 patients experienced an improvement in low back pain, lumbar function, walking ability and social life domains respectively. No improvement was observed in the mental health domain. Most patients experienced low scores across all domains.

A comparison of the mean difference between the scores of the five functional domains before and after thermobalancing therapy showed a statistically significant improvement across all domains in the treatment group. No significant improvement was observed in the control group, but a statistically significant worsening of lumbar function and mental health were seen further emphasising the need for effective treatment. This data is presented in Figure 4 and in Table 3.

The changes in the NPRS and the JOABPEQ scores before and after Thermobalancing therapy with Dr Allen's Device show significant improvement in pain perception in all patients in the treatment group.

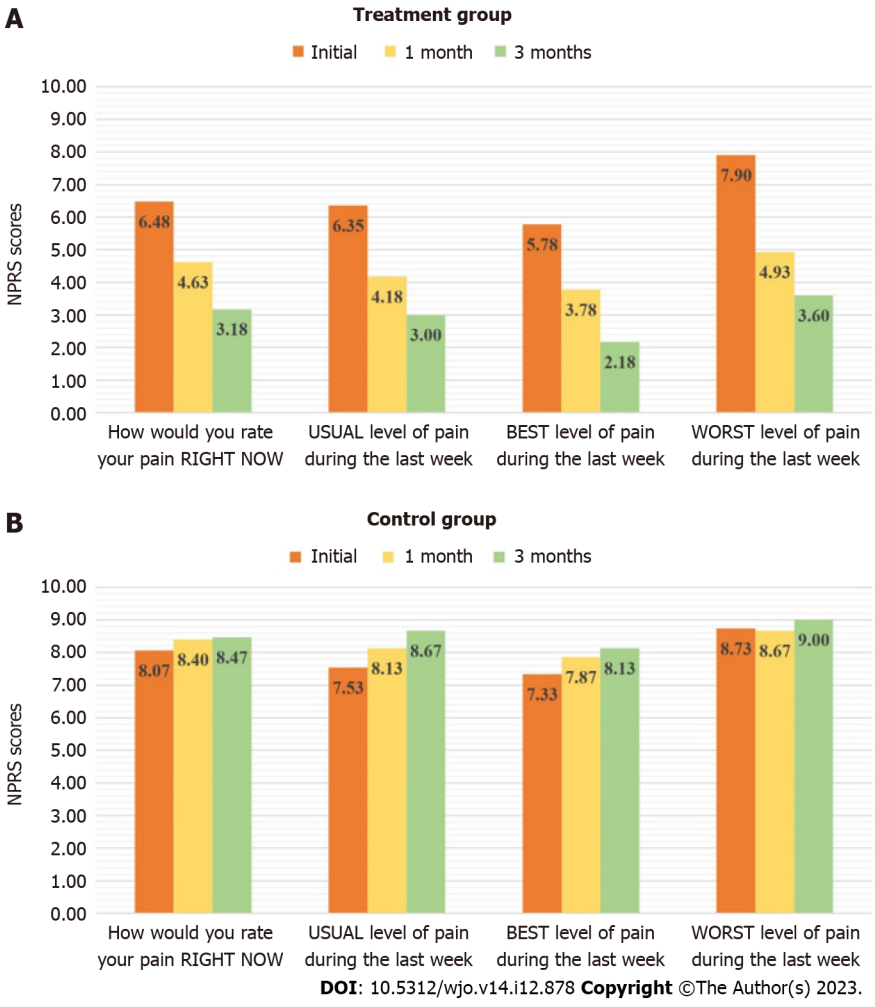
Harms

The use of Dr Allen's Device for low back pain treatment did not cause any adverse events in the participating individuals. This observation confirms that thermobalancing therapy and Dr Allen's Device are safe.

Table 1 Patient characteristics and correlation analysis

Characteristic	Treatment group	Correlation coefficient (r)	Control group	Correlation coefficient (r)
Number of patients (*n*)	40		15	
Age (mean ± SD)	42.2 ± 8.49	-0.1124[a]; 0.099[b]	38.06 ± 5.98	0.4919[a]; 0.045[b]
Gender (M:F)	18:22	0.2353[a]; -0.08[b]	11:4	0.1183[a]; -0.34[b]
NSLBP:LDH	1:1	-0.131[a]; 0.126[b]	7:8	0.1396[a]; 0.172[b]
NPRS – how would you rate your pain right now?	6.48 ± 1.63		8.07 ± 1.16	
JOABPEQ – low back pain	8.9 ± 14.38		10.40 ± 12.66	

[a]Correlation analysis with initial NPRS (How would you rate your pain right now?) score.
[b]Correlation analysis with initial JOABPEQ (Low back pain) score.
NSLBP: Non-specific low back pain; LDH: Lumbar disc herniation; NPRS: Numerical Pain Rating Scale; JOABPEQ: The Japanese Orthopedic Association Back Pain Evaluation Questionnaire.



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Figure 3 The comparison of mean Numerical Pain Rating Scale (NPRS) scores in the treatment and control groups at initial evaluation and at 1 and 3 mo. A: Treatment group; B: Control group.

DISCUSSION

The aim of this study was to determine the effect of Thermobalancing therapy on CLBP, defined as pain that continues for 12 wk or longer, and to assess the general improvement in the HRQoL in male and female patients when used as monotherapy compared with patients who received no treatment. The objective of this study was not to compare one treatment with another but to show the efficacy of the prolonged use of the intervention on the treatment group and, as

Table 2 Comparison of Numerical Pain Rating Scale scores before and after Thermobalancing therapy with Dr Allen's Device

	NPRS parameters	Initial (mean ± SD)	1 mo (mean ± SD)	3 mo (mean ± SD)	*P* value (0-3 mo)
Treatment group	How would you rate your pain RIGHT NOW	6.48 ± 1.63	4.63 ± 1.00	3.18 ± 1.87	**< 0.001**
	P value	**< 0.001**[a]	**< 0.001**[b]		
	USUAL level of pain during the last week	6.35 ± 1.23	4.18 ± 0.96	3.0 ± 1.43	**< 0.001**
	P value	**< 0.001**[a]	**< 0.001**[b]		
	BEST level of pain during the last week	5.78 ± 1.25	3.78 ± 0.97	2.18 ± 1.62	**< 0.001**
	P value	**< 0.001**[a]	**< 0.001**[b]		
	WORST level of pain during the last week	7.9 ± 1.50	4.93 ± 1.10	3.6 ± 2.01	**< 0.001**
	P value	**< 0.001**[a]	**< 0.001**[b]		
Control group	How would you rate your pain RIGHT NOW	8.07 ± 1.16	8.4 ± 0.63	8.47 ± 0.64	> 0.05
	P value	> 0.05[a]	> 0.05[b]		
	USUAL level of pain during the last week	7.53 ± 0.92	8.13 ± 0.52	8.67 ± 0.49	> 0.05
	P value	> 0.05[a]	> 0.05[b]		
	BEST level of pain during the last week	7.33 ± 0.98	7.87 ± 0.64	8.13 ± 0.74	> 0.05
	P value	> 0.05[a]	> 0.05[b]		
	WORST level of pain during the last week	8.73 ± 1.10	8.67 ± 0.49	9.00 ± 0.38	> 0.05
	P value	> 0.05[a]	> 0.05[b]		

[a]*P* value comparing NPRS score at 0 and 1 mo.
[b]*P* value comparing NPRS score at 1 and 3 mo.
NPRS: Numerical Pain Rating Scale; SD: Standard deviation.

expected, the final data showed a significant improvement in pain in the treatment group and no change in the control group indicating that the intervention was efficacious.

A difference in baseline NPRS scores of the treatment and control groups was observed. This can be attributed to the difference in the sizes of the treatment (n = 40) and control (n = 15) groups. Since this difference in baseline values occurred despite efficient randomisation, we consider the data valid.

The results of our study show that Thermobalancing therapy is safe and reduces the intensity of back pain, consequently improving the level of activity among patients with LDH and NSLBP. The results showed that there was significant difference in the improvement of daily activities between the treatment and control groups with the treatment group showing a striking functional improvement. However, the difference in effectiveness between the NSLBP treatment group and the LDH treatment group was not significant, implying that Dr Allen's Device was equally effective in improving the symptoms and functional activity in chronic low back pain due to lumbar disc herniation or other non-specific causes.

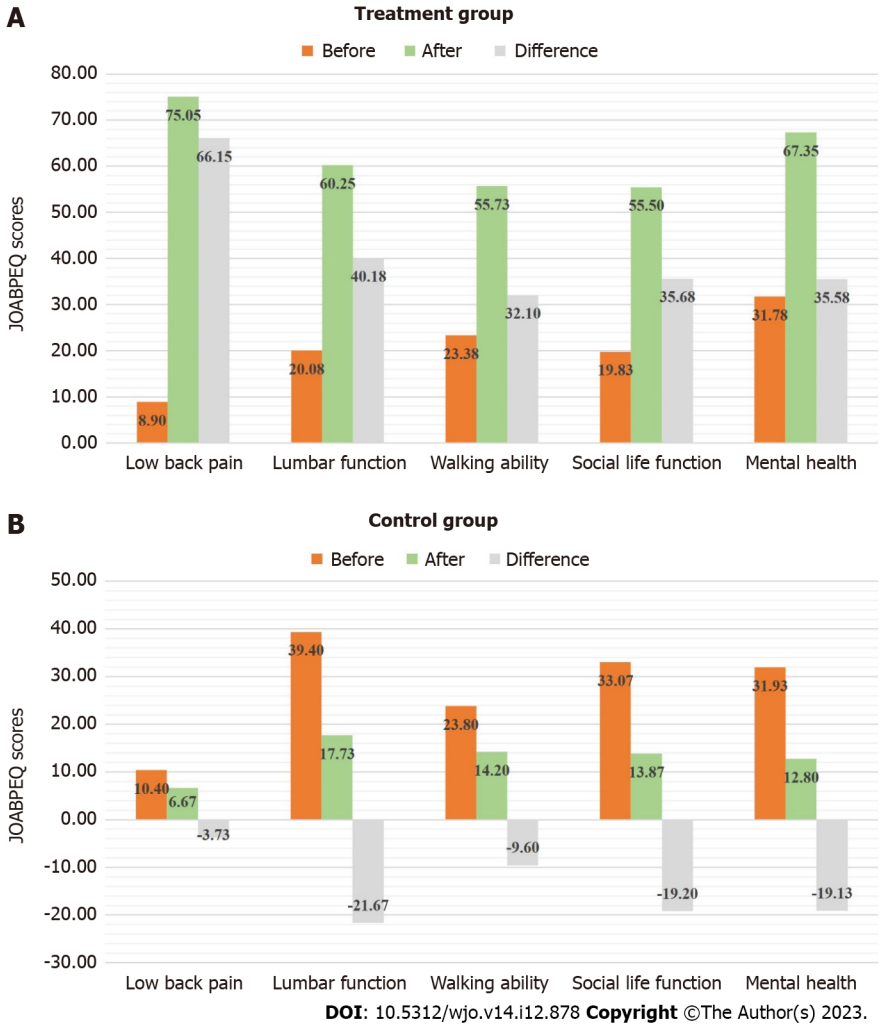
These findings allow to suggest that Dr Allen's Device can be used as the first-line therapy for chronic low back pain.

Low back pain can occur due to a variety of causes, and, in most instances, the cause is multifactorial. The pain can be caused due to a pathology in either the soft tissues, the vertebrae, the joints, intervertebral discs, or neurovascular structures. The numerous treatment modalities available for low back pain include conservative treatments like self-care, psychological care, physical rehabilitation and symptomatic care, and surgical procedures in refractory cases where the pain is not amenable to any conservative option. But most treatment modalities are singular in their effectiveness and, therefore, are not effective when more than one cause of the pain concurrently exist[20].

Dr Allen's Device for low back treatment is a novel, conservative option in the treatment of chronic pain in the lower spine. It is easy to use with no identified adverse effects in the short or long term. It is a comfortable, wearable device which allows long term patient compliance. As observed in our study, thermobalancing therapy and Dr Allen's Device provide pain relief in chronic low back pain due to intervertebral disc related causes as well as other causes, thereby making it a holistic treatment option for this condition.

Low back pain is more common in females than in males and its prevalence increases with age. A study evaluated physical and mental health indicators to assess the quality of life in patients with low back pain and found that irrespective of sociodemographic conditions, and the presence of other comorbidities or causes of chronic pain, low back pain can significantly lower quality of life[21].

The NPRS scale and the JOABPEQ are indicators of pain intensity and quality of life respectively. Both these indicators have been found to be reliable, responsive, and valid as indicators of pain and functional abilities. The combined use of NPRS scale and JOABPEQ as done in our study have been found to be the most appropriate tools to assess pain as well as



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Figure 4 The comparison of mean Japanese Orthopedic Association Back Pain Evaluation Questionnaire (JOABPEQ) functional domains at initial and final evaluations at 3 mo, and their difference. A: Treatment group; B: Control group.

quality of life in patients with low back pain[22].

The strengths of our study are the combined use of a pain intensity scale and a quality-of-life questionnaire enabling us to better understand the benefits of Thermobalancing therapy on individual well-being.

Back pain is associated with physical, psychological, emotional, social changes, and even inappropriate exercise[23,24]. However, a survey found no significant association between LBP and psychological stress[25]. Health systems must prioritise policies that empower doctors and consumers to make informed choices, encourage clinicians to provide appropriate care to those who need it most and provide financial support for evidence-based non-pharmacological treatment[26].

Dr Allen's Device is a valuable medical innovation for the at-home use[27]. Its patented design accumulates the naturally emitted body heat and spreads it to the affected organs and areas of the body to which it is applied[28]. This out-of-hospital treatment targets the cause of pain at the capillary level. It improves blood circulation locally, that reduces inflammation and pressure in the affected tissue and, consequently, relieves chronic pain and other clinical symptoms[29, 30].

Limitations

The limitation of our study is the lack of an alternative treatment mode in the control group to compare the efficacy of Thermobalancing therapy with available first line treatment modalities for low back pain. In line with previous clinical trials on this treatment modality for other chronic diseases, such as chronic prostatitis, BPH and KSD, blinding was not performed due to the impracticality of a placebo group using such a wearable medical device for a long duration.

CONCLUSION

This research confirms that the use of non-invasive Dr Allen's Device gradually relieves chronic low back pain and improves the level of activity in patients with LDH or NSLBP. The study highlights the importance of this novel out-of-

Table 3 Comparison of the Japanese Orthopedic Association Back Pain Evaluation Questionnaire (JOABPEQ) functional domains before and after Thermobalancing therapy with Dr Allen's Device

	JOABPEQ functional domains	Initial evaluation	Final evaluation	Difference	*P* value
Treatment group	Low back pain	8.9 ± 14.38	75.05 ± 20.97	66.15	**< 0.001**
	Lumbar function	20.08 ± 18.24	60.25 ± 18.38	40.17	**< 0.001**
	Walking ability	23.38 ± 19.09	55.73 ± 21.07	32.35	**< 0.001**
	Social life function	19.83 ± 14.02	55.50 ± 17.37	35.67	**< 0.001**
	Mental health	31.78 ± 20.85	67.35 ± 13.83	35.57	**< 0.001**
Control group	Low back pain	10.40 ± 12.66	6.67 ± 13.13	-3.73	0.29
	Lumbar function	39.40 ± 25.57	17.73 ± 14.69	-21.67	**0.01**
	Walking ability	23.80 ± 30.96	14.20 ± 16.01	-9.6	0.69
	Social life function	33.07 ± 24.10	13.87 ± 9.24	-19.2	**0.01**
	Mental health	31.93 ± 19.76	12.80 ± 6.83	-19.13	**< 0.001**

JOABPEQ: The Japanese Orthopedic Association Back Pain Evaluation Questionnaire.

hospital treatment option as all participants in the treatment group experienced a significant improvement in their health-related quality of life as a result of using Dr Allen's Device at home during a 3-mo period and reported no side effects or complications. Overall, the study demonstrates high efficacy and safety of thermobalancing therapy and Dr Allen's Device for low back treatment in male and female patients with chronic low back pain. Thus, this wearable medical device can be used as the first-line therapy for chronic pain in the lower spine, and for effective at-home management of low back pain due to LDH and other non-specific causes.

ARTICLE HIGHLIGHTS

Research background

Chronic low back pain (CLBP) is a highly prevalent cause of disability worldwide. Of the numerous causes of low back pain, lumbar disc herniation (LDH) is a major contributor accounting for around 9% of CLBP in the population. The main symptom of LDH is chronic pain in the lower spine area that can impact the quality of life and heavily burden individuals, their families, and society. Standard treatments include pain management with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids and anticonvulsants, steroid injections, and spinal surgeries.

Research motivation

Multiple adverse effects of the standard treatment options for low back pain limit their use and highlight the pressing need for a new conservative, safe and effective mode of treatment.

Research objectives

This is the first clinical study that attempts to demonstrate the efficacy and safety of Dr Allen's Device for Low Back Pain Treatment in patients with chronic low back pain due to lumbar disc herniation (LDH) or non-specific low back pain (NSLBP), as well as the ability of this therapy to improve health-related quality of life.

Research methods

A total of 55 patients with chronic low back pain were recruited and randomised for the clinical trial. Thermobalancing therapy with Dr Allen's Device for Low Back Pain Treatment was used as a monotherapy for a 3-month period. The Numerical Pain Rating Scale (NPRS) and the Japanese Orthopedic Association Back Pain Evaluation Questionnaire (JOABPEQ) were used to assess the effectiveness of treatment. The effect on chronic low back pain was assessed as the primary health outcome.

Research results

The study showed that most patients in the treatment group experienced a significant pain reduction in the low back area, an improvement in the lumbar function, walking ability, social life, and mental health, with no patients showing worsening of these parameters. It was confirmed that the treatment with Dr Allen's Device was effective and safe in patients with non-specific low back pain and lumbar disc herniation.

Research conclusions

Thermobalancing therapy with Dr Allen's Device can be recommended for an effective at-home management of chronic low back pain.

Research perspectives

The results suggest that this treatment may also be effective and safe for other types of chronic back pain and further research in this direction is needed.

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FOOTNOTES

Author contributions: Allen S, Rashid A, Adjani A and Akram M designed the research study; Akram M, Khan FS and Khalil MT performed the research; Sherwani R contributed as statistician; Allen S, Rashid A, Adjani A and Akram M analysed the data and wrote the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: This study was performed in line with the principles of the Declaration of Helsinki. The study was reviewed and approved by the Ethics Review Committee of the Government College University Faisalabad (Approval No. GCUF/ERC/111).

Clinical trial registration statement: This study is registered at https://www.irct.ir/trial/69235. The IRCT registration number is: IRCT20211022052833N2.

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CASE REPORT

Unicompartimental knee arthroplasty metallosis treated with uni-on-uni revision: A case report

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Abstract

BACKGROUND

Metallosis is the result of metallic wear debris in the soft tissues and is associated to both local and systemic inflammatory response. Metallosis has been reported after total hip and total knee arthroplasty (TKA), but rarely after a unicompartimental knee arthroplasty (UKA). In the context of UKA metallosis, surgeons often opt for revision using a TKA. However, in this paper, the authors successfully treated UKA revising the metal back only.

CASE SUMMARY

Prior to treat our patient we conducted a literature research through which we identified eleven cases of metallosis after UKA, ten (90.9%) were treated revising using though a TKA. Only one case was managed through a uni-on-uni revision, reporting high knee function. Our patient complained worsening pain and function after a snap occurred at 16 mo after UKA implantation. At 18 mo following surgical debridment and uni-on-uni revision surgery, our patient exhibited a relevant improvement in Oxford Knee Score and a reduction of metal ion levels in the blood.

CONCLUSION

Our study highlights that in case of metallosis after UKA, the treatment may be based on surgical debridement and just revising the mobilized components.

Key Words: Metallosis; Unicompartimental knee arthroplasty; Revision; Uni-on-uni revision; case report; Review; Case report

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Core Tip: Metallosis is a rare but serious complication of unicompartimental knee arthroplasty. It is generally treated through surgical debridment and revision to a total knee arthroplasty. However, in case of absence of critical signs of implant malpositioning, soft tissue impairment or bone loss, it could be successfully resolved through surgical debridment and uni-on-uni revision.

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INTRODUCTION

Metallosis is a condition in which prosthetic metallic wear produces debris that could be observed in soft tissues, causing both local and systemic inflammation, and could be associated to malignant tumors and systemic toxicity[1,2]. Metallosis had been associated mainly with total hip arthroplasty (THA)[3]. In fact, it could be observed in 2%-5% of metal-on-metal THA implants, yet it was also described in the context of total knee arthroplasty (TKA) and less frequently unicompartimental knee arthroplasty (UKA)[4]. Metallosis treatment contemplates wide surgical debridement and revision surgery. Nevertheless, the authors noticed that the revision seems to differ from the damage entity. The rare cases of metallosis after an UKA are generally treated through a revision with TKA[5-15]. In this article, we review the literature and introduce a case of 77 years old man presenting an UKA metallosis treated with debridement and UKA tibial metalback revision.

CASE PRESENTATION

Chief complaints

This article reports the case of a 77 years old patient with a metallosis after a UKA.

History of present illness

13-mo before, the patient perceived a "snap", that was initially conservatively treated, considering the complete and painless range of motion documented during outpatient evaluation.

History of past illness

Sixteen months prior to the metallosis diagnosis, the patient underwent to a medial UKA for unicompartimental knee osteoarthritis.

Personal and family history

The patient had no other relevant co-morbidities.

Physical examination

In the three months after the "snap," the patient started to report a constant worsening of knee pain and a substantial reduction of joint function [oxford knee score (OKS) of 27/48].

Laboratory examinations

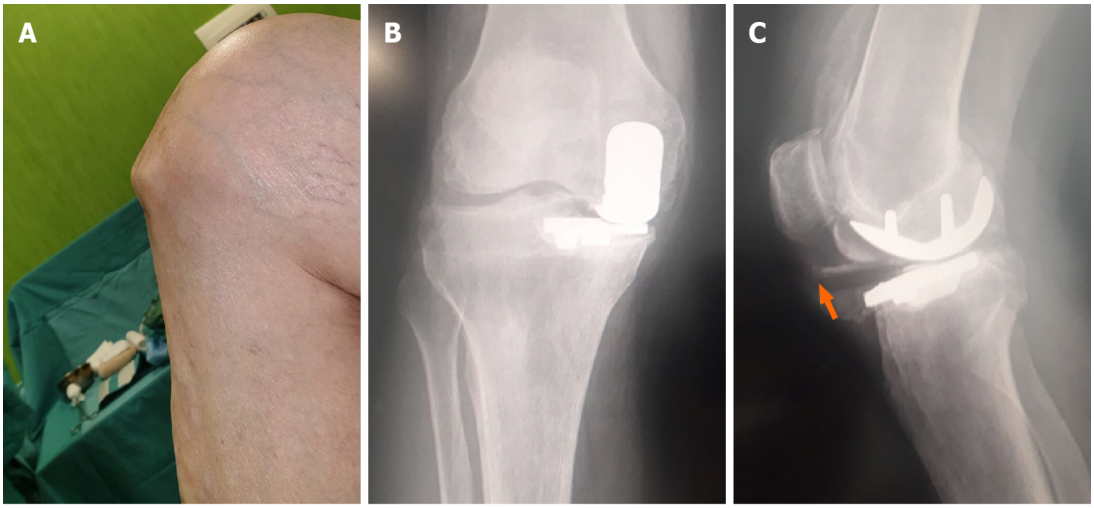
Baseline blood ion levels were in line with a diagnosis of metallosis (Chrome 1.26 μg/L, Cobalt 3.94 μg/L).

Imaging examinations

The imaging performed at that time confirmed tibial implant loosening (Figure 1) and revision surgery was necessary after excluding infection[16-18].

Multidisciplinary expert consultation

Prior to treat the patient, the research team decided to evaluate all the possible procedures. Therefore, a literature research was conducted through PubMed by two independent reviewers (Braile A and Conza G) using the following terms in their various combinations "Unicompartmental knee arthroplasty," "metallosis," "liner dislocation", "fixed-bearing", "mobile-bearing". Studies compatible with our criteria were included and controversies between the two reviewers were analyzed by a third author for the inclusion decision (Salini V).



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Figure 1 Patient's preoperative evaluation. A: Clinics; B: Radiographs; C: Liner dislocation is indicated with white arrow.

The literature search was conducted only in PubMed given that 90% of high-quality studies can be retrieved from this database, as reported by Rollin *et al*[19]. Therefore, to summarize the knowledge around a specific topic, PubMed research should be considered cost-effective as practitioners are able to easily retrieve most of the literature by using it[19, 20]. All articles on metallosis after UKA in English, Spanish and Italian languages were included and analyzed in the present review. Articles with incomplete follow-up were excluded. The references cited in the included articles were also reviewed to identify further relevant studies. Data from each retrieved study were collected using a pre-arranged form. Out of 45 records identified, 20 presented criteria for further review. Eleven articles were then excluded after abstract review because did not meet the inclusion criteria. One further article was included after reviewing references cited in the included articles. Therefore, 10 articles, including 11 patients were retrieved and analyzed in the present study (Figure 2).

Patient age averaged 66.4 years (54-76 years), metallosis occurred at a mean time of 42.58 mo from the UKA. Out of 11 patients, 9 (81.8%) were treated through revision TKA. Two cases necessitated a second revision TKA at a mean of 39 mo. The functional outcome improved in all eleven cases (Table 1).

FINAL DIAGNOSIS

Intraoperatively, signs of soft tissue metallosis were evident (Figure 3). Following soft-tissue debridement and specimen collection, a component stability test confirmed isolated loosening of the tibial implant. Surgical specimen and baseline blood ion levels confirmed metallosis (Chrome 1.26 μg/L, Cobalt 3.94 μg/L).

TREATMENT

The mobilized tibial component was revised using a larger Genus UNI Alderortho implant (Cormano, Italy).

OUTCOME AND FOLLOW-UP

We assessed the patient functional status through OKS and blood ion levels as previously recommended[21,22]. The patient presented a normal postoperative course. Complete range of motion, OKS score improvement (40/48), and good knee alignment were reported at 18 mo (Figure 4), while normalization of Ion blood levels (Chrome 0.95 μg/L, Cobalt 1.06 μg/L) were documented at 30 d after the uni-on-uni revision (Table 2).

DISCUSSION

Although UKA is an effective bone-preserving surgical option for unicompartmental symptomatic knee osteoarthritis in young and middle-aged patients[23], several complications may arise after its implantation. Due to the increasing number of arthroplasties performed yearly, optimizing the complication management is necessary.

In our case, we attributed metallosis and implant failure due to the progressive subclinical spinout of the polyethylene liner in an undersized tibial component which led to a posterior overload on the tibial implant. The surgeons performed

Table 1 Litterature review

Article info					Studied population									Outcomes					
N.	Ref.	Year	Journal	Type	Population (n.)	Sex	Age (yr)	Implant type	Months elapsed between implantation and bearing dislocation	Metal ions (Cr/Cb)	Type of precedure	Function pre-op	Knee ROM pre-op	Metal ions (Cr/Cb) last follow-up	Function last follow-up	Knee ROM last follow-up	General complications	Infection	Fracture	Implant loosening (yes /months)
1	Sanchis-Alfonso *et al*[5]	2007	*KSSTA*	Case report	1	M	54	Fixed bearing		NA	Revision with TKA			NA						
2	Apostolopoulos *et al*[6]	2014	*J Long Term Eff Med Implants*	Case report	1	M	67	Mobile bearing	54	NA				NA			None	No	No	Yes /54
3	Vecchini *et al* [10]	2019	*Acta Biomed*	Case report	1	M	71	NA		NA	Revision with TKA		10-110	NA		0-130	None	No	No	
4	Greco *et al*[11]	2018	*The knee*	Case report	1	M	72	Fixed bearing		NA	Revision with TKA			NA			None	No	No	
5	Rajgopal *et al* [13]	2018	*Arthroplast today*	Case report	1	M	58	NA	24	NA	Revision with TKA	KSS 48 OKS 19 UCLA 3	0-100	NA	KSS 82 OKS 40 UCLA 7		None	No	No	Yes /24
6	Vajapey *et al*[8]	2021	*Arthroplasty*	Case series	2	F	76	NA	60	NA	Revision with TKA		30-120	NA			None	No	No	
7	Kiran *et al*[14]	2021	*JBJS Case connector*	Case report	1	M	61	Fixed bearing	60	NA	Revision with TKA		NA	NA	OKS 39		None	None	None	
8	Foran *et al*[9]	2013	*Clin Orthop Relat Res*	Case series	1	NA	NA	NA	56	NA	Revision with TKA			NA						
9	Luyet *et al*[12]	2015	*Acta Ortop. Belg.*	Case report	1	F	67	NA	1,5	NA	Revision with UKA	ksk 59 KSF 60	0-90	NA	Ksk 87 KSF 90	0-110		No	No	
10	Pescador *et al* [15]	2016	*Reumatol Clin.*	Case report	1	F	72	NA		NA	Revision with TKA			NA						
TOT.					11	6 M /4 F	Mean: 66, 4	3 Fixed /1 Mobile	Mean: 42, 58		9 TKA /1 UKA									

NA: Not available; TKA: Total knee arthroplasty; UKA: Unicompartmental knee artrhoplasthy; KSS: Knee society score; UCLA: UCLA activity scale; OKS: Oxford knee score; KSF: Knee society function score.

Table 2 Illustrating oxford knee score and blood ion levels before and after revision surgery

	Pre-revision	Last follow-up
OKS	27	40
Chrome (μg/L)	126	106
Cobalt (μg/L)	334	95

OKS: Oxford knee score.



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Figure 2 Summary of article inclusion process.

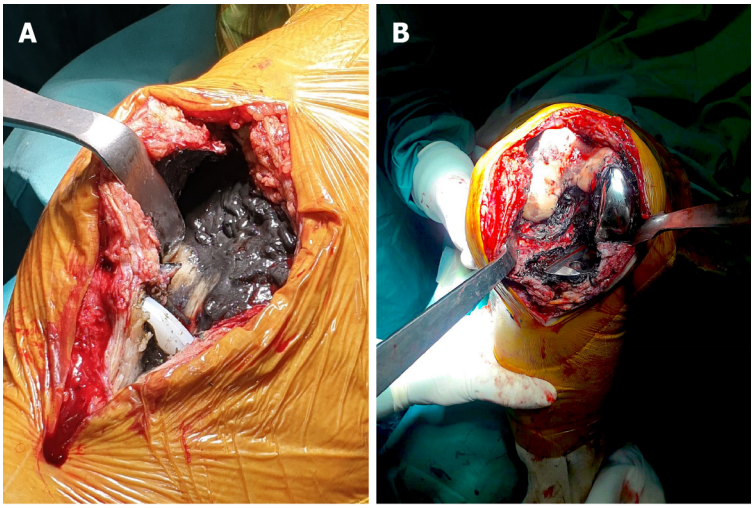
UKA revision with a new UKA larger tibial implant against general recommendations because no tibial slope or coronal malalignment were present[24-27].

Very few cases of UKA revision with a new UKA implant were described in the available literature. Luyet *et al*[12] in a case of anterior dislocation of the polyethylene liner at 6 wk, presenting as a painful and swollen knee[13] furtherly complicated by metallosis decided to treat it through a uni-on-uni revision. Following the surgery, the patient presented good clinical and radiological outcomes in a 2 year follow-up[12]. Good clinical outcomes were reported after a Uni-on-uni revision also in an another a recent review about metallosis after knee replacement[4]. Epinette *et al*[27] in a retrospective study of 36 UKA-to-UKA revision surgery described this treatment as a reliable option, with lower morbidity and better functional outcomes compared with UKA-to-TKA revision. The authors suggested to reserve in patients with limited bone defects and no extension of the lesions[27].

Our review is limited by several factors including low patient number, the absence of a statistical analysis related to the nature of the review, and lack of literature on UKA metallosis. However, to the best of our knowledge, this is the first study reporting bloodstream ion changes while confirming clinical improvement following uni-on-uni revision in case of UKA metallosis. However, we believe that further analysis is necessary to confirm successful uni-on-uni revisions in case of metallosis.

CONCLUSION

In conclusion, we suggest that aseptic UKA metallosis without critical signs of malpositioning, soft tissue impairment or bone loss could be treated with surgical debridement and unicompartimental knee revision arthroplasty. This kind of approach could lead to a significant improvement of functional outcomes, and blood ion levels.



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Figure 3 Intraoperative photographs documenting peri-prosthetic soft tissue metallosis. A: Note the luxated bearing; B: Note the metal back debris.



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Figure 4 Postoperative history. A and B: Postoperative X-rays; C-E: Clinical evaluation documenting range of motion at final follow-up; F and G: Radiographies documenting implant alignment at final follow-up.

FOOTNOTES

Author contributions: Braile A, Conza G and Salini V performed material preparation and data collection; Placella G, Toro G, Salini V performed data analysis and interpretation; Abu Mukh A and De Cicco A written the first draft of the manuscript; Placella G and Toro G revised the paper and wrote the final version of the manuscript; Toro G and Salini V supervised the entire study; all authors commented on previous versions of the manuscript; all authors read and approved the final manuscript; all authors contributed to the study conception and design.

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