

World Journal of *Nephrology*

World J Nephrol 2021 January 25; 10(1): 1-7



OPINION REVIEW

- 1 Emperor's syndrome in the COVID-19 era: Time for patient-centered nephrology?

Bacharaki D, Diamandopoulos A

ABOUT COVER

Editorial Board Member of *World Journal of Nephrology*, Dr. Yoshihide Fujigaki is a Professor at Teikyo University School of Medicine (Japan). Having received his MD degree (1984) and PhD degree (1991) from Hamamatsu University, School of Medicine (Japan), he pursued advanced study of the mechanisms of in situ immune complex formation in glomerulus and proteinuria in the Department of Immunology, Institute of Medical Microbiology and Hygiene, Freiburg University (Germany) under Professor Arnold Vogt as a research fellow sponsored by an Alexander von Humboldt Research Fellowship (1992-1995). His ongoing research career efforts have focused on the mechanisms of injury and repair in animal models of acute kidney injury complimented by his clinical practice in acute kidney injury, glomerulonephritis and renal pathology. He currently serves as editorial board member for several scientific journals and has published more than 150 peer-reviewed articles. (L-Editor: Filipodia)

AIMS AND SCOPE

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

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, etc.

INDEXING/ABSTRACTING

The *WJN* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Li-Li Wang; Production Department Director: Yun-Xiaoqian Wu; Editorial Office Director: Yan-Xia Xing.

NAME OF JOURNAL

World Journal of Nephrology

ISSN

ISSN 2220-6124 (online)

LAUNCH DATE

February 6, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Li Zuo

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2220-6124/editorialboard.htm>

PUBLICATION DATE

January 25, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Emperor's syndrome in the COVID-19 era: Time for patient-centered nephrology?

Dimitra Bacharaki, Athanasios Diamandopoulos

ORCID number: Dimitra Bacharaki 0000-0002-1722-2131; Athanasios Diamandopoulos 0000-0001-9970-0522.

Author contributions: Bacharaki D wrote the paper; Diamandopoulos A supervised the historical background.

Conflict-of-interest statement: The authors declare no conflicts of interest related to this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Pathology

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Dimitra Bacharaki, Department of Nephrology, Attikon University Hospital, Chaidari 12462, Greece

Athanasios Diamandopoulos, EKPA, Louros Foundation for the History of Medicine, Chaidari 12462, Greece

Corresponding author: Dimitra Bacharaki, MD, PhD, Doctor, Department of Nephrology, Attikon University Hospital, Rimini 1, Chaidari 12462, Greece. bacharaki@gmail.com

Abstract

The coronavirus disease-19 (COVID-19) pandemic has been a wake-up call in which has forced us to react worldwide. Health policies and practices have attracted particular attention in terms of human and financial cost. Before COVID-19, chronic kidney disease was already considered a risk multiplier in patients with diabetes and hypertension, the two now being the major risk factors for COVID-19 infection and adverse outcome. In contrast to the urgent need for action, the nephrology field is considered to be in a state of stagnation regarding the management of chronic kidney disease patients who still experience unacceptably high morbidity and mortality. Ironically and paradoxically in a field lacking robust clinical trials, clinical practice is driven by guidelines-based medicine on weak evidence. The Emperor's syndrome, referring to Hans Christian Andersen's fairy tale, has been described in medicine as voluntary blindness to an obvious truth, being a weak evidence-based therapeutic intervention or weak health care. A promising positive example of improving heart and kidney outcomes is the emerging treatment with sodium-glucose cotransporter 2 inhibitors. COVID-19 could boost actions for patient-centered care as a positive shift in nephrology care.

Key Words: Emperor's syndrome; Chronic kidney disease; Guidelines-based medicine; Patient-centered care; COVID-19; Evidence-based medicine

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: In chronic kidney disease mortality is still unacceptably high. Despite many "whistle-blowers" of a "naked" Emperor (healthcare, polypharmacy without robust

Grade A (Excellent): 0
 Grade B (Very good): 0
 Grade C (Good): C
 Grade D (Fair): 0
 Grade E (Poor): 0

Received: May 20, 2020

Peer-review started: May 20, 2020

First decision: June 15, 2020

Revised: October 4, 2020

Accepted: November 11, 2020

Article in press: November 11, 2020

Published online: January 25, 2021

P-Reviewer: Tanaka H

S-Editor: Zhang L

L-Editor: Webster JR

P-Editor: Wang LL



evidence), the change in clinical practice is slow. Examples are the absence of patient participation in the decision-making process, the low percentage of peritoneal dialysis in Europe and the United States, and the lack of algorithm-based therapeutic interventions. Sodium-glucose cotransporter 2 inhibitors are a positive example of evidence-based multitask treatment. The coronavirus disease-19 pandemic is a good time for reflection and action regarding a shift to patient-centered care in nephrology.

Citation: Bacharaki D, Diamandopoulos A. Emperor's syndrome in the COVID-19 era: Time for patient-centered nephrology? *World J Nephrol* 2021; 10(1): 1-7

URL: <https://www.wjgnet.com/2220-6124/full/v10/i1/1.htm>

DOI: <https://dx.doi.org/10.5527/wjn.v10.i1.1>

INTRODUCTION

The last decades have witnessed the rise of two major health problems, the “non-communicable diseases” (namely cardiovascular disease, cancer, chronic respiratory disease and diabetes)^[1], and global pandemics, the most recent being coronavirus disease-19 (COVID-19)^[2]. Chronic kidney disease (CKD) although not listed in the above, is a risk multiplier for cardiovascular morbidity and mortality^[3] and is thus emerging as a global cause of death^[4]. Only recently a promising therapeutic treatment in CKD management has emerged due to the beneficial effects of sodium-glucose cotransporter 2 inhibitors on heart and kidney outcomes^[4].

Apart from this foreseen emerging treatment, the field of nephrology regarding CKD management suffers from stagnation, due mainly to a lack of robust clinical trials for clinically meaningful endpoints, or lack of positive results^[5]. There are also factors inherent to CKD, such as the high percentage of older patients with many comorbidities who are excluded from randomized controlled trials^[6], and the complex pathophysiology of the interaction of heart kidney adverse outcomes^[7]. Traditional cardiovascular risk factors (arterial hypertension, diabetes mellitus, and dyslipidemia) cannot explain the increased morbidity and mortality, so other factors related to CKD per se are considered to be implicated, such as oxidative stress, uremia, and inflammation, marking CKD as a prototype disease of premature ageing^[8]. A major contributor to mortality is also considered to be mineral and bone abnormalities that accompany CKD, leading to accelerated atherosclerosis, vascular and heart valve calcification, collectively described as CKD-mineral and bone disorder^[9].

THE PROBLEM

Ironically and paradoxically, in this complex field of CKD which lacks robust evidence, the contemporary nephrologist is called to manage CKD patients, who are at very high risk of cardiovascular morbidity and mortality, especially in those with end-stage renal disease, with guidelines-based medicine produced from weak evidence^[7]. Furthermore, during the decision-making process the patient is not in the center of this process, but is a passive recipient^[10].

This also holds true for the choice of renal replacement treatment (hemodialysis or peritoneal dialysis) which is guided in major part by the healthcare policy^[11]. The COVID-19 pandemic is like a hurricane that besides devastation provides the dynamic for changes in many fields, political and medical^[11,12]. In this context, it has provided a wake-up call in relation to peritoneal dialysis (PD), being as high as 85% in Hong Kong with a PD-first policy, and < 15% in the rest of the world. PD offers an “at home” therapy which diminishes the risk of contamination compared to hemodialysis in specialized hemodialysis centers, but at the same time poses less financial burden and offers time flexibility in patients’ lives^[11].

This situation of voluntary blindness to an obvious truth in the medical field, already described as “The Emperor's clothes syndrome”^[13] refers to the homonymous fairy tale by Hans Christian Andersen, where the Emperor (healthcare) is naked yet nobody dares to cry it out.

Actually there have been voices that “cried out” but they are muted in clinical practice. In the present article we highlight different aspects that contribute to the

observed “Emperor’s syndrome” in the clinical management of CKD patients and suggest a paradigm shift toward patient-centered care. We perceive patient management from 3 perspectives, the historical perception of the triangle “disease, therapist, patient”, the medical view and the patient’s view.

HISTORICAL PERCEPTION

Looking back at the timeline of the history of medicine^[14], the perception of the “disease, therapist and treatment” has changed drastically from a “patient-centered” view to “evidence-based” medicine. The turning point was the “Germ theory of disease” in the 19th century, which changed the perception of disease from a “holistic view” as an “imbalance” inside the organism to a “specific cause for a specific disease”. Together with this change of view, the treatment approach shifted from a “holistic” view that aimed to “restore” the balance to a narrow approach that targeted the specific cause of the disease. The patient’s role diminished from an active contributor, through personal beliefs, adaptation and lifestyle choices, to a mere passive recipient of the treatment. He is no longer “unique”, but a “number” in a trial, observational or randomized, which will provide the necessary information to form “guidelines” for the disease^[15].

But are these “Guidelines” at least a solid ground on which to rely upon safely for patient management in the form of Evidence-Based Medicine (EBM)? EBM should integrate the best available evidence from the doctor’s experience and the patient’s point of view. This ideal definition of EBM, as introduced by Professor Sackett *et al*^[16], was at the heart of medical practice by Hippocrates (460-370BC), the Greek Father of Medicine^[17]. He instructed doctors to analyze pre-existing data, communicate with the patient and adapt treatment to the individual patient, who is considered unique and called to participate actively in the treatment through changes in lifestyle patterns^[17].

The clothes of the “naked Emperor” (our healthcare) is what we consider nowadays EBM since it has been degraded to “Guidelines-based Medicine”^[18]. Furthermore, Professor Ioannidis emphasized the fact that EBM has been hijacked^[19] in our modern times, since medicine, healthcare, science denialism and quacks provides a complex interplay that leads people astray in their life choices, including health.

It seems that history has made circles in this perception. “Authority” based Medicine of the Past, under the leadership of Hippocrates, Galen and Aristotle, has been replaced by “Guidelines” of contemporary EBM. The homology is that as contemporary “Guidelines” are followed blindly, Galen’s and Aristotle’s statements were not contradicted by their successors, given their prestige and “authority”, even though, ironically, both actively encouraged experimentation and the questioning of established theory^[20].

MEDICAL POINT OF VIEW VS PATIENTS’ VIEW

At present, the patient is regarded as a conglomeration of different diseases-each demanding a specific treatment, governed by “guidelines” from expert committees. In nephrology, this task is covered by the Kidney Disease Improving Global Outcomes (KDIGO) initiative^[21]. These guidelines have 2 grades of “strength of recommendation”, 1 for “strong” and 2 for “weak” (equals suggestion). Each of them is accompanied by a letter (A, B, C, D) corresponding to a level of “Quality of Evidence”, respectively “High”, “Moderate”, “Low” and “Very Low”. Therefore, there are 8 options for each guideline, plus “statements that are not graded” as expert opinion.

PRESENT EXAMPLES OF GUIDELINE-DRIVEN CLINICAL PRACTICE

Hyperphosphatemia: A frequent occurrence in advanced CKD, carrying the fear of accompanying phosphate (Ph) cardiovascular toxicity. The KDIGO 2017 update suggests lowering Ph levels to the normal range (2C)^[9]. This can be achieved with Ph binders, drugs that modify Ph migration from bone *via* parathyroid hormone control, diet and dialysis modification. Despite the “suggestion” and the accompanying “low quality of evidence (C)” for the use of Ph binders in the CKD population, in the real world the corresponding pill burden (average number 19) represents a major burden

for patients in their daily life^[22] and a burden for the healthcare system in terms of financial cost^[23]. Even more frustrating is the fact that there is no definitive proof that “correction” of hyperphosphatemia translates into improved outcomes, such as cardiovascular and all-cause mortality^[24].

Furthermore, the current practice management is not guided by an algorithm based (for example) on the calcification propensity of the individual patient, although the large cross-sectional calcification outcome in renal disease (CORD) study (933 patients from 47 centers in 6 European countries) showed that “Abdominal Aortic Calcification, detected by lateral lumbar radiograph, is associated with several risk factors of uraemic calcification” and thus “could form part of a cardiovascular risk stratification”^[25]. Of note, in the CORD study “19% of patients had no visible calcification in their abdominal aorta, even though some of them were > 80 years of age”. Despite the implication that “the ‘non-calcified’ patients have some typical biochemical and/or genetic features that protect them from calcification” and the strong prognostication role of abdominal aortic calcification as a simple clinical tool for mortality^[26], there is actually scientific paucity regarding in-depth investigation of the pathophysiology and clinical management of the “non-calcifiers”. The non-stratification of the calcification propensity could also potentially annulate therapeutic strategies, for example manipulation of serum magnesium^[27], or pharmaceutical parathyroidectomy by cinacalcet, as in the EVOLVE trial^[28].

Dyslipidemia: A very significant and modifiable factor for cardiovascular morbidity and mortality in the general population with high prevalence in the CKD population, dyslipidemia is characterized by high triglycerides, low high-density lipoprotein-cholesterol and altered lipoprotein composition^[29]. In the general population, the main culprit is considered to be low-density lipoprotein-cholesterol which is targeted with distinct drug classes (statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors) alone or in combination, to ever decreasing lower levels^[30]. Although there are some sceptics regarding the use of statins in the general population, suggesting that these drugs stimulate atherosclerosis and heart failure^[31], in end-stage renal disease the question becomes even harder “Should Statins Be Banned from Dialysis?”^[32]. This controversy derives from the fact that the apparent benefit in cardiovascular risk of statins in the general population diminishes as renal function declines and is almost null in maintenance dialysis patients. This led to the KDIGO 2013 suggestion that statins should not be stopped in dialysis patients if already prescribed (2c), but should not be initiated either (2a)^[33].

In real world practice, nephrologists still widely prescribe statins in dialysis patients, which are considered safe and effective drugs^[34], even though a recent observational study suggested that statins may promote vascular calcification in CKD patients^[35].

On the other hand, much cheaper, pharmaceutical or not, ways of reducing cardiovascular risk are not promoted. For example, as shown by our group and others, the manipulation of serum and dialysate magnesium (Mg). Serum Mg, driven in part by dialysate Mg, is inversely associated with vascular calcification^[36], and cardiac hypertrophy^[37]. Mortality has been shown to be correlated both with serum^[38] and dialysate Mg^[39,40]. Another neglected tool is the Mediterranean diet, a magic poly-weapon against all traditional and non-traditional CV risk factors^[41]. Although the Mediterranean diet is associated with beneficial surrogate goals (Ph load, oxidative stress, inflammation, metabolic acidosis, blood pressure control, lipid control), cardiac parameters^[42] and possibly even mortality^[43], it is not a goal strongly implemented in clinical practice.

Are patients aware of the statistics and do they take part in the decision-making process? What would their preference be between implementing a Mediterranean type diet, and using multiple drugs for blood pressure, Ph load and lipid control?

Considering hyperphosphatemia and dyslipidemia management as described above, the “naked Emperor” is in front of us in clinical practice when a patient is characterized as “non-compliant” and the prescribed treatment is of low evidence in terms of EBM. Furthermore, there is extensive literature on the notion of patient non-adherence, or non-compliance; these two notions are used in the same context in the bibliography, but today the first is preferred as the second implies doctor’s authority. That is because the literature testifies to a shift in the healthcare perspective from “every patient is a potential defaulter” towards not “labelling” patients as adherent or not and acknowledging patients’ self-knowledge^[44].

A good strategy for “hyperphosphatemia” and “dyslipidemia” management could be to reconcile evidence-based inputs (ideally from robust stratified studies) to patient-centered decisions. Given that CKD patients have multiple co- morbidities and considering the patient as the sum of distinct clinical entities, by targeting each of them

with a guidelines-based approach, do we treat the diseases or the patient^[45]? At the end of the day is personalized medicine just good medicine^[46]?

If patient management is already confusing in the field of nephrology for the reasons stated above along with the difficulties in conducting clinical trials^[47], it becomes even more so considering the scepticism around the experimentation from which guidelines are drawn. Professor Ioannidis in the provocative article “Why Most Published Research Findings Are False”^[48] urges us as doctors to be cautious in the interpretation of the published literature. Furthermore, there is an ongoing debate regarding the acceptance of the *P* statistical value taken as the “bible” for clinical decisions or be more sceptic about it^[49].

CONCLUSION

In a field lacking robust clinical trials, such as CKD, nephrologists are called to manage these high-risk CKD patients with low evidence guidelines-driven medicine and at the same time they do not usually include patients in the decision-making process. The Emperor (healthcare) is naked and although there have been voices that cry out, maybe the hurricane of COVID-19 could serve as a wake-up call for many aspects of the social, political and medical fields.

REFERENCES

- 1 **Richards NC**, Gouda HN, Durham J, Rampatige R, Rodney A, Whittaker M. Disability, noncommunicable disease and health information. *Bull World Health Organ* 2016; **94**: 230-232 [PMID: 26966336 DOI: 10.2471/BLT.15.156869]
- 2 **Fan VY**, Jamison DT, Summers LH. Pandemic risk: how large are the expected losses? *Bull World Health Organ* 2018; **96**: 129-134 [PMID: 29403116 DOI: 10.2471/BLT.17.199588]
- 3 **Couser WG**, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int* 2011; **80**: 1258-1270 [PMID: 21993585 DOI: 10.1038/ki.2011.368]
- 4 **Fernandez-Fernandez B**, Sarafidis P, Kanbay M, Navarro-González JF, Soler MJ, Górriz JL, Ortiz A. SGLT2 inhibitors for non-diabetic kidney disease: drugs to treat CKD that also improve glycaemia. *Clin Kidney J* Oct 2020; **13**: 728-733 [DOI: 10.1093/ckj/sfaa198]
- 5 **Yaseen M**, Hassan W, Awad R, Ashqar B, Neyra J, Heister T, Malik O, El-Husseini A. Impact of Recent Clinical Trials on Nephrology Practice: Are We in a Stagnant Era? *Kidney Dis (Basel)* 2019; **5**: 69-80 [PMID: 31019921 DOI: 10.1159/000495139]
- 6 **O'Hare AM**, Rodriguez RA, Bowling CB. Caring for patients with kidney disease: shifting the paradigm from evidence-based medicine to patient-centered care. *Nephrol Dial Transplant* 2016; **31**: 368-375 [PMID: 25637639 DOI: 10.1093/ndt/gfv003]
- 7 **Go AS**, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296-1305 [PMID: 15385656 DOI: 10.1056/NEJMoa041031]
- 8 **Ebert T**, Pawelzik SC, Witasz A, Arefin S, Hobson S, Kublickiene K, Shiels PG, Bäck M, Stenvinkel P. Inflammation and Premature Ageing in Chronic Kidney Disease. *Toxins (Basel)* 2020; **12** [PMID: 32260373 DOI: 10.3390/toxins12040227]
- 9 **Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group**. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl (2011)* 2017; **7**: 1-59 [PMID: 30675420 DOI: 10.1016/j.kisu.2017.04.001]
- 10 **Weaver RR**. Reconciling evidence-based medicine and patient-centred care: defining evidence-based inputs to patient-centred decisions. *J Eval Clin Pract* 2015; **21**: 1076-1080 [PMID: 26456314 DOI: 10.1111/jep.12465]
- 11 **Kam-Tao Li P**, Rosenberg ME. Foreign Perspective on Achieving a Successful Peritoneal Dialysis-First Program. American Society of Nephrology, Kidney360 Publish Ahead of Print, published on May 13, 2020 [DOI: 10.34067/KID.0000712019]
- 12 **Fuchs VR**. Health Care Policy After the COVID-19 Pandemic. *JAMA* 2020; **324**: 233-234 [PMID: 32530458 DOI: 10.1001/jama.2020.10777]
- 13 **Gross F**. The Emperor's clothes syndrome. *N Engl J Med* 1971; **285**: 863 [PMID: 5570860 DOI: 10.1056/NEJM197110072851524]
- 14 **Hajar R**. History of medicine timeline. *Heart Views* 2015; **16**: 43-45 [PMID: 25838882 DOI: 10.4103/1995-705x.153008]
- 15 **Robson WA**, Philip T, Douglas R, Guthrie J, Richardson RG, Underwood EA. History of medicine. Encyclopædia Britannica. <https://www.britannica.com/science/history-of-medicine>
- 16 **Sackett DL**, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what

- it is and what it isn't. *BMJ* 1996; **312**: 71-72 [PMID: 8555924 DOI: 10.1136/bmj.312.7023.71]
- 17 **Tsiompanou E**, Marketos SG. Hippocrates: timeless still. *J R Soc Med* 2013; **106**: 288-292 [PMID: 23821709 DOI: 10.1177/0141076813492945]
 - 18 **Tebala GD**. The Emperor's New Clothes: a Critical Appraisal of Evidence-based Medicine. *Int J Med Sci* 2018; **15**: 1397-1405 [PMID: 30275768 DOI: 10.7150/ijms.25869]
 - 19 **Ioannidis JP**. Evidence-based medicine has been hijacked: a report to David Sackett. *J Clin Epidemiol* 2016; **73**: 82-86 [PMID: 26934549 DOI: 10.1016/j.jclinepi.2016.02.012]
 - 20 **Bacharaki D**, Diamandopoulos A. The Emperor's New Clothes in Nephrology: Past and Present. Proceedings of 11th Congress of International Association for the History of Nephrology. *Arch Hell Med* 37: 83-86
 - 21 **Kasiske BL**, Wheeler DC. Kidney Disease: Improving Global Outcomes--an update. *Nephrol Dial Transplant* 2014; **29**: 763-769 [PMID: 24286979 DOI: 10.1093/ndt/gft441]
 - 22 **Chiu YW**, Teitelbaum I, Misra M, de Leon EM, Adzize T, Mehrotra R. Pill burden, adherence, hyperphosphatemia, and quality of life in maintenance dialysis patients. *Clin J Am Soc Nephrol* 2009; **4**: 1089-1096 [PMID: 19423571 DOI: 10.2215/CJN.00290109]
 - 23 **de Francisco AL**. Phosphate binders. Is selection determined by price? *Nefrologia* 2012; **32**: 235-239 [PMID: 22466264 DOI: 10.3265/Nefrologia.pre2011.Dec.11318]
 - 24 **Vervloet M**. Modifying Phosphate Toxicity in Chronic Kidney Disease. *Toxins (Basel)* 2019; **11**: 522 [PMID: 31505780 DOI: 10.3390/toxins11090522]
 - 25 **Honkanen E**, Kaupilla L, Wikström B, Rensma PL, Krzesinski JM, Aasarod K, Verbeke F, Jensen PB, Mattelaer P, Volck B; CORD study group. Abdominal aortic calcification in dialysis patients: results of the CORD study. *Nephrol Dial Transplant* 2008; **23**: 4009-4015 [PMID: 18676346 DOI: 10.1093/ndt/gfn403]
 - 26 **Niu Q**, Hong Y, Lee CH, Men C, Zhao H, Zuo L. Abdominal aortic calcification can predict all-cause mortality and CV events in dialysis patients: A systematic review and meta-analysis. *PLoS One* 2018; **13**: e0204526 [PMID: 30240443 DOI: 10.1371/journal.pone.0204526]
 - 27 **Giannakopoulos P**, Fokas S, Drosaki E, Tsotsorou O, Duni A, Theodoridis M, Stylianou K, Ntounousi E, Passadakis P, Katsoudas S, Kyriazis P, Bacharaki D, Vlahakos D. P1168 Abdominal Aortic Calcification Score Modifies the Prognostic Value of Serum Magnesium Levels on All Cause Mortality in Peritoneal Dialysis Patients. *Nephrol Dial Transplant* 2020; **35** [DOI: 10.1093/ndt/gfaa142.P1168]
 - 28 **EVOLVE Trial Investigators**, Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012; **367**: 2482-2494 [PMID: 23121374 DOI: 10.1056/NEJMoa1205624]
 - 29 **Tannock L**. Dyslipidemia in Chronic Kidney Disease. [Updated 2018 Jan 22]. In: Feingold KR, Anawalt B, Boyce A. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK305899>
 - 30 **Berberich AJ**, Hegele RA. LDL cholesterol: lower, faster, younger? *Lancet Diabetes Endocrinol* 2020; **8**: 5-7 [PMID: 31862152 DOI: 10.1016/S2213-8587(19)30389-4]
 - 31 **Okuyama H**, Langsjoen PH, Hamazaki T, Ogushi Y, Hama R, Kobayashi T, Uchino H. Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms. *Expert Rev Clin Pharmacol* 2015; **8**: 189-199 [PMID: 25655639 DOI: 10.1586/17512433.2015.1011125]
 - 32 **De Vriese AS**. Should Statins Be Banned from Dialysis? *J Am Soc Nephrol* 2017; **28**: 1675-1676 [PMID: 28468822 DOI: 10.1681/ASN.2017020201]
 - 33 **Sarnak MJ**, Bloom R, Muntner P, Rahman M, Saland JM, Wilson PW, Fried L. KDOQI US commentary on the 2013 KDIGO Clinical Practice Guideline for Lipid Management in CKD. *Am J Kidney Dis* 2015; **65**: 354-366 [PMID: 25465166 DOI: 10.1053/j.ajkd.2014.10.005]
 - 34 **Budzisz E**, Nowicki M. Opinions of nephrologists on the efficacy and tolerance of statins in hemodialysis patients. *Ren Fail* 2017; **39**: 277-282 [PMID: 27885903 DOI: 10.1080/0886022X.2016.1260032]
 - 35 **Chen Z**, Qureshi AR, Parini P, Hurt-Camejo E, Ripsweiden J, Brismar TB, Barany P, Jaminon AM, Schurgers LJ, Heimbürger O, Lindholm B, Stenvinkel P. Does statins promote vascular calcification in chronic kidney disease? *Eur J Clin Invest* 2017; **47**: 137-148 [PMID: 28036114 DOI: 10.1111/eci.12718]
 - 36 **Molnar AO**, Biyani M, Hammond I, Harmon JP, Lavoie S, McCormick B, Sood MM, Wagner J, Pena E, Zimmerman DL. Lower serum magnesium is associated with vascular calcification in peritoneal dialysis patients: a cross sectional study. *BMC Nephrol* 2017; **18**: 129 [PMID: 28385153 DOI: 10.1186/s12882-017-0549-y]
 - 37 **Dermizaki E-K**, Giannikouris I, Stavroulopoulos A, Hatzidimitriou D, Makridis D, Tsotsorou O, Balafa O, Dounousi E, Stylianou K, Triantafyllis G, Katsinas C, Passadakis P, Kyriazis P, Katsoudas S, Bacharaki D, Vlahakos D. SP542 Lower Serum Magnesium (Smg) is A Strong Predictor of Left Ventricular Hypertrophy (LvH) and Patterns of Lv Remodeling in Patients With Stage 5 Chronic Kidney Disease (Ckd). *Nephrol Dial Transplant* 2018; **33**: i531 [DOI: 10.1093/ndt/gfy104.SP542]
 - 38 **Xiong J**, He T, Wang M, Nie L, Zhang Y, Wang Y, Huang Y, Feng B, Zhang J, Zhao J. Serum magnesium, mortality, and cardiovascular disease in chronic kidney disease and end-stage renal disease patients: a systematic review and meta-analysis. *J Nephrol* 2019; **32**: 791-802 [PMID: 30888644 DOI: 10.1007/s40620-019-00601-6]
 - 39 **Markaki A**, Kyriazis J, Stylianou K, Fragkiadakis GA, Perakis K, Margioris AN, Ganotakis ES,

- Daphnis E. The role of serum magnesium and calcium on the association between adiponectin levels and all-cause mortality in end-stage renal disease patients. *PLoS One* 2012; **7**: e52350 [PMID: 23285003 DOI: [10.1371/journal.pone.0052350](https://doi.org/10.1371/journal.pone.0052350)]
- 40 **Tosti V**, Bertozzi B, Fontana L. Health Benefits of the Mediterranean Diet: Metabolic and Molecular Mechanisms. *J Gerontol A Biol Sci Med Sci* 2018; **73**: 318-326 [PMID: 29244059 DOI: [10.1093/gerona/glx227](https://doi.org/10.1093/gerona/glx227)]
- 41 **Chauveau P**, Aparicio M, Bellizzi V, Campbell K, Hong X, Johansson L, Kolko A, Molina P, Sezer S, Wanner C, Ter Wee PM, Teta D, Fouque D, Carrero JJ; European Renal Nutrition (ERN) Working Group of the European Renal Association–European Dialysis Transplant Association (ERA-EDTA). Mediterranean diet as the diet of choice for patients with chronic kidney disease. *Nephrol Dial Transplant* 2018; **33**: 725-735 [PMID: 29106612 DOI: [10.1093/ndt/gfx085](https://doi.org/10.1093/ndt/gfx085)]
- 42 **Bacharaki D**, Markaki A, Tsotsorou O, Korovesi A, Kasti A, Koinaki S, Hatzidimitriou D, Georgoulidou A, Karassavidou D, Katsinas C, Mavromatisdis K, Stylianou K, Katsoudas S, Theodoridis M, Kyriazis I, Vlahakos D. Mediterranean diet score shows inverse association with left ventricular mass and predicts cardiac geometry in renal dialysis patients. International Congress on Nutrition and Metabolism in Renal Disease (ICRNM June 2018).
- 43 **Giannikouris IE**, Georgoulidou A, Dermizaki E-K, Korovesi A, Kokkalis A, Stavroulopoulos A, Perakis K, Theodoridis M, Passadakis P, Dounousi E, Markaki A, Kyriazis P, Tsotsorou O, Katsoudas S, Bacharaki D, Vlahakos D. Mediterranean diet and mortality in chronic kidney disease (ckd) stage 5d (dialysis) patients. SP386. *Nephrol Dial Transplant* 2019 [DOI: [10.1093/ndt/gfz103.SP386](https://doi.org/10.1093/ndt/gfz103.SP386)]
- 44 **Russell S**, Daly J, Hughes E, op't Hoog C. Nurses and 'difficult' patients: negotiating non-compliance. Philosophical and Ethical Issues. *J Adv Nurs* 2003; **43**: : 281-287 [DOI: [10.1046/j.1365-2648.2003.02711.x](https://doi.org/10.1046/j.1365-2648.2003.02711.x)]
- 45 **Upshur RE**, Tracy S. Chronicity and complexity: is what's good for the diseases always good for the patients? *Can Fam Physician* 2008; **54**: 1655-1658 [PMID: 19074692]
- 46 **Taal MW**. Personalized medicine in nephrology: a novel approach or just good medicine? *Curr Opin Nephrol Hypertens* 2018; **27**: 395-397 [PMID: 30095481 DOI: [10.1097/MNH.0000000000000448](https://doi.org/10.1097/MNH.0000000000000448)]
- 47 **Baigent C**, Herrington WG, Coresh J, Landray MJ, Levin A, Perkovic V, Pfeffer MA, Rossing P, Walsh M, Wanner C, Wheeler DC, Winkelmayer WC, McMurray JJV; KDIGO Controversies Conference on Challenges in the Conduct of Clinical Trials in Nephrology Conference Participants. Challenges in conducting clinical trials in nephrology: conclusions from a Kidney Disease-Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2017; **92**: 297-305 [PMID: 28709600 DOI: [10.1016/j.kint.2017.04.019](https://doi.org/10.1016/j.kint.2017.04.019)]
- 48 **Ioannidis JP**. Why most published research findings are false. *PLoS Med* 2005; **2**: e124 [PMID: 16060722 DOI: [10.1371/journal.pmed.0020124](https://doi.org/10.1371/journal.pmed.0020124)]
- 49 **Jiménez-Paneque R**. The questioned p value: clinical, practical and statistical significance. *Medwave* 2016; **16**: e6534 [PMID: 27636600 DOI: [10.5867/medwave.2016.08.6534](https://doi.org/10.5867/medwave.2016.08.6534)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>



World Journal of *Nephrology*

World J Nephrol 2021 March 25; 10(2): 8-28



ORIGINAL ARTICLE

Observational Study

- 8 Low-molecular-weight dextran for optical coherence tomography may not be protective against kidney injury in patients with renal insufficiency

Misawa T, Sugiyama T, Kanaji Y, Hoshino M, Yamaguchi M, Hada M, Nagamine T, Nogami K, Yasui Y, Usui E, Lee T, Yonetsu T, Sasano T, Kakuta T

CASE REPORT

- 21 Siblings with coronavirus disease 2019 infection and opposite outcome—the hemodialysis's better outcome paradox: Two case reports

Bacharaki D, Chrysanthopoulou E, Grigoropoulou S, Giannakopoulos P, Simitsis P, Frantzeskaki F, Flevari A, Karagiannis M, Sardeli A, Kavatha D, Antoniadou A, Vlahakos D

ABOUT COVER

Editorial Board Member, Erling Bjerregaard Pedersen, Professor Emeritus, dr. med, Department of Clinical Medicine, Aarhus University and University Clinic in Nephrology and Hypertension, Hospital Jutland West, Denmark. mail@ebped.dk

AIMS AND SCOPE

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

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc.*

INDEXING/ABSTRACTING

The WJN is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Li-Li Wang; Production Department Director: Yun-Xiaoqian Wu; Editorial Office Director: Yan-Xia Xing.

NAME OF JOURNAL

World Journal of Nephrology

ISSN

ISSN 2220-6124 (online)

LAUNCH DATE

February 6, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Li Zuo

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2220-6124/editorialboard.htm>

PUBLICATION DATE

March 25, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Observational Study

Low-molecular-weight dextran for optical coherence tomography may not be protective against kidney injury in patients with renal insufficiency

Toru Misawa, Tomoyo Sugiyama, Yoshihisa Kanaji, Masahiro Hoshino, Masao Yamaguchi, Masahiro Hada, Tatsuhiro Nagamine, Kai Nogami, Yumi Yasui, Eisuke Usui, Tetsumin Lee, Taishi Yonetsu, Tetsuo Sasano, Tsunekazu Kakuta

ORCID number: Toru Misawa 0000-0003-0764-0644; Tomoyo Sugiyama 0000-0002-3754-6117; Yoshihisa Kanaji 0000-0001-6535-4377; Masahiro Hoshino 0000-0003-3661-1914; Masao Yamaguchi 0000-0003-0728-1362; Masahiro Hada 0000-0003-1499-9188; Tatsuhiro Nagamine 0000-0001-6242-849X; Kai Nogami 0000-0002-0622-959X; Yumi Yasui 0000-0003-3394-1563; Eisuke Usui 0000-0002-5454-3743; Tetsumin Lee 0000-0002-9457-072X; Taishi Yonetsu 0000-0002-1798-5008; Tetsuo Sasano 0000-0003-3582-6104; Tsunekazu Kakuta 0000-0002-4004-5292.

Author contributions: Misawa T and Kakuta T contributed to the study conception and design; Misawa T, Sugiyama T, Kanaji Y, Hoshino M, Yamaguchi M, Hada M, Nagamine T, Nogami K and Yasui Y conducted material preparation and data collection; Misawa T conducted data analysis and wrote the first draft of the manuscript; all authors commented on previous versions of the manuscript, read and approved the final manuscript.

Institutional review board statement: This study was

Toru Misawa, Tomoyo Sugiyama, Yoshihisa Kanaji, Masahiro Hoshino, Masao Yamaguchi, Masahiro Hada, Tatsuhiro Nagamine, Kai Nogami, Yumi Yasui, Eisuke Usui, Tetsumin Lee, Tsunekazu Kakuta, Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, Ibaraki 300-0028, Japan

Taishi Yonetsu, Department of Interventional Cardiology, Tokyo Medical and Dental University, Tokyo 113-8519, Japan

Tetsuo Sasano, Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo 113-8519, Japan

Corresponding author: Tsunekazu Kakuta, MD, PhD, Doctor, Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, 4-1-1 Otsuno, Tsuchiura, Ibaraki 300-0028, Japan. kaz@joy.email.ne.jp

Abstract

BACKGROUND

Low-molecular-weight dextran (LMWD) is considered a safe alternative to contrast media for blood displacement during optical coherence tomography (OCT) imaging.

AIM

To investigate whether the use of LMWD for OCT is protective against kidney injury in patients with advanced renal insufficiency.

METHODS

In this retrospective cohort study, we identified 421 patients with advanced renal insufficiency (estimated glomerular filtration rate < 45 mL/min/1.73 m²) who underwent coronary angiography or percutaneous coronary intervention; 79 patients who used additional LMWD for OCT imaging (LMWD group) and 342 patients who used contrast medium exclusively (control group). We evaluated the differences between these two groups and performed a propensity score-matched subgroup comparison.

performed in compliance with Institutional Ethics Committee Guidelines of Tsuchiura Kyodo General Hospital, and the study received its approval.

Informed consent statement: All patients provided written informed consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

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.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Urology and nephrology

Country/Territory of origin: Japan

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: December 29, 2020

Peer-review started: December 30, 2020

First decision: February 15, 2021

RESULTS

The median total volume of contrast medium was 133.0 mL in the control group *vs* 140.0 mL in the LMWD group. Although baseline renal function was not statistically different between these two groups, the LMWD group demonstrated a strong trend toward the progression of renal insufficiency as indicated by the greater change in serum creatinine level during the 1-year follow-up compared with the control group. Patients in the LMWD group experienced worsening renal function more frequently than patients in the control group. Propensity score matching adjusted for total contrast media volume consistently indicated a trend toward worsening renal function in the LMWD group at the 1-year follow-up. Delta serum creatinine at 1-year follow-up was significantly greater in the LMWD group than that in the control group [0.06 (-0.06, 0.29) *vs* -0.04 (-0.23, 0.08) mg/dL, *P* = 0.001], despite using similar contrast volume.

CONCLUSION

OCT using LMWD may not be protective against worsening renal function in patients with advanced renal insufficiency.

Key Words: Coronary artery disease; Kidney injury; Contrast media; Dextran; Optical coherence tomography; Renal insufficiency

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Low-molecular-weight dextran (LMWD) is considered a safe alternative to contrast during optical coherence tomography (OCT) imaging. We evaluated differences between patients who used additional LMWD for OCT (LMWD group) and those who used contrast exclusively (control group) and performed a propensity score-matched subgroup comparison. The LMWD group demonstrated a strong trend toward the progression of renal insufficiency during the 1-year follow-up. Propensity score-matched analysis indicated a trend toward worsening renal function in the LMWD group at the 1-year follow-up. Additional use of LMWD for OCT may not be protective against worsening renal function in patients with advanced renal insufficiency.

Citation: Misawa T, Sugiyama T, Kanaji Y, Hoshino M, Yamaguchi M, Hada M, Nagamine T, Nogami K, Yasui Y, Usui E, Lee T, Yonetsu T, Sasano T, Kakuta T. Low-molecular-weight dextran for optical coherence tomography may not be protective against kidney injury in patients with renal insufficiency. *World J Nephrol* 2021; 10(2): 8-20

URL: <https://www.wjgnet.com/2220-6124/full/v10/i2/8.htm>

DOI: <https://dx.doi.org/10.5527/wjn.v10.i2.8>

INTRODUCTION

The presence of renal insufficiency has been reported to be associated with the increased risk of cardiovascular events^[1]. Contrast-induced acute kidney injury (AKI) is a contributing factor to poor outcomes after angiographic procedures^[2-4]. The incidence of contrast-induced AKI increases sharply as renal function decreases^[5]. Some patients may even experience a prolonged decrease in renal function late after the index procedure^[6]. Moreover, the presence of prolonged renal insufficiency in the long-term was associated with the increased risk of cardiovascular events^[7]. Renal insufficiency and the total contrast volume are widely known as risk factors for contrast-induced AKI^[3,4]. Thus, reducing total contrast volume during coronary angiography and/or percutaneous coronary intervention (PCI) is an important priority to prevent contrast-induced worsening renal function, particularly in patients with advanced renal dysfunction.

Recently, intracoronary optical coherence tomography (OCT) has been widely used to assess coronary plaque characteristics and optimize PCI in patients with coronary artery disease^[8,9]. OCT imaging requires blood displacement from the vessel lumen, and contrast media is the standard flushing agent, although the potential risk of

Revised: February 22, 2021**Accepted:** March 11, 2021**Article in press:** March 11, 2021**Published online:** March 25, 2021**P-Reviewer:** Sureshkumar K**S-Editor:** Fan JR**L-Editor:** A**P-Editor:** Wang LL

contrast-induced AKI exists^[2,3]. Previous studies have demonstrated the feasibility of low-molecular-weight dextran (LMWD) as a safe alternative to contrast media for blood displacement during OCT imaging. Previous studies reported that OCT using LMWD might decrease the required total amount of contrast without losing image quality^[10,11]. On the other hand, LMWD-induced AKI has been repeatedly reported^[12-15]. Therefore, the protective role of LMWD against kidney injury remains uncertain in patients with advanced renal insufficiency, particularly regarding the long-term influence.

In the present study, we sought to investigate whether the additional use of LMWD for OCT imaging is protective against kidney injury in patients with advanced renal insufficiency undergoing coronary angiography and/or PCI by using propensity score-matched subgroup analysis during 1-year follow-up.

MATERIALS AND METHODS

Study population

This study was performed in compliance with our institutional ethics committee guidelines, and the study received its approval. All patients provided written informed consent before invasive coronary angiography or PCI for future data utilization.

In this retrospective cohort study, we identified 700 patients with advanced renal insufficiency [estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m²] who underwent diagnostic coronary angiography or PCI between March 2016 and June 2019 at Tsuchiura Kyodo General Hospital. The study period was chosen because, after March 2016, the total volume of injected flushing agents, including contrast medium and LMWD, was accurately documented by the use of an automated power injector. The final decision to perform an OCT examination by LMWD was at the operator's discretion. Patients receiving maintenance dialysis were excluded from the analysis. Patients with insufficient data regarding the use of contrast/LMWD or follow-up renal function were also excluded from the analysis. Thus, the final analysis included 421 patients with advanced renal insufficiency, including 342 patients with contrast medium exclusively (control group) and 79 patients receiving additional LMWD for OCT imaging (LMWD group) (Figure 1). We compared patients' clinical characteristics and the factors associated with renal function between these two groups using propensity score-matched subgroup analysis. All patient data and procedural details were obtained from patients' medical records.

Coronary angiography and PCI

Each patient underwent diagnostic coronary angiography *via* the radial artery with a 5-French system, and PCI with a 6-French or 7-French system. A low-osmolarity contrast medium (iopamidol; Fuji Pharma Co., Ltd., Tokyo, Japan) was injected using an automated power injector (ACIST CVi; ACIST Medical Systems Inc., Eden Prairie, MN, United States) at a rate of approximately 3.0-4.0 mL/s. All patients undergoing PCI were treated by coronary drug-eluting stent implantation. To determine the appropriate stent size and obtain optimal stent expansion, we used online quantitative coronary angiography and intracoronary imaging, including OCT and intravascular ultrasound findings. The type of stent was chosen at the operator's discretion, and the interventionist determined the PCI strategy.

OCT image acquisition

OCT images were acquired using frequency-domain OCT systems: Abbott OCT (ILUMIEN OPTIS; Abbott Vascular, Santa Clara, CA, United States) or Terumo optical frequency-domain imaging system (Lunawave; Terumo Corporation, Tokyo, Japan). The technique of OCT image acquisition has been described elsewhere^[8]. OCT imaging pullbacks were performed automatically by the dedicated devices while injecting the flushing agent, which was either contrast medium or LMWD-40 (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan), at a flow rate of 3.0-4.5 mL/s *via* the guiding catheter using an automated power injector. Pullback speed was 18 mm/s with the Abbott OCT system and 20 mm/s with the Terumo optical frequency-domain imaging system.

Renal function assessment

Laboratory data were sampled before coronary angiography and/or PCI at the

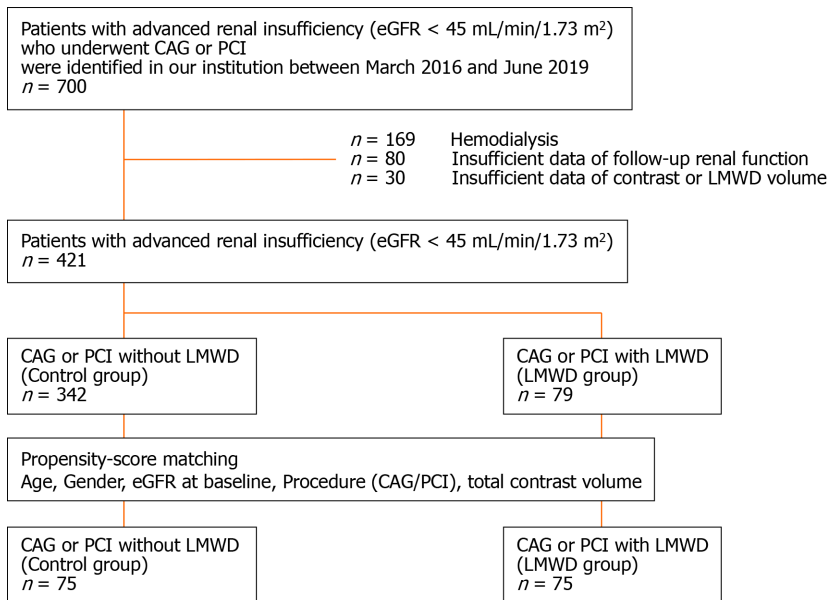


Figure 1 The patient population in this study. CAG: Coronary angiography; eGFR: Estimated glomerular filtration rate; LMWD: Low-molecular-weight dextran; OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention.

protocol-specified timing for evaluating renal function. Morning fasting blood samples on the day of the procedure were obtained in patients undergoing elective procedures. In patients with acute coronary syndrome (ACS) and those undergoing urgent procedures, blood samples were obtained at admission. We calculated eGFR using the equation modified for Japanese patients: $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} \times 0.739$ (for women)^[16]. Advanced renal insufficiency was defined as $\text{eGFR} < 45 \text{ mL/min/1.73 m}^2$ ^[17].

Contrast-induced AKI was defined as a $\geq 0.3 \text{ mg/dL}$ increase in serum creatinine level from baseline within 5 d after the procedure^[18]. Worsening renal function in the long-term was defined as a $\geq 0.3 \text{ mg/dL}$ increase in serum creatinine level from baseline to the 1-year follow-up^[19]. We evaluated the incidence of contrast-induced AKI and worsening renal function, and serial changes in serum creatinine level within 5 d, and at 1 mo and 1-year post-procedure. We defined delta creatinine (ΔCre) as the difference between post- and pre-procedural serum creatinine levels. Risks for contrast-induced renal dysfunction were stratified by the Mehran risk score^[20].

Hydration protocol

Our institutional standard protocol for hydration was applied in all patients undergoing elective procedures and in selected patients with ACS. Intravenous normal saline (1.5 mL/kg/h) was administrated for at least 3 h before contrast exposure after blood sampling for baseline renal function, and was continued for at least 12 h after the procedure. After the literature review, this protocol was approved by the institutional ethics committee on the condition of close clinical monitoring for signs of intolerance in patients with heart failure^[21].

Statistical analysis

The statistical analysis was performed using R version 3.6.2 (The R Project for Statistical Computing, Vienna, Austria). Categorical data are expressed as absolute frequencies and percentages and were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables are expressed as mean $\pm$ SD for normally distributed variables and median (25th-75th percentile) for non-normally distributed variables. Analyses were performed with the Mann-Whitney *U* test for non-normally distributed variables. Changes in serum creatinine (baseline, 5 d, 1 mo, and 1-year post-procedure) were evaluated using one-way repeated measures analysis of variance.

To reduce the effect of bias regarding exposure to LMWD in this observational study, we adjusted for significant differences in patients' baseline characteristics between the control and LMWD groups using propensity score-matched subgroup analysis. We applied propensity score-matched subgroup analysis, adjusted for age, sex, indication (coronary angiography or PCI), baseline eGFR level, and total contrast

volume. The propensity score-matched subgroup analysis adjusted for these confounders was performed with a 1:1 algorithm using nearest-neighbor matching with a caliper width of ± 0.10 and no replacement. The effect of the additional use of LMWD on renal function was assessed between these propensity score-matched subgroups. The relationship between worsening renal function (dependent variable), flushing agent, and other potential confounders was evaluated using multivariate logistic regression analysis (stepwise forward method) to assess whether LMWD use remained associated with worsening renal function. The associated variables in the univariate analyses ($P < 0.10$) were entered into the propensity score-matched models. We used the Hosmer–Lemeshow test to establish the goodness-of-fit of the model, and $P > 0.05$ indicated that the model provided a valid representation. Receiver operating characteristic (ROC) curves were analyzed to determine the optimal cut-off values for the confounding variables to predict worsening renal function. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Patients' baseline characteristics

The final analysis included 342 patients in the control group and 79 patients in the LMWD group (Figure 1). Patients' characteristics in these two groups are shown in Table 1. The baseline eGFR level and the distribution of GFR categories were not different between the two groups. A median volume of 133.0 mL of contrast medium was used in the control group. In the LMWD group, a median LMWD volume of 67.6 mL for OCT imaging plus 140.0 mL of contrast medium was used. No anaphylactic reactions occurred. Hemodialysis was required in one patient in the control group during the 1-year follow-up.

Renal function post-procedure in the entire study cohort

The LMWD group demonstrated a strong trend toward the progression of renal insufficiency as indicated by the greater change in serum creatinine levels during the 1-year follow-up compared with the control group (Table 1, Figure 2A). Contrast-induced AKI occurred in 9 patients (11.4%) in the LMWD group and 42 patients (12.3%) in the control group ($P = 1.000$). However, patients in the LMWD group experienced worsening renal function more frequently than patients in the control group (Table 1).

Propensity score-matched comparisons

A propensity score-matched cohort adjusted for age, sex, indication (coronary angiography or PCI), baseline eGFR level, and total contrast volume yielded 150 (75 patients each in the control and LMWD groups) well-matched patients regarding potential confounding baseline variables for the clinical and procedural characteristics. A comparison of renal function after the procedure between the control and LMWD groups in the propensity score-matched cohort is shown in Table 2. The baseline eGFR level and the distribution of GFR categories were not different between the two groups. Moreover, no patients had GFR category 5 in the matched cohort. The incidence of contrast-induced AKI was not significantly different between the two groups. In contrast, the LMWD group demonstrated a strong trend toward the progression of renal insufficiency as indicated by the greater change in serum creatinine level during the 1-year follow-up compared with the control group (Table 2, Figure 2B). Although the prevalence of worsening renal function was not statistically different (25.3% *vs* 12.0%, $P = 0.059$), ΔCre at 1-year follow-up was significantly greater in the LMWD group than that in the Control group [0.06 (-0.06, 0.29) *vs* -0.04 (-0.23, 0.08) mg/dL, $P = 0.001$], despite using similar contrast volume. ROC curve analyses demonstrated that the optimal cut-off values for LMWD volume and baseline eGFR level to predict worsening renal function were 52.0 mL for LMWD volume [area under the curve (AUC): 0.614; 95% confidence interval (CI), 0.504-0.724] and 38.4 mL/min/1.73 m² for baseline eGFR level (AUC: 0.654; 95%CI: 0.555-0.753). Multivariable logistic regression analysis revealed that the factors independently associated with worsening renal function were greater LMWD volume (≥ 52.0 mL) [odds ratio (OR): 2.83, $P = 0.019$] and lower baseline eGFR level (< 38.4 mL/min/1.73 m²) (OR: 4.27, $P = 0.004$) (Table 3). The Hosmer–Lemeshow test provided a P value of 0.993 in the matched cohort, which indicated a proper goodness-of-fit for this model. Moreover, greater LMWD volume particularly identified patients with a high risk for worsening renal function in worse baseline renal function (Figure 3).

Table 1 Patients' characteristics and renal function (entire study cohort)

	Total (n = 421)	Control (n = 342)	LMWD (n = 79)	P value
Sex				
Male	281 (66.7)	219 (64.0)	62 (78.5)	0.017
Female	140 (33.3)	123 (36.0)	17 (21.5)	
Age, yr	75.0 [69.0, 80.0]	76.0 [69.0, 80.0]	74.0 [68.0, 79.0]	0.178
Body mass index, kg/m ²	24.0 [21.1, 26.2]	23.9 [21.1, 26.0]	24.4 [21.3, 26.6]	0.273
Procedure				
Coronary angiography	279 (66.3)	238 (69.6)	41 (51.9)	0.004
PCI	142 (33.7)	104 (30.4)	38 (48.1)	
Diagnosis				
Stable CAD	350 (83.1)	288 (84.2)	62 (78.5)	0.243
Acute coronary syndrome	71 (16.9)	54 (15.8)	17 (21.5)	
Prior myocardial infarction	155 (36.8)	106 (31.0)	49 (62.0)	< 0.001
Prior PCI	209 (49.6)	148 (43.3)	61 (77.2)	< 0.001
Prior CABG	22 (5.2)	20 (5.8)	2 (2.5)	0.397
Hypertension	266 (63.2)	210 (61.4)	56 (70.9)	0.122
Dyslipidemia	178 (42.3)	140 (40.9)	38 (48.1)	0.257
Diabetes mellitus	218 (51.8)	172 (50.3)	46 (58.2)	0.214
Stroke	21 (5.0)	20 (5.8)	1 (1.3)	0.147
Current smoking	56 (13.3)	35 (10.2)	21 (26.6)	< 0.001
Serum creatinine, mg/dL	1.33 [1.22, 1.56]	1.33 [1.20, 1.52]	1.36 [1.27, 1.62]	0.057
eGFR, mL/min/1.73 m ²	38.4 [32.9, 42.3]	38.5 [32.6, 42.4]	36.9 [33.1, 41.8]	0.368
GFR category				
3b (30 ≤ eGFR < 45)	352 (83.6)	284 (83.0)	68 (86.1)	0.783
4 (15 ≤ eGFR < 30)	64 (15.2)	54 (15.8)	10 (12.6)	
5 (eGFR < 15)	5 (1.2)	4 (1.2)	1 (1.3)	
Hemoglobin A1c, %	6.3 [5.8, 6.9]	6.3 [5.7, 7.0]	6.4 [6.0, 6.9]	0.109
Low-density lipoprotein cholesterol, mg/dL	86 [71, 107]	87 [72, 108]	82 [70, 103]	0.301
Hemoglobin, g/dL	11.8 [10.5, 13.4]	11.8 [10.5, 13.4]	12.1 [10.9, 13.5]	0.375
C-reactive protein, mg/dL	0.14 [0.05, 0.42]	0.13 [0.05, 0.40]	0.15 [0.06, 0.53]	0.180
NT-proBNP, pg/mL	864.5 [279.8, 3471.3]	991.0 [288.3, 3700.0]	633.0 [177.3, 1775.5]	0.099
LVEF, %	57 [44, 66]	58 [44, 66]	52 [43, 63]	0.140
Mehran risk score	8 [6, 11]	8 [6, 11]	8 [7, 11]	0.710
Catheterization procedure				
Total agent volume, mL	150.0 [103.0, 226.0]	133.0 [92.0, 192.3]	207.0 [167.5, 271.8]	< 0.001
Total contrast volume, mL	135.0 [95.0, 193.0]	133.0 [92.0, 192.3]	140.0 [102.0, 195.0]	0.618
LMWD volume, mL	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	67.6 [43.3, 86.0]	< 0.001
OCT	79 (40.6)	92 (26.9)	79 (100.0)	< 0.001
Renal function post-procedure				
ΔCre within 5 d, mg/dL	-0.01 [-0.11, 0.13]	0.00 [-0.10, 0.14]	-0.03 [-0.14, 0.12]	0.414
ΔCre at 1 mo, mg/dL	-0.01 [-0.15, 0.11]	-0.01 [-0.16, 0.11]	-0.01 [-0.13, 0.09]	0.686

ΔCre at 1 yr, mg/dL	0.01 [-0.13, 0.18]	0.00 [-0.14, 0.16]	0.07 [-0.04, 0.34]	0.004
Acute kidney injury	51 (12.1)	42 (12.3)	9 (11.4)	1.000
Worsening renal function (ΔCre ≥ 0.3 mg/dL/1 yr)	80 (19.0)	58 (17.0)	22 (27.8)	0.039

Data are presented as *n* (%) or median (25th-75th percentile). CABG: Coronary artery bypass graft surgery; CAD: Coronary artery disease; ΔCre: Delta creatinine; eGFR: Estimated glomerular filtration rate; LMWD: Low-molecular-weight dextran; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type natriuretic peptide; OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention.

DISCUSSION

The main findings of the present study are: (1) The additional use of LMWD for OCT was identified in 18.8% (79/421) of the study patients with advanced renal insufficiency; (2) The LMWD group demonstrated a strong trend toward the progression of renal insufficiency as indicated by the greater change in serum creatinine level during the 1-year follow-up compared with the control group; (3) After propensity score matching, the LMWD group demonstrated a significant trend in the progression of renal insufficiency at the 1-year follow-up; and (4) Multivariable logistic regression analysis revealed that greater LMWD volume and lower baseline eGFR level were independently associated with worsening renal function in the propensity score-matched cohort. To the best of our knowledge, this is the first study to demonstrate that the additional use of LMWD for OCT imaging may not be protective against worsening renal function in patients with advanced renal insufficiency, particularly with respect to the long-term influence.

Impact of renal insufficiency for worse outcomes

Various studies have reported that renal insufficiency is independently associated with cardiovascular events and mortality^[22-24]. Notably, patients with eGFR < 45 mL/min/1.73 m² were associated with a 1.49-fold increase in the risk of cardiovascular events compared with patients with eGFR > 75 mL/min/1.73 m², which resulted in a substantial reduction in life expectancy for patients with eGFR < 45 mL/min/1.73 m²^[25,26]. Hypertension and diabetes mellitus are important causes of kidney dysfunction, which increase the risk of cardiovascular events. One of the mechanisms of cardiovascular complications in renal insufficiency involves endothelial dysfunction. Bajaj *et al*^[27] reported that coronary microvascular dysfunction was associated with impaired left ventricular mechanics and cardiovascular events in patients with chronic kidney impairment.

Contrast and LMWD for OCT imaging

OCT enables clear visualization of culprit and non-culprit plaque morphologies^[8,9] and PCI optimization^[28,29]. LMWD is considered a safe alternative to contrast media for blood displacement during OCT imaging. Moreover, a recent study demonstrated that the changes in serum creatinine level just after the procedure did not differ between the patients treated with OCT guidance and those with intravascular ultrasound guidance, which included mainly normal and mild renal insufficiency^[30]. However, these previous studies enrolled a relatively small number of patients, and sample sizes were too small to draw definitive recommendations for the safety of additional use of LMWD for OCT in patients with advanced renal insufficiency. In contrast, our study involved a much larger number of patients with advanced renal insufficiency receiving LMWD additionally as a substitute flushing agent. In daily clinical practice, the additional use of LMWD for OCT has been preferentially performed in patients with advanced renal insufficiency to reduce the total contrast volume and prevent contrast-induced AKI. However, the safety of LMWD over contrast medium against kidney injury, particularly over the long-term, has not been fully studied. To our knowledge, our study is the first report examining the possibility of LMWD-related kidney injury when LMWD is used for OCT combined with contrast medium in patients with advanced renal insufficiency during a 1-year follow-up.

LMWD and renal impairment

In the previous studies that reported the association between LMWD and AKI^[12-15], the total LMWD volume was much greater than that used for OCT because LMWD was used mainly to correct hypovolemia as a substitute for plasma concentrate. In contrast, in our study, the LMWD group showed a strong trend toward worsening renal

Table 2 Patients' characteristics and renal function (matched cohort)

	Total (n = 150)	Control (n = 75)	LMWD (n = 75)	P value
Sex				
Male	119 (79.3)	61 (81.3)	58 (77.3)	0.687
Female	31 (20.7)	14 (18.7)	17 (22.7)	
Age, yr	75.0 [67.5, 80.0]	75.0 [69.0, 80.0]	74.0 [67.0, 79.5]	0.643
Body mass index, kg/m ²	23.7 [21.0, 25.9]	23.0 [20.8, 25.4]	24.5 [21.3, 26.8]	0.030
Procedure				
Coronary angiography	84 (56.0)	43 (57.3)	41 (54.7)	0.869
PCI	66 (44.0)	32 (42.7)	34 (45.3)	
Diagnosis				
Stable CAD	121 (80.7)	61 (81.3)	60 (80.0)	1.000
Acute coronary syndrome	29 (19.3)	14 (18.7)	15 (20.0)	
Prior myocardial infarction	77 (51.3)	30 (40.0)	47 (62.7)	0.009
Prior PCI	93 (62.0)	34 (45.3)	59 (78.7)	< 0.001
Prior CABG	4 (2.7)	2 (2.7)	2 (2.7)	1.000
Hypertension	98 (65.3)	45 (60.0)	53 (70.7)	0.230
Dyslipidemia	63 (42.0)	28 (37.3)	35 (46.7)	0.321
Diabetes mellitus	81 (54.0)	37 (49.3)	44 (58.7)	0.326
Stroke	5 (3.3)	4 (5.3)	1 (1.3)	0.367
Current smoking	29 (19.3)	9 (12.0)	20 (26.7)	0.037
Serum creatinine, mg/dL	1.36 [1.25, 1.63]	1.37 [1.26, 1.71]	1.35 [1.25, 1.61]	0.612
eGFR, mL/min/1.73 m ²	37.6 [32.8, 42.0]	38.0 [31.0, 42.2]	37.0 [33.2, 41.8]	0.949
GFR category				
3b (30 ≤ eGFR < 45)	125 (83.3)	59 (78.7)	66 (88.0)	0.189
4 (15 ≤ eGFR < 30)	25 (16.7)	16 (21.3)	9 (12.0)	
5 (eGFR < 15)	0 (0.0)	0 (0.0)	0 (0.0)	
Hemoglobin A1c, %	6.3 [5.9, 6.9]	6.1 [5.7, 6.9]	6.5 [6.0, 7.0]	0.058
Low-density lipoprotein cholesterol, mg/dL	87 [70, 108]	88 [72, 114]	81 [70, 103]	0.155
Hemoglobin, g/dL	11.8 [10.5, 13.4]	11.5 [10.3, 13.5]	12.1 [10.9, 13.3]	0.230
C-reactive protein, mg/dL	0.14 [0.05, 0.46]	0.12 [0.05, 0.35]	0.15 [0.06, 0.53]	0.320
NT-proBNP, pg/mL	835.5 [244.8, 3265.3]	1560.0 [270.0, 4268.5]	632.0 [175.0, 1679.5]	0.076
LVEF, %	53 [43, 64]	56 [44, 64]	52 [43, 63]	0.697
Mehran risk score	8 [7, 11]	8 [7, 11]	8 [7, 11]	0.548
Catheterization procedure				
Total agent volume, mL	174.1 [120.0, 244.8]	130.0 [88.0, 196.5]	209.7 [170.1, 271.8]	< 0.001
Total contrast volume, mL	138.0 [97.5, 200.0]	130.0 [88.0, 196.5]	142.0 [104.5, 200.0]	0.408
LMWD volume, mL	7.6 [0.0, 68.2]	0.0 [0.0, 0.0]	68.5 [43.9, 86.0]	< 0.001
OCT	95 (63.3)	20 (26.7)	75 (100.0)	< 0.001
Renal function post-procedure				
ΔCre within 5 d, mg/dL	-0.03 [-0.15, 0.13]	-0.04 [-0.15, 0.14]	-0.03 [-0.14, 0.10]	0.848
ΔCre at 1 mo, mg/dL	-0.03 [-0.17, 0.09]	-0.06 [-0.23, 0.10]	-0.02 [-0.14, 0.08]	0.276

ΔCre at 1 yr, mg/dL	0.01 [-0.14, 0.19]	-0.04 [-0.23, 0.08]	0.06 [-0.06, 0.29]	0.001
Acute kidney injury	14 (9.3)	7 (9.3)	7 (9.3)	1.000
Worsening renal function (ΔCre ≥ 0.3 mg/dL/1 yr)	28 (18.7)	9 (12.0)	19 (25.3)	0.059

Data are presented as *n* (%) or median (25th-75th percentile). CABG: Coronary artery bypass graft surgery; CAD: Coronary artery disease; ΔCre: Delta creatinine; eGFR: Estimated glomerular filtration rate; LMWD: Low-molecular-weight dextran; LVEF: Left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type natriuretic peptide; OCT: Optical coherence tomography; PCI: Percutaneous coronary intervention.

Table 3 Univariable and multivariable logistic regression model for predicting worsening renal function (ΔCre ≥ 0.3 mg/dL/1-year) in matched cohort

Variable	Univariable				Multivariable			
	OR	95%CI lower limit	95%CI upper limit	P value	OR	95%CI lower limit	95%CI upper limit	P value
Female	1.72	0.68	4.39	0.256				
Age	0.96	0.92	0.99	0.036				Not selected
Body mass index, kg/m ²	1.02	0.92	1.13	0.759				
PCI	1.61	0.70	3.67	0.260				
Acute coronary syndrome	1.92	0.75	4.95	0.175				
Prior myocardial infarction	1.33	0.58	3.05	0.496				
Prior PCI	1.68	0.69	4.11	0.258				
Hypertension	0.95	0.40	2.23	0.897				
Diabetes mellitus	2.04	0.86	4.87	0.107				
Stroke	1.09	0.12	10.20	0.938				
Current smoking	1.17	0.43	3.22	0.756				
eGFR < 38.4 mL/min/1.73 m ²	4.18	1.58	11.00	0.004	4.27	1.59	11.40	0.004
LVEF, %	0.98	0.95	1.01	0.220				
Mehran risk score	1.07	0.98	1.17	0.127				
Total agent volume, mL	1.00	0.99	1.01	0.533				
Total contrast volume, mL	0.99	0.99	1.01	0.776				
LMWD volume ≥ 52 mL	2.76	1.19	6.37	0.018	2.83	1.18	6.76	0.019

CI: Confidence interval; eGFR: Estimated glomerular filtration rate; LMWD: Low-molecular-weight dextran; LVEF: Left ventricular ejection fraction; OR: Odds ratio; PCI: Percutaneous coronary intervention.

function at the 1-year follow-up, after propensity score-matched comparisons, even though LMWD volume for OCT was a median of 68.5 (43.9, 86.0) mL. The pathogenesis of contrast-induced AKI involves several mechanisms, such as nephrotoxic effects on tubular epithelial cells, tubular obstruction, decreased renal perfusion, and renal vasoconstriction^[4]. Osmotic nephrosis characterized by vacuolization and swelling of proximal tubular cells is induced by many substrates such as contrast medium and LMWD^[15]. LMWD is also associated with hyperoncotic kidney injury^[13]. Excretion of LMWD particles could be reduced, particularly in the presence of renal insufficiency. In previous studies, approximately 70% of LMWD was excreted by the kidneys within 24 h, while the remaining LMWD was excreted over several days^[14,31]. Administration of LMWD accompanied by a certain amount of contrast medium could potentially cause prolonged renal insufficiency in the long-term.

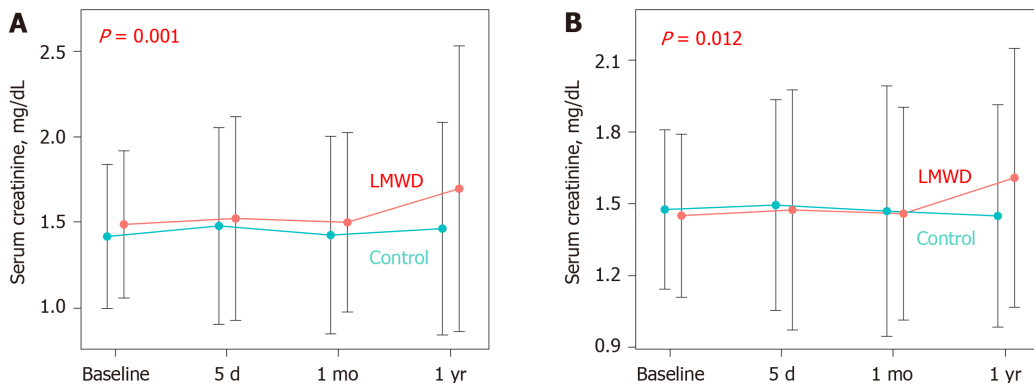


Figure 2 Serial comparison of serum creatinine levels at baseline, and within 5 d, 1 mo, and 1-year post-procedure. A: Entire study cohort. Renal function was consistently lower in the low-molecular-weight dextran (LMWD) group than in the control group; B: Propensity score-matched cohort. The LMWD group demonstrated a trend toward worsening renal insufficiency during the 1-year follow-up compared with the control group. LMWD: Low-molecular-weight dextran.

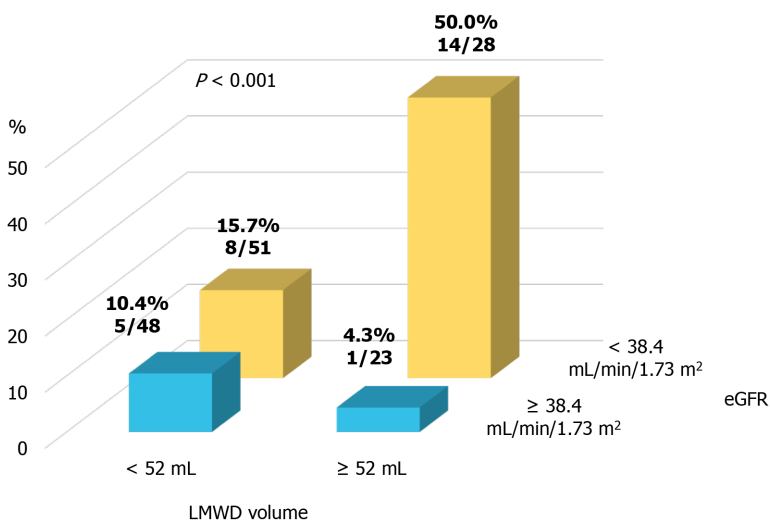


Figure 3 Prevalence of worsening renal function stratified by the cut-off values for low-molecular-weight dextran volume and baseline estimated glomerular filtration rate level in propensity score-matched cohort. eGFR: Estimated glomerular filtration rate; LMWD: Low-molecular-weight dextran.

Clinical implications

The present study indicated that the additional use of LMWD in patients with advanced renal insufficiency showed a strong trend toward renal impairment at the 1-year follow-up. Our results also suggested that greater LMWD volume may be a contributing factor to the progression of long-term renal dysfunction in patients with advanced renal insufficiency. Excessive use of LMWD in place of contrast medium may not effectively decrease the prevalence of renal impairment after OCT imaging.

Our results, including the propensity score-matched comparison, suggest that using LMWD for OCT in patients with advanced renal insufficiency should be avoided, or at least care should be exercised to reduce the amount of LMWD. The present study also suggested the importance of long-term follow-up of renal function after LMWD use for OCT imaging. Since our study is of hypothesis generating nature, further studies are needed to test this hypothesis.

Study limitations

First, this was a retrospective study from a single center with a relatively small sample size and, thus, has inherent limitations. Although we used propensity score matching to adjust for differences in patients' baseline clinical characteristics, including renal function, the final decision regarding the choice of flushing agents for OCT was at the operator's discretion, and selection bias cannot be canceled. Second, because we collected data from our institutional OCT registry, some patients with ACS underwent pre- and post-PCI OCT examinations for the culprit lesion, and some underwent OCT

examination for the non-culprit lesion before or after culprit lesion assessment/treatment for the clinical research. This nature of the study cohort might have led to an increase in contrast medium and/or LMWD volume. Third, we did not evaluate the influence of medical therapy and clinical status post-procedure on the incidence of contrast-induced AKI and worsening renal function, which could have affected our results. Although this study evaluated the renal function only within 5 d, and at 1 mo and 1-year post-procedure, the mid-term effect of LMWD on renal function was not fully studied. Fourth, the prevalence and severity of proteinuria and the cause of renal insufficiency were not assessed, and both could be closely related to the progression of renal dysfunction. Finally, we did not assess clinical outcomes or perform extensive subgroup analyses because of the relatively small number of events.

CONCLUSION

In this retrospective study, we observed the greater extent of the progression of renal dysfunction and the higher prevalence of worsening renal function, particularly at the 1-year follow-up, in patients with advanced renal insufficiency who underwent OCT imaging using LMWD. These findings provide a novel insight regarding LMWD use by interventionalists who are involved in OCT examinations. Further large, prospective studies are warranted.

ARTICLE HIGHLIGHTS

Research background

Low-molecular-weight dextran (LMWD) is considered a safe alternative to contrast media for blood displacement during optical coherence tomography (OCT) imaging. On the other hand, LMWD-induced acute kidney injury has been repeatedly reported.

Research motivation

The protective role of LMWD against kidney injury remains uncertain in patients with advanced renal insufficiency, particularly regarding the long-term influence.

Research objectives

To investigate whether the use of LMWD for OCT is protective against kidney injury in patients with advanced renal insufficiency.

Research methods

In this retrospective cohort study, we identified 421 patients with advanced renal insufficiency (estimated glomerular filtration rate < 45 mL/min/1.73 m²) who underwent coronary angiography or percutaneous coronary intervention; 79 patients who used additional LMWD for OCT imaging (LMWD group) and 342 patients who used contrast medium exclusively (control group). We evaluated the differences between these two groups and performed a propensity score-matched subgroup comparison.

Research results

Although baseline renal function was not statistically different between these two groups, the LMWD group demonstrated a strong trend toward the progression of renal insufficiency as indicated by the greater change in serum creatinine level during the 1-year follow-up compared with the control group. Patients in the LMWD group experienced worsening renal function more frequently than patients in the control group. Propensity score matching adjusted for total contrast media volume consistently indicated a trend toward worsening renal function in the LMWD group at the 1-year follow-up. Delta serum creatinine at 1-year follow-up was significantly greater in the LMWD group than that in the control group [0.06 (-0.06, 0.29) *vs* -0.04 (-0.23, 0.08) mg/dL, *P* = 0.001], despite using similar contrast volume.

Research conclusions

Additional use of LMWD for OCT may not be protective against worsening renal function in patients with advanced renal insufficiency.

Research perspectives

Since our study is of hypothesis generating nature, further large, prospective studies are warranted.

REFERENCES

- 1 **Parikh NI**, Hwang SJ, Larson MG, Levy D, Fox CS. Chronic kidney disease as a predictor of cardiovascular disease (from the Framingham Heart Study). *Am J Cardiol* 2008; **102**: 47-53 [PMID: 18572034 DOI: 10.1016/j.amjcard.2008.02.095]
- 2 **Gruberg L**, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, Pichard AD, Satler LF, Leon MB. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *J Am Coll Cardiol* 2000; **36**: 1542-1548 [PMID: 11079656 DOI: 10.1016/s0735-1097(00)00917-7]
- 3 **Rihal CS**, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002; **105**: 2259-2264 [PMID: 12010907 DOI: 10.1161/01.cir.0000016043.87291.33]
- 4 **Mehran R**, Dangas GD, Weisbord SD. Contrast-Associated Acute Kidney Injury. *N Engl J Med* 2019; **380**: 2146-2155 [PMID: 31141635 DOI: 10.1056/NEJMr1805256]
- 5 **McCullough PA**, Choi JP, Feghali GA, Schussler JM, Stoler RM, Vallabahn RC, Mehta A. Contrast-Induced Acute Kidney Injury. *J Am Coll Cardiol* 2016; **68**: 1465-1473 [PMID: 27659469 DOI: 10.1016/j.jacc.2016.05.099]
- 6 **Wang F**, Peng C, Zhang G, Zhao Q, Xuan C, Wei M, Wang N. Delayed kidney injury following coronary angiography. *Exp Ther Med* 2016; **12**: 530-534 [PMID: 27347090 DOI: 10.3892/etm.2016.3315]
- 7 **Turin TC**, James MT, Jun M, Tonelli M, Coresh J, Manns BJ, Hemmelgarn BR. Short-term change in eGFR and risk of cardiovascular events. *J Am Heart Assoc* 2014; **3**: e000997 [PMID: 25213565 DOI: 10.1161/JAHA.114.000997]
- 8 **Prati F**, Regar E, Mintz GS, Arbustini E, Di Mario C, Jang IK, Akasaka T, Costa M, Guagliumi G, Grube E, Ozaki Y, Pinto F, Serruys PW; Expert's OCT Review Document. Expert review document on methodology, terminology, and clinical applications of optical coherence tomography: physical principles, methodology of image acquisition, and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J* 2010; **31**: 401-415 [PMID: 19892716 DOI: 10.1093/eurheartj/ehp433]
- 9 **Prati F**, Guagliumi G, Mintz GS, Costa M, Regar E, Akasaka T, Barlis P, Tearney GJ, Jang IK, Arbustini E, Bezerra HG, Ozaki Y, Bruining N, Dudek D, Radu M, Erglis A, Motreff P, Alfonso F, Toutouzas K, Gonzalo N, Tamburino C, Adriaenssens T, Pinto F, Serruys PW, Di Mario C; Expert's OCT Review Document. Expert review document part 2: methodology, terminology and clinical applications of optical coherence tomography for the assessment of interventional procedures. *Eur Heart J* 2012; **33**: 2513-2520 [PMID: 22653335 DOI: 10.1093/eurheartj/ehs095]
- 10 **Ozaki Y**, Kitabata H, Tsujioka H, Hosokawa S, Kashiwagi M, Ishibashi K, Komukai K, Tanimoto T, Ino Y, Takarada S, Kubo T, Kimura K, Tanaka A, Hirata K, Mizukoshi M, Imanishi T, Akasaka T. Comparison of contrast media and low-molecular-weight dextran for frequency-domain optical coherence tomography. *Circ J* 2012; **76**: 922-927 [PMID: 22301848 DOI: 10.1253/circj.CJ-11-1122]
- 11 **Frick K**, Michael TT, Alomar M, Mohammed A, Rangan BV, Abdullah S, Grodin J, Hastings JL, Banerjee S, Brilakis ES. Low molecular weight dextran provides similar optical coherence tomography coronary imaging compared to radiographic contrast media. *Catheter Cardiovasc Interv* 2014; **84**: 727-731 [PMID: 23804461 DOI: 10.1002/ccd.25092]
- 12 **Feest TG**. Low molecular weight dextran: a continuing cause of acute renal failure. *Br Med J* 1976; **2**: 1300 [PMID: 1000202 DOI: 10.1136/bmj.2.6047.1300]
- 13 **Moran M**, Kapsner C. Acute renal failure associated with elevated plasma oncotic pressure. *N Engl J Med* 1987; **317**: 150-153 [PMID: 2439908 DOI: 10.1056/nejm198707163170306]
- 14 **Zwaveling JH**, Meulenbelt J, van Xanten NH, Hené RJ. Renal failure associated with the use of dextran-40. *Neth J Med* 1989; **35**: 321-326 [PMID: 2483959]
- 15 **Dickenmann M**, Oettl T, Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. *Am J Kidney Dis* 2008; **51**: 491-503 [PMID: 18295066 DOI: 10.1053/j.ajkd.2007.10.044]
- 16 **Japan nephrology society**. [Special issue: Clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2012]. *Nihon Jinzo Gakkai Shi* 2012; **54**: 1034-1191 [PMID: 23387281]
- 17 **Farrington K**, Covic A, Nistor I, Aucella F, Clyne N, De Vos L, Findlay A, Fouque D, Grodzicki T, Iyasere O, Jager KJ, Joosten H, Macias JF, Mooney A, Nagler E, Nitsch D, Taal M, Tattersall J, Stryckers M, van Asselt D, Van den Noortgate N, van der Veer S, van Biesen W. Clinical Practice Guideline on management of older patients with chronic kidney disease stage 3b or higher (eGFR<45 mL/min/1.73 m²): a summary document from the European Renal Best Practice Group. *Nephrol Dial Transplant* 2017; **32**: 9-16 [PMID: 28391313 DOI: 10.1093/ndt/gfw411]
- 18 **Mehran R**, Faggioni M, Chandrasekhar J, Angiolillo DJ, Bertolet B, Jobe RL, Al-Joundi B, Brar S, Dangas G, Batchelor W, Prasad A, Gurm HS, Tumlin J, Stone GW. Effect of a Contrast Modulation

- System on Contrast Media Use and the Rate of Acute Kidney Injury After Coronary Angiography. *JACC Cardiovasc Interv* 2018; **11**: 1601-1610 [PMID: 30139467 DOI: 10.1016/j.jcin.2018.04.007]
- 19 **Bleyer AJ**, Shemanski LR, Burke GL, Hansen KJ, Appel RG. Tobacco, hypertension, and vascular disease: risk factors for renal functional decline in an older population. *Kidney Int* 2000; **57**: 2072-2079 [PMID: 10792626 DOI: 10.1046/j.1523-1755.2000.00056.x]
 - 20 **Mehran R**, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004; **44**: 1393-1399 [PMID: 15464318 DOI: 10.1016/j.jacc.2004.06.068]
 - 21 **Balemans CE**, Reichert LJ, van Schelven BI, van den Brand JA, Wetzels JF. Epidemiology of contrast material-induced nephropathy in the era of hydration. *Radiology* 2012; **263**: 706-713 [PMID: 22535561 DOI: 10.1148/radiol.12111667]
 - 22 **Freeman RV**, Mehta RH, Al Badr W, Cooper JV, Kline-Rogers E, Eagle KA. Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. *J Am Coll Cardiol* 2003; **41**: 718-724 [PMID: 12628712 DOI: 10.1016/s0735-1097(02)02956-x]
 - 23 **Herzog CA**, Ma JZ, Collins AJ. Comparative survival of dialysis patients in the United States after coronary angioplasty, coronary artery stenting, and coronary artery bypass surgery and impact of diabetes. *Circulation* 2002; **106**: 2207-2211 [PMID: 12390949 DOI: 10.1161/01.cir.0000035248.71165.eb]
 - 24 **Sørensen CR**, Brendorp B, Rask-Madsen C, Køber L, Kjølser E, Torp-Pedersen C. The prognostic importance of creatinine clearance after acute myocardial infarction. *Eur Heart J* 2002; **23**: 948-952 [PMID: 12069449 DOI: 10.1053/ehj.2001.2989]
 - 25 **Anavekar NS**, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; **351**: 1285-1295 [PMID: 15385655 DOI: 10.1056/NEJMoa041365]
 - 26 **Turin TC**, Tonelli M, Manns BJ, Ravani P, Ahmed SB, Hemmelgarn BR. Chronic kidney disease and life expectancy. *Nephrol Dial Transplant* 2012; **27**: 3182-3186 [PMID: 22442392 DOI: 10.1093/ndt/gfs052]
 - 27 **Bajaj NS**, Singh A, Zhou W, Gupta A, Fujikura K, Byrne C, Harms HJ, Osborne MT, Bravo P, Andrikopolou E, Divakaran S, Bibbo CF, Hainer J, Skali H, Taqueti V, Steigner M, Dorbala S, Charytan DM, Prabhu SD, Blankstein R, Deo RC, Solomon SD, Di Carli MF. Coronary Microvascular Dysfunction, Left Ventricular Remodeling, and Clinical Outcomes in Patients With Chronic Kidney Impairment. *Circulation* 2020; **141**: 21-33 [PMID: 31779467 DOI: 10.1161/CIRCULATIONAHA.119.043916]
 - 28 **Meneveau N**, Souteyrand G, Motreff P, Caussin C, Amabile N, Ohlmann P, Morel O, Lefrançois Y, Descotes-Genon V, Silvain J, Braik N, Chopard R, Chatot M, Ecarnot F, Tauzin H, Van Belle E, Belle L, Schiele F. Optical Coherence Tomography to Optimize Results of Percutaneous Coronary Intervention in Patients with Non-ST-Elevation Acute Coronary Syndrome: Results of the Multicenter, Randomized DOCTORS Study (Does Optical Coherence Tomography Optimize Results of Stenting). *Circulation* 2016; **134**: 906-917 [PMID: 27573032 DOI: 10.1161/CIRCULATIONAHA.116.024393]
 - 29 **Kubo T**, Shinke T, Okamura T, Hibi K, Nakazawa G, Morino Y, Shite J, Fusazaki T, Otake H, Kozuma K, Ioji T, Kaneda H, Serikawa T, Kataoka T, Okada H, Akasaka T; OPINION Investigators. Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION trial): one-year angiographic and clinical results. *Eur Heart J* 2017; **38**: 3139-3147 [PMID: 29121226 DOI: 10.1093/eurheartj/ehx351]
 - 30 **Kurogi K**, Ishii M, Sakamoto K, Komaki S, Kusaka H, Yamamoto N, Takashio S, Arima Y, Yamamoto E, Kaikita K, Tsujita K. Optical Coherence Tomography-Guided Percutaneous Coronary Intervention With Low-Molecular-Weight Dextran-Effect on Renal Function. *Circ J* 2020; **84**: 917-925 [PMID: 32350234 DOI: 10.1253/circj.CJ-20-0093]
 - 31 **Nearman HS**, Herman ML. Toxic effects of colloids in the intensive care unit. *Crit Care Clin* 1991; **7**: 713-723 [PMID: 1713807 DOI: 10.1016/S0749-0704(18)30302-6]

Siblings with coronavirus disease 2019 infection and opposite outcome—the hemodialysis's better outcome paradox: Two case reports

Dimitra Bacharaki, Evangelia Chrysanthopoulou, Sotiria Grigoropoulou, Panagiotis Giannakopoulos, Panagiotis Simitsis, Frantzeska Frantzeskaki, Aikaterini Flevari, Minas Karagiannis, Aggeliki Sardeli, Dimitra Kavatha, Anastasia Antoniadou, Demetrios Vlahakos

ORCID number: Dimitra Bacharaki 0000-0002-1722-2131; Evangelia Chrysanthopoulou 0000-0002-1257-818X; Sotiria Grigoropoulou 0000-0001-5400-5673; Panagiotis Giannakopoulos 0000-0001-8204-0820; Panagiotis Simitsis 0000-0001-8215-7893; Frantzeska Frantzeskaki 0000-0002-3897-6282; Aikaterini Flevari 0000-0003-1552-4504; Minas Karagiannis 0000-0003-4081-2591; Aggeliki Sardeli 0000-0002-0597-6841; Dimitra Kavatha 0000-0002-1805-8695; Anastasia Antoniadou 0000-0003-0991-9198; Demetrios Vlahakos 0000-0002-8463-9607.

Author contributions: Bacharaki D treated the HD patient as Consultant Nephrologist, reviewed the literature, and drafted the manuscript; Chrysanthopoulou E, Simitsis P, Frantzeskaki F and Flevari A contributed to acquisition, selection, interpretation, revision and recording of the data and contributed to the treatment of the critically ill patient in the ICU; Grigoropoulou S, Giannakopoulos P, Karagiannis M and Sardeli A contributed to the treatment of the patients in the clinic and during hemodialysis and contributed to the preparation of the table and figure of the manuscript; Kavatha

Dimitra Bacharaki, Panagiotis Giannakopoulos, Minas Karagiannis, Aggeliki Sardeli, Demetrios Vlahakos, Department of Nephrology, B Propaedeutiki Internal Medicine Clinic, Attikon University Hospital, Chaidari 12064, Greece

Evangelia Chrysanthopoulou, Panagiotis Simitsis, Frantzeska Frantzeskaki, Aikaterini Flevari, Intensive Care Unit, Attikon University Hospital, Chaidari 12064, Greece

Sotiria Grigoropoulou, Dimitra Kavatha, Anastasia Antoniadou, D Internal Medicine Clinic, Attikon University Hospital, Chaidari 12064, Greece

Corresponding author: Dimitra Bacharaki, MD, PhD, Doctor, Department of Nephrology, B Propaedeutiki Internal Medicine Clinic, Attikon University Hospital, Rimini 1, Chaidari 12064, Greece. bacharaki@gmail.com

Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) is a highly contagious infection caused by the severe acute respiratory syndrome coronavirus 2 virus and has a unique underlying pathogenesis. Hemodialysis (HD) patients experience high risk of contamination with COVID-19 and are considered to have higher mortality rates than the general population by most but not all clinical series. We aim to highlight the peculiarities in the immune state of HD patients, who seem to have both immune-activation and immune-depression affecting their outcome in COVID-19 infection.

CASE SUMMARY

We report the opposite clinical outcomes (nearly asymptomatic course *vs* death) of two diabetic elderly patients infected simultaneously by COVID-19, one being on chronic HD and the other with normal renal function. They were both admitted in our hospital with COVID-19 symptoms and received the same treatment by protocol. The non-HD sibling deteriorated rapidly and was intubated and transferred to the Intensive Care Unit, where he died despite all supportive care. The HD sibling, although considered more “high-risk” for adverse outcome, followed a benign course and left the hospital alive and well.

D and Antoniadou A as Infectious Disease Specialists in the COVID-19 department and Vlahakos D as Head of the Nephrology department supervised the patients' care and the manuscript.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: No conflict of interest from none of the authors.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Specialty type: Urology and nephrology

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: October 1, 2020

Peer-review started: October 1, 2020

First decision: November 12, 2020

Revised: December 5, 2020

CONCLUSION

These cases may shed light on aspects of the immune responses to COVID-19 between HD and non-HD patients and stimulate further research in pathophysiology and treatment of this dreadful disease.

Key Words: Case report; Hemodialysis; Siblings; COVID-19; Host response; Immune-activation; Immune-depression

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: The pandemic of novel severe acute respiratory syndrome coronavirus 2 is life threatening only for a limited subgroup of patients who manifest severe respiratory failure (SRF). Hemodialysis (HD) patients are in a paradox state of immune-activation and immune-depression, and it is not yet clear if they are more or less vulnerable to SRF. We report the case of two siblings with coronavirus disease 2019 (COVID-19) infection at the same time and opposite outcome, death of the brother with normal renal function and rather indolent course of the brother on HD. This case challenges the relevance of HD as an independent risk factor for COVID-19 associated mortality.

Citation: Bacharaki D, Chrysanthopoulou E, Grigoropoulou S, Giannakopoulos P, Simitsis P, Frantzeskaki F, Flevari A, Karagiannis M, Sardeli A, Kavatha D, Antoniadou A, Vlahakos D. Siblings with coronavirus disease 2019 infection and opposite outcome—the hemodialysis's better outcome paradox: Two case reports. *World J Nephrol* 2021; 10(2): 21-28

URL: <https://www.wjgnet.com/2220-6124/full/v10/i2/21.htm>

DOI: <https://dx.doi.org/10.5527/wjn.v10.i2.21>

INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originating from China on December 2019 poses still a major health and financial problem worldwide^[1]. It is a respiratory virus, highly contagious mostly by large droplet transmission, and causes common cold or no symptoms in nearly 80%. However, in a subset of 20%, the infection causes sudden deterioration with severe pneumonia and respiratory failure necessitating intubation, a condition with high mortality rates^[2].

Stable hemodialysis (HD) patients present with the paradox of immune-activation and immune-depression^[3]. We report the case of two siblings infected at the same time, one of them on maintenance HD due to end stage renal disease (ESRD) (patient 1, HD) and the other with normal renal function (patient 2, non HD). Although ESRD is associated with increased overall mortality compared to age-matched controls^[4] and in particular with COVID-19^[5,6], the sibling on HD survived and the other died from multiorgan failure attributed to COVID-19 infection. This case report emphasizes the need for further studies to discover prognostic markers, which will allow us to plan more effective treatment algorithms.

CASE PRESENTATION

Chief complaints

We report the contrasting outcome of two Caucasian diabetic, elderly brothers simultaneously infected by COVID-19 and referred to our hospital early in the course of disease. The laboratory timeline from admission to outcome is shown in [Figure 1](#). [Table 1](#) depicts the main clinical and laboratory characteristics on day 1 and during admission.

Patient 1: The younger brother, a 65-year-old male, complained of malaise and developed mild fever (37.3 °C) on April 23, 2020.

Patient 2: The older brother, a 78-year-old male, developed non-productive cough,

Accepted: December 27, 2020

Article in press: December 27, 2020

Published online: March 25, 2021

P-Reviewer: Gubensek J

S-Editor: Gao CC

L-Editor: Filipodia

P-Editor: Wang LL



mild sore throat and fever up to 38 °C on April 20, 2020.

History of present illness

Patient 1: He had been hospitalized and treated in a private clinic with HD facilities for diabetic foot and had completed a 10-d course with antibiotics (ticarcillin/clavulanic acid) when he developed fever.

Patient 2: He had been visiting his brother regularly during his hospitalization for his leg infection.

Patients 1 and 2: SARS-CoV-2 was detected in a nasopharyngeal swab specimen by real-time reverse-transcriptase polymerase chain reaction on April 23, and the next day both siblings were admitted to our hospital.

History of past illness

Patient 1: ESRD due to diabetic nephropathy, maintained on regular HD for 6 years.

Patient 2: Obese patient with type 2 diabetes mellitus and normal kidney function.

Personal and family history

Patients 1 and 2 have no special personal and family history.

Physical examination

Patient 1: Clinical examination on admission revealed a malnourished man [body mass index (BMI) 28 kg/m²] looking older than the stated age, with bilateral 2+ leg edema, temperature of 37.3 °C, pulse rate of 70 beats per min, blood pressure of 90/60 mmHg, respiratory rate of 22 breaths per min and oxygen saturation 98% while breathing ambient air. Lung auscultation revealed bibasilar crackles.

Patient 2: Clinical examination on admission revealed an obese man (BMI 31 kg/m²), temperature of 38.3 °C, pulse rate of 85 beats per min, blood pressure of 128/80 mmHg, respiratory rate of 22 breaths per min and oxygen saturation 95% on room air.

Laboratory examinations

Laboratory assessment shown in [Table 1](#) and [Figure 1](#).

Patient 1: Normal white blood cell (WBC) count with lymphocytes > 1000/μL and mildly elevated C-reactive protein (CRP 45.3 mg/L) and ferritin (342 ng/mL).

Patient 2: Leukocytosis (WBC 12015/μL) with lymphopenia (675/μL) and high CRP (210 mg/L) and ferritin (542 ng/mL).

Imaging examinations

Chest computed tomography (CT) revealed bilateral pleural effusions and ground glass infiltration with central distribution, characteristic of COVID-19 pneumonia^[7].

For patient 1, pulmonary infiltration was < 10%, corresponding to a CT severity score of 10^[7]; while for patient 2, pulmonary infiltration was > 25%-49%, corresponding to a CT severity score of 19.

FINAL DIAGNOSIS

COVID-19 disease with respiratory involvement. Patient 1 was considered also hypervolemic on admission.

TREATMENT

Patients 1 and 2

They were both treated for COVID-19, according to the current protocol of the Infectious Disease department, with a loading dose of 200 mg of hydroxychloroquine at day 1, followed by 100 mg b.i.d. for 5 d, along with azithromycin 500 mg daily during the same period time. They both received prophylactic anticoagulation with tinzaparin 3500 IU subcutaneously once daily.

Table 1 Clinical and laboratory characteristics on day 1 and during admission

Clinical and laboratory characteristics	Patient 1, HD	Patient 2, non HD
Age	65	78
Sex	M	M
Race	Caucasian	Caucasian
BMI	28	31
Malnourished	Yes	No
Diabetes mellitus	Type 2	Type 2
Other	PAD	No
Days from illness onset to admission	3	3
Fever	Yes	Yes
Cough	No	Yes
Dyspnea	No	No
CT score	10	19
Respiratory failure	No	Yes
Gastrointestinal bleeding	Yes	Yes
WBC count (k/ μ L)	5900	13.500
Neutrophil count	4035	12.015
Lymphocyte count (k/ μ L)	1227	675
NLR	3.3	17.8
Ferritin (ng/mL)	341	542
CRP (mg/L)	45.3	210
Albumin (g/dL)	3.5	4.9
D- dimers (ng/mL)	3191	39364
eGFR (mL/min/1.73 m ²) (MDRD)	< 15	65
Frailty index	7	7
Charlson comorbidity index	7	4

BMI: Body mass index; CRP: C-reactive protein; CT: Computed tomography; eGFR: Estimated glomerular filtration rate; HD: Hemodialysis; M: Men; MDRD: Modification of diet in renal disease; NLR: Neutrophil-lymphocyte ratio; PAD: Peripheral artery disease; WBC: White blood cells.

Patient 1 continued his thrice weekly HD schedule and reached euvolemia within the next week by increasing dialysis ultrafiltration gradually. On HD day, tinzaparin was given only during HD session, at the dialysis circuit.

OUTCOME AND FOLLOW-UP

Patient 1 had a mild COVID-19 disease, while patient 2 deteriorated rapidly into the critical form with severe respiratory failure and eventually died.

Patient 1: On April 30, 2020, while on acetylsalicylic acid 100 mg and tinzaparin 3500 IU daily, he developed severe gastrointestinal bleeding, reaching a nadir value of hemoglobin of 8.1 g/dL from a baseline value of 10.1 g/dL on admission and received two units of red blood cells and one unit of fresh frozen plasma. Anticoagulation was stopped until hemoglobin stabilization. Colonoscopy was not diagnostic. His hospitalization was uneventful thereafter, without respiratory distress or need for supplementary oxygen. He was discharged after two negative SARS-CoV-2 polymerase chain reaction tests on May 14, 2020.

Patient 2: On the second hospitalization day he developed severe respiratory distress

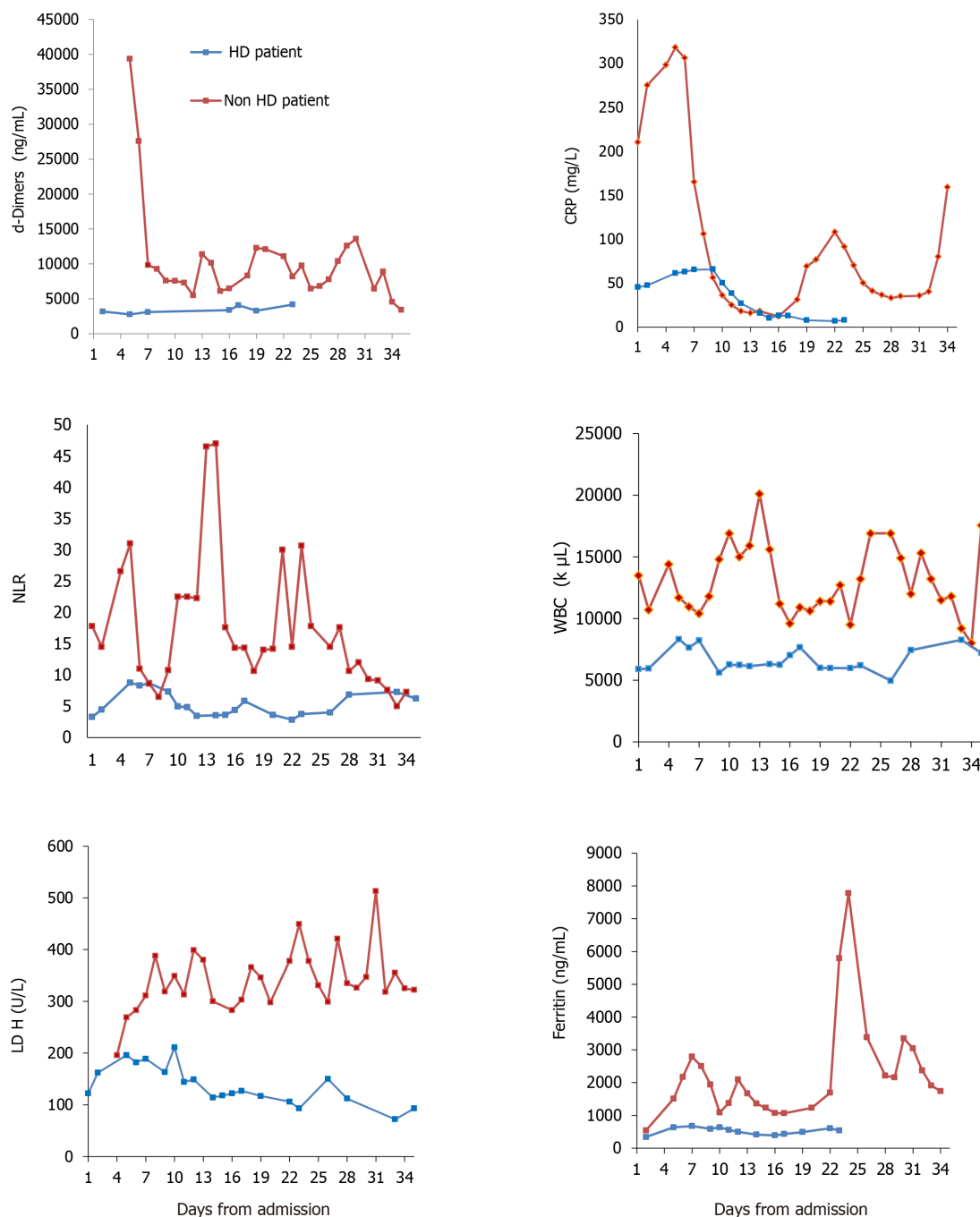


Figure 1 Laboratory parameters on day 1 and during admission for patient 1 on hemodialysis and patient 2 with normal renal function on admission (non-hemodialysis). CRP: C-reactive protein; LDH: Lactate dehydrogenase; NLR: Neutrophils to lymphocytes ratio; WBC: White blood count.

syndrome requiring intubation and admission to the intensive care unit (ICU). He was placed on intermittent prone position for the first 3 d in ICU with satisfactory response. On day 2 in ICU, his condition was complicated by fast atrial fibrillation, circulatory collapse and acute kidney injury (AKI). Tocilizumab, an interleukin-6 inhibitor, was given intravenously at 8 mg/kg (750 mg) in two infusions, 12 h apart, as per ICU protocol for severe COVID-19. After 2 d, treatment with continuous renal replacement treatment (hemodiafiltration) for AKI was initiated. On day 8 in ICU, he suffered from gastrointestinal bleeding requiring red blood cell transfusions. On May 12, 2020, he developed a gram-negative bacteremia with *Pseudomonas aeruginosa* and a pneumonia due to *Acinetobacter baumannii*. On May 15, he was also offered a 2 h duration hemoabsorption-session with hemoabsorber HA-330 (Jafron, adsorbent material styrene divinylbenzene copolymers, Jafron, Zhuhai, China) as per ICU protocol. HA-330 filters are used as “salvage therapy” in critically ill septic patients with multiorgan failure (renal failure included). Hemoabsorption was not continued

because of lack of improvement and on May 21, 2020 he died because of septic shock and multiorgan failure. SARS-CoV-2 was detected in repeated nasopharyngeal swab specimens throughout the ICU stay.

DISCUSSION

We present the case of two elderly diabetic brothers infected with COVID-19. The younger brother on HD for 6 years, complicated with peripheral artery disease, diabetic foot with gangrene and malnutrition survived and left the hospital alive and well. The older brother with arterial hypertension and normal renal function had a turbulent course, was intubated and eventually died in ICU from sepsis.

The clinical question on outcome of COVID-19 infection in patients on HD remains controversial. The European Renal Association COVID-19 Database collaboration, including 768 dialysis patients, concluded that the 28-d probability of death with COVID-19 in patients on dialysis is high (25% for all patients and 33.5% among those admitted in the hospital) and is associated predominantly with frailty and also with age. Surprisingly none of the known co-morbidities showed statistical significance by multivariate analysis, apart from obesity $> 35 \text{ kg/m}^2$ BMI and heart failure^[5]. The much larger OpenSafely platform concluded that dialysis or ESRD (kidney dialysis around 24,000 patients) was associated with an almost four-fold increased risk of COVID-19 related deaths. Age above 60 years, diabetes and obesity $> 35 \text{ kg/m}^2$ were also independent risk factors for mortality^[6]. Other studies from Spain^[8] and United States^[9] reported a high COVID-19 related mortality among dialysis patients. In contrast, Naaraayan *et al*^[10] found that patients with ESRD-HD have a milder course of COVID-19 illness. These discrepancies may be in part due to the unique pathogenesis of COVID-19 with two distinct immune responses from the host, as recently described^[11], or to differences in the genetic background.

To evaluate the severity of the clinical condition of the siblings at baseline, we measured the total comorbidity burden by the use of Charlson comorbidity index^[12]. The index score was 7 for patient 1 and 4 for patient 2, corresponding to an estimated 10-year survival rate of 0% and 53%, respectively. Of note, according to the Clinical Frailty Scale, both brothers had the same high frailty score of 7 on admission^[13].

From a laboratory point of view (radiology and blood panel), the HD patient had a better profile from the start, according to the data emerged from the general population^[14]. He appeared “less inflamed” on admission (Table 1 and Figure 1) with lower WBC, no lymphopenia, lower neutrophil to lymphocyte ratio^[15], less CRP and ferritin^[16] levels and lower pulmonary CT imaging score. Other positive prognostic markers for the HD patient in the first 5 d of admission were lower lactate dehydrogenase^[17] and d-dimers^[18] (Figure 1). Of note, both siblings had gastrointestinal bleeding, which has been reported as one of the manifestations of COVID-19 infection^[19].

Cardiac troponin was not predictive of outcome, although it has been described as predictive in a study^[14], notably with no dialysis patients included. Increased troponin levels in patients with kidney disease may be due to cardiac injury associated with chronic structural heart disease rather than acute ischemia, especially when the levels do not change rapidly over time^[20]. Interestingly troponin levels were high from the admission in the HD patient and decreased afterwards. On the contrary, they were low in the non-survivor and started to rise only after intubation and AKI.

The strength of this report is that it involves two brothers with presumably similar genetic background and similar co-morbidities, except for the renal function. To the best of our knowledge, this is the first report of COVID-19 disease in a family with member(s) maintained on chronic HD.

CONCLUSION

We report the opposite outcome of two diabetic elderly brothers infected simultaneously by COVID-19, in which, despite the odds, the one on HD survived and the other with normal renal function followed the typical severe form and died. The surprising different outcome of these two brothers questions the relevance of HD as an independent risk factor of COVID-19-related death and emphasizes the need for further research.

- 1 **Pak A**, Adegoye OA, Adekunle AI, Rahman KM, McBryde ES, Eisen DP. Economic Consequences of the COVID-19 Outbreak: the Need for Epidemic Preparedness. *Front Public Health* 2020; **8**: 241 [PMID: [32574307](#) DOI: [10.3389/fpubh.2020.00241](#)]
- 2 **Rothan HA**, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020; **109**: 102433 [PMID: [32113704](#) DOI: [10.1016/j.jaut.2020.102433](#)]
- 3 **Kato S**, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, Tranaeus A, Stenvinkel P, Lindholm B. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008; **3**: 1526-1533 [PMID: [18701615](#) DOI: [10.2215/CJN.00950208](#)]
- 4 **Prichard SS**. Comorbidities and their impact on outcome in patients with end-stage renal disease. *Kidney Int* 2000; **57**: 100-104 [DOI: [10.1046/j.1523-1755.2000.07417.x](#)]
- 5 **Hilbrands LB**, Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Jager KJ, Kieneker LM, Noordzij M, Pena MJ, Vries H, Arroyo D, Covic A, Crespo M, Goffin E, Islam M, Massy ZA, Montero N, Oliveira JP, Roca Muñoz A, Sanchez JE, Sridharan S, Winzeler R, Gansevoort RT; ERACODA Collaborators. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. *Nephrol Dial Transplant* 2020; **35**: 1973-1983 [PMID: [33151337](#) DOI: [10.1093/ndt/gfaa261](#)]
- 6 **Williamson EJ**, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HL, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultz A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; **584**: 430-436 [PMID: [32640463](#) DOI: [10.1038/s41586-020-2521-4](#)]
- 7 **Yang R**, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, Luo Y, Gao C, Zeng W. Chest CT Severity Score: An Imaging Tool for Assessing Severe COVID-19. *Radiol Cardiothorac Imag* 2020; **2**: e200047 [DOI: [10.1148/ryct.2020200047](#)]
- 8 **Goicoechea M**, Sánchez Cámara LA, Macías N, Muñoz de Morales A, Rojas ÁG, Bascuñana A, Arroyo D, Vega A, Abad S, Verde E, García Prieto AM, Verdalles Ú, Barbieri D, Delgado AF, Carbayo J, Mijaylova A, Acosta A, Melero R, Tejedor A, Benitez PR, Pérez de José A, Rodríguez Ferrero ML, Anaya F, Rengel M, Barraca D, Luño J, Aragoncillo I. COVID-19: clinical course and outcomes of 36 hemodialysis patients in Spain. *Kidney Int* 2020; **98**: 27-34 [PMID: [32437770](#) DOI: [10.1016/j.kint.2020.04.031](#)]
- 9 **Flythe JE**, Assimon MM, Tugman MJ, Chang EH, Gupta S, Shah J, Sosa MA, Renaghan AD, Melamed ML, Wilson FP, Neyra JA, Rashidi A, Boyle SM, Anand S, Christov M, Thomas LF, Edmonston D, Leaf DE; STOP-COVID Investigators. Characteristics and Outcomes of Individuals With Pre-existing Kidney Disease and COVID-19 Admitted to Intensive Care Units in the United States. *Am J Kidney Dis* 2020 [PMID: [32961244](#) DOI: [10.1053/j.ajkd.2020.09.003](#)]
- 10 **Naaraayan A**, Nimkar A, Hasan A, Pant S, Durdevic M, Elenius H, Nava Suarez C, Basak P, Lakshmi K, Mandel M, Jesmajian S. End-Stage Renal Disease Patients on Chronic Hemodialysis Fare Better With COVID-19: A Retrospective Cohort Study From the New York Metropolitan Region. *Cureus* 2020; **12**: e10373 [PMID: [33062496](#) DOI: [10.7759/cureus.10373](#)]
- 11 **Giamarellos-Bourboulis EJ**, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. *Cell Host Microbe* 2020; **27**: 992-1000. e3 [PMID: [32320677](#) DOI: [10.1016/j.chom.2020.04.009](#)]
- 12 **Charlson ME**, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; **40**: 373-383 [PMID: [3558716](#) DOI: [10.1016/0021-9681\(87\)90171-8](#)]
- 13 **Rockwood K**, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; **173**: 489-495 [PMID: [16129869](#) DOI: [10.1503/cmaj.050051](#)]
- 14 **Du RH**, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, Guo GY, Du J, Zheng CL, Zhu Q, Hu M, Li XY, Peng P, Shi HZ. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020; **55** [PMID: [32269088](#) DOI: [10.1183/13993001.0000000000000000](#)]

- 10.1183/13993003.00524-2020]
- 15 **Liu Y**, Du X, Chen J, Jin Y, Peng L, Wang HHX, Luo M, Chen L, Zhao Y. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *J Infect* 2020; **81**: e6-e12 [PMID: [32283162](#) DOI: [10.1016/j.jinf.2020.04.002](#)]
- 16 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: [32171076](#) DOI: [10.1016/S0140-6736\(20\)30566-3](#)]
- 17 **Henry BM**, Aggarwal G, Wong J, Benoit S, Vikse J, Plebani M, Lippi G. Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: A pooled analysis. *Am J Emerg Med* 2020; **38**: 1722-1726 [PMID: [32738466](#) DOI: [10.1016/j.ajem.2020.05.073](#)]
- 18 **Zhang L**, Yan X, Fan Q, Liu H, Liu X, Liu Z, Zhang Z. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. *J Thromb Haemost* 2020; **18**: 1324-1329 [PMID: [32306492](#) DOI: [10.1111/jth.14859](#)]
- 19 **Gulen M**, Satar S. Uncommon presentation of COVID-19: Gastrointestinal bleeding. *Clin Res Hepatol Gastroenterol* 2020; **44**: e72-e76 [PMID: [32505730](#) DOI: [10.1016/j.clinre.2020.05.001](#)]
- 20 **Ellis K**, Dreisbach AW, Lertora JL. Plasma elimination of cardiac troponin I in end-stage renal disease. *South Med J* 2001; **94**: 993-996 [PMID: [11702827](#) DOI: [10.1097/00007611-200194100-00011](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>



World Journal of *Nephrology*

World J Nephrol 2021 May 25; 10(3): 29-36



MINIREVIEWS

- 29 Nephrogenic systemic fibrosis: A frivolous entity

Bhargava V, Singh K, Meena P, Sanyal R

ABOUT COVER

Editorial Board Member of *World Journal of Nephrology*, Jacob A Akoh, MBBS, FMCS, FEBS, FACS, Consultant General/Transplant Surgeon & Honorary Associate Professor, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth PL6 8DH, United Kingdom. jacob.akoh@nhs.net

AIMS AND SCOPE

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

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc.*

INDEXING/ABSTRACTING

The WJN is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; **Production Department Director:** Xiang Li; **Editorial Office Director:** Yan-Xia Xing.

NAME OF JOURNAL

World Journal of Nephrology

ISSN

ISSN 2220-6124 (online)

LAUNCH DATE

February 6, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Li Zuo

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2220-6124/editorialboard.htm>

PUBLICATION DATE

May 25, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Nephrogenic systemic fibrosis: A frivolous entity

Vinant Bhargava, Kulwant Singh, Priti Meena, Rupan Sanyal

ORCID number: Vinant Bhargava 0000-0002-3360-4666; Kulwant Singh 0000-0001-6184-3368; Priti Meena 0000-0001-6073-8101; Rupan Sanyal 0000-0002-3360-4661.

Author contributions: Meena P performed the majority of the writing, prepared the figures and tables; Bhargava V performed data acquisition and writing; Singh K and Sanyal R provided input in writing the paper.

Conflict-of-interest statement: There is no conflict of interest to disclose.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Urology and nephrology

Vinant Bhargava, Priti Meena, Department of Nephrology, Institute of Renal Science, SIR Ganga Ram Hospital, New Delhi 110060, India

Kulwant Singh, Department of Nephrology, Ivy Hospital, Mohali Punjab 160071, India

Rupan Sanyal, Department of Radiology, University of Alabama School of Medicine, FL, 35294-3412, United States

Corresponding author: Priti Meena, DNB, MBBS, MD, Chief Doctor, Department of Nephrology, Institute of Renal Science, SIR Ganga Ram Hospital, Sarhadi Gandhi Marg, New Delhi 110060, India. pritimn@gmail.com

Abstract

Gadolinium-based contrast agents (GBCAs) used in magnetic resonance imaging are vital in providing enhanced quality images, essential for diagnosis and treatment. Nephrogenic systemic fibrosis (NSF) with GBCAs has been a deterrent for the physician and has led to avoidance of these agents in patients with impaired kidney function. NSF is a progressive debilitating multisystem condition described classically in patients with renal insufficiency exposed to gadolinium contrast media. It is characterized by an induration and hardening of the skin. NSF is described to first involve the extremities and can imperceptibly involve internal organs. Lack of therapeutic interventions to treat NSF makes it more challenging and warrants deep insight into the pathogenesis, risk factors and treatment strategies.

Key Words: Magnetic resonance imaging; Gadolinium-based contrast agents; Nephrogenic systemic fibrosis; Chronic kidney disease; Dialysis; End stage kidney disease

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Nephrogenic systemic fibrosis is a chronic debilitating fibrosing disorder resulting in progressive hardening or induration of the skin. It mostly develops in patients with impaired kidney function. This review aims to provide insight into the pathogenesis, risk factors, clinical features and challenges in the management of nephrogenic systemic fibrosis.

Citation: Bhargava V, Singh K, Meena P, Sanyal R. Nephrogenic systemic fibrosis: A frivolous entity. *World J Nephrol* 2021; 10(3): 29-36

Country/Territory of origin: India**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

Received: January 9, 2021**Peer-review started:** January 9, 2021**First decision:** March 1, 2021**Revised:** March 21, 2021**Accepted:** May 7, 2021**Article in press:** May 7, 2021**Published online:** May 25, 2021**P-Reviewer:** Yorioka N**S-Editor:** Liu M**L-Editor:** Webster JR**P-Editor:** Xing YX**URL:** <https://www.wjgnet.com/2220-6124/full/v10/i3/29.htm>**DOI:** <https://dx.doi.org/10.5527/wjn.v10.i3.29>

INTRODUCTION

Nephrogenic systemic fibrosis (NSF) was first described in 1997 by Cowper *et al*[1] in a renal transplant recipient with poor graft function. He described this as a scleromyxedema-like condition. However, no data on NSF were published until 2000[1]. This later emerged as one of the greatest concerns for nephrologists. NSF was originally named nephrogenic fibrosing dermatopathy due to the characteristic skin findings[2]. However, subsequent studies showed that some patients also had systemic involvement. Symptoms typically include thickening of the skin with pruritus. Symptoms and signs may progress rapidly, with some patients developing contractures and joint immobility. This may be fatal in a few patients. In this review, we attempt to explain the pathogenesis, risk factors, clinical features and therapeutic interventions in NSF.

CLINICAL FEATURES

Cutaneous and subcutaneous involvement

The skin lesions are predominantly erythematous papules or nodules which coalesce to form indurated plaques. The lesions are commonly distributed symmetrically and initially involve the lower extremities. They then spread proximally to involve the upper extremities. Furthermore, the trunk is usually involved, and the head is mostly spared except for a scleral plaque. During evolution, lesions are slightly edematous and erythematous associated with itching and a burning sensation. With time they become hard and “woody” sometimes assuming a “cobblestone” appearance. The timing of the appearance of skin lesions following gadolinium-based contrast agents (GBCAs) exposure is controversial. It may vary from a few months to several years (1 d to 10 years)[3]. The course of skin lesions is usually unremitting and chronic. However, a rapid progressive fulminant course has also been reported in approximately 5% of patients[4].

SYSTEMIC INVOLVEMENT

Several case studies have reported the involvement of subcutaneous structures such as fascia, joints, muscle and periarticular tissue and tendons[5]. Involvement of joints can be severe and compromise range of motion with loss of ambulation and confinement to a wheelchair. Deep fibrosis results in flexion contractures of joints mainly in the hands, wrists, knees and ankles. Data from Mendoza *et al*[6] showed fibrosis of deep visceral organs such as diaphragm muscles, the myocardium including small coronary arterioles, lungs, kidneys and testes. Another analysis by Schieren *et al*[7] revealed esophageal dysmotility with consecutive liver fibrosis and esophageal varices. Visceral involvement in the form of cardiomyopathy and pulmonary fibrosis was also reported by Swartz *et al*[8]. Yellow scleral plaques are also a frequent finding in patients of NSF, and are seen clinically in young patients. These scleral plaques differ from the typical Cogan plaques of aging (present in older age) that are due to calcium phosphate deposition, and acellular collagen in the sclera with no inflammatory response[9].

DIFFERENTIAL DIAGNOSIS

Various disorders may mimic the skin lesions of NSF. In patients with similar skin lesions, conditions such as lipodermatosclerosis, deep morphea, scleromyxedema, eosinophilic fasciitis, and chronic-graft-versus-host disease should also be considered.

HISTOPATHOLOGICAL FINDINGS

NSF is characterized by dermal fibrosis. In the early phase, collagen bundles are found dispersed within edema and mucin. The circulating fibrocytes are interspersed between the strands of collagen. The CD34 positive dendritic processes encircling collagen bundles are present. These circulating fibrocytes are dual positive (CD34 and procollagen I) suggesting characteristics of mesenchymal stem cells of bone marrow origin. In advanced lesions there is proliferation of spindle shaped dermal fibrocytes leading to thick and fibrosed dermis. NSF skin lesion histology is typically characterized by markedly increased cellularity, persistence of thick bundled collagen, preserved clefts and CD34 positive fibrocytes in the absence of inflammation[10]. Moreover, Mendoza *et al*[6] found an early dermal infiltration with CD 68+/factor XIIIa+ dendritic cells by immunohistochemistry and *in situ* hybridization studies. Immunohistochemistry has revealed substantial upregulated expression of transforming growth factor β 1 (TGF β 1) mRNA in the dermis, and affected tissue of NSF with TGF β 1 upregulation could be a pathogenetic event in this entity.

GBCAS

Gadolinium (Gd) is a metal of the lanthanide series recognized for its high paramagnetic properties. Ionized Gd is toxic and requires chelation with a ligand for clinical use. GBCAs are categorized based on their biochemical structure (linear *vs* macrocyclic) and chelate charge (nonionic *vs* ionic). Macrocyclic chelates (for example gadobutrol, gadoterate meglumine, and gadoteridol) bind Gd more tightly than linear chelates (gadodiamide) and are more stable both *in vitro* and *in vivo*. They have a lower dissociation rate; thus, there is a reduced association with NSF[11]. The recommended dose is 0.1 mmol/kg[12]. They have minimal protein binding capacity, and a short half-life of 1.5 h in patients with normal kidney function. Elimination of GBCAs is impaired and retention takes place in those with renal insufficiency[13]. Based on the reported incidence of NSF, the American College of Radiology (ACR) Committee on Drugs and Contrast Media has classified Gd-based contrast agents into various groups[14] (Table 1).

RISK FACTORS

Chronic kidney disease

Although the true cause of NSF is still unknown; almost all patients who develop NSF have an underlying kidney dysfunction. Approximately 90% of the patients described in the registry have end-stage kidney disease and they are either on hemodialysis or peritoneal dialysis[15]. The remaining patients have some degree of chronic kidney dysfunction or acute kidney injury (AKI). From the previously published literature, it can be estimated that one or more exposures to group 1 GBCA may pose a risk in developing NSF in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m²[16].

Endothelial dysfunction is common in chronic kidney disease (CKD) patients, which interferes with platelets to interact and attach to damaged endothelium and thus can be a critical risk factor. Moreover, vascular surgery related procedures, central catheter placement, right atrial clots from indwelling hemodialysis catheters, deep venous thrombosis or thrombosed vascular access are frequently observed before the occurrence of NSF[17]. Thus, it can be speculated that this endothelial dysfunction primes for a secondary event or a trigger such as Gd that eventually initiates the process of fibrosis.

AKI

AKI or acute dysfunction of the kidney can also be a risk factor for NSF. NSF has been noted in 10%-20% of patients with AKI, often superimposed upon baseline CKD. NSF has also developed in patients with AKI without underlying CKD[18].

Frequency and dose of exposure

There are case reports of NSF after a single exposure and single dose of GBCAs. Higher cumulative doses of Gd, either administered in a single dose or multiple administrations can augment the chances of developing NSF[19].

Table 1 American College of Radiology manual classification of gadolinium-based agents relative to nephrogenic systemic fibrosis**Group I: Agents associated with the greatest number of NSF cases:**

Gadodiamide (Omniscan® – GE Healthcare)

Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)

Gadoversetamide (OptiMARK® – Guerbet)

Group II: Agents associated with few, if any, cases of NSF:

Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)

Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals; Gadovist in many countries)

Gadoteric acid (Dotarem® – Guerbet, Clariscan – GE Healthcare)

Gadoteridol (ProHance® – Bracco Diagnostics)

Group III: Agents for which data remains limited regarding NSF risk, but for which few, if any cases of NSF have been reported:

Gadoxetate disodium (Eovist – Bayer HealthCare Pharmaceuticals; Primovist in many countries)

NSF: Nephrogenic systemic fibrosis.

Other possible risk factors

As only some patients with kidney dysfunction develop NSF following the use of Gd and other patients do not, cofactors may have a contributory role. These include metabolic acidosis; raised serum levels of iron, calcium, and phosphate; the use of high-dose erythropoietin stimulating agents, pre-existing vasculopathy, and other acute proinflammatory states[20-22]. However, the probable role of these cofactors has not yet been well-established. Therefore, routine screening prior to Gd administration is not advised.

Possible risk factors for NSF are shown in [Table 2](#).

POSTULATED MECHANISM

The exact mechanism of NSF is unknown. It is hypothesized that usually a trigger is needed to initiate the fibrosing process and Gd may act as a potential trigger for NSF development in patients with kidney disease. The most widely held hypothesis is that kidney dysfunction impairs the renal excretion of Gd which prolongs its half-life and increases the chance of Gd dissociation from the chelate. Kidneys are responsible for the elimination of almost all (97%) Gd contrast from the body. Reduced kidney function results in a substantial increase in its half-life from 1.5 h (normal kidney function) to 5.61 h and 9.18 h at CKD stage 4 and 5, respectively[23]. Free Gd can bind with anions such as phosphate or iron, and form insoluble precipitates that are deposited in various tissues[24]. Vascular injury and endothelial dysfunction enhance free Gd invasion into tissues, where Gd is phagocytosed by macrophages to release local profibrotic cytokines and sends signals to attract circulating fibrocytes into the tissues. These circulating fibrocytes are cardinal cells that play the interlinking role between Gd deposition and the initiation of fibrosis. In tissues, circulating fibrocytes commence the fibrosing process that is similar to the normal healing process followed by scar formation. This hypothesis is held up by the presence of excess Gd in the affected tissues of NSF patients when compared to unaffected tissues[25] ([Figure 1](#)). A few studies have shown Gd in tissues using scanning electron microscopy and energy dispersive X-ray spectroscopy[26]. However, these techniques are complicated and are not considered a pre-requisite for the diagnosis of NSF.

CURRENT STATUS OF NSF IN THE ERA OF NEW GBCAS

Since their introduction in magnetic resonance imaging (MRI), there have been many advances in GBCAs during the last 30 years. The risk of developing NSF with newer GBCAs, even in patients with impaired kidney function or on dialysis, is exceedingly small. This risk is further reduced by prescribing low standard recommended dosages and avoiding repeated use.

Table 2 Patients at high risk of nephrogenic systemic fibrosis
Risk factors for NSF

Patients on dialysis (hemodialysis or peritoneal dialysis)

Advanced or end-stage CKD (CKD 4 or 5, eGFR < 30 mL/min/1.73 m²) without dialysis

Acute kidney injury

Proinflammatory state in a patient with impaired kidney function

Higher doses and multiple administrations of GBCAs, within a short period of time

NSF: Nephrogenic systemic fibrosis; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate.

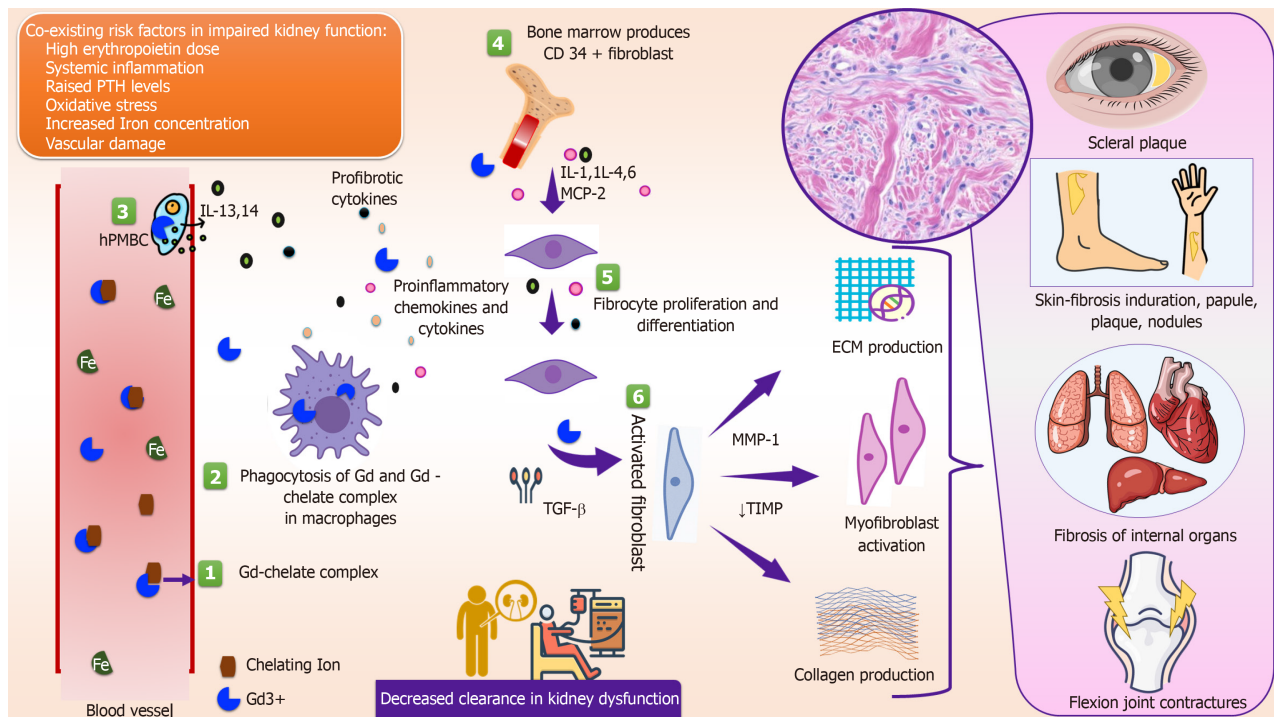


Figure 1 Postulated pathophysiology of nephrogenic systemic fibrosis. PTH: Parathyroid Hormone; ECM: Extracellular matrix; hPMBC: Human peripheral mononuclear blood cells; MCP-2: Monocyte chemoattractant protein-2; MMP: Metalloproteinases; TIMP: Tissue inhibitor of metalloproteinase.

In a large retrospective analysis by Chrysochou *et al*[27] from the United Kingdom, in 74 patients with stage 5 CKD without dialysis undergoing GBCA-enhanced MRI (with gadobenate dimeglumine), no NSF events were reported. Similarly, following the administration of gadobenate dimeglumine, Altun *et al*[28] reported no NSF events in over 25000 patients, including at-risk patients (CKD stage 4 and 5) and 549 patients on dialysis. All patients were given gadobenate dimeglumine at the standard dose (0.1 mmol/kg). Various studies including, the Pro-FINEST prospective multicenter trial (255 patients), the RESCUE trial a prospective European multicenter study (70 patients), and the SECURE study (476 patients) have assessed the safety of gadoterate meglumine in patients with acute and CKD or on dialysis. No NSF was reported in any of these studies[29-31]. The ACR guidelines also cite that the risk of NSF is sufficiently low or possibly non-existent with group II agents[32]. Due to limited dose exposure, underpowering, and the retrospective nature of some studies, clinicians should be aware and not misinterpret these guidelines as newer agents having unconditional safety.

PREVENTIVE STRATEGIES

It is important to identify patients at risk of developing NSF when group I GBCAs are

used. They should be screened for conditions and other factors that may be associated with renal function impairment. eGFR should be calculated for every patient using readily available Modification of Diet in Renal Disease or the Chronic Kidney Disease Epidemiology Collaboration calculators. However, in dialysis patients or known AKI cases, calculation of eGFR is not useful and is unnecessary as these patients are at high risk for NSF and group I GBCAs should be avoided. Some questionnaires that include risk factors for compromised kidney function can also be produced which can include questions on the history of kidney disease including dialysis and kidney transplantation. Although there are many other factors which may contribute to renal impairment such as multiple myeloma, systemic lupus erythematosus, urinary tract infection, medicines such as nonsteroidal anti-inflammatory drugs and aminoglycosides, the ACR Committee on Drugs and Contrast Media does not routinely recommend screening for these possible risk factors as the advantages of screening for these risk factors are considered low. The risk of NSF among patients exposed to standard doses of group II GBCAs is sufficiently low and assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration. The lowest recommended dose of GBCAs should be used in at-risk patients to attain the required clinical information. If multiple doses/sessions of Gd are required in these patients then group II agents should be preferred. Limited data exist on the beneficial effects of postprocedural hemodialysis.

MANAGEMENT

Multiple interventions, alone or in combination have been tried but none of them have been beneficial. There is no proven efficacious therapy for the management of NSF. Due to the rare nature of this condition, most of the studies involve a small number of cases and lack long-term follow-up. Although some patients have shown improvement in skin condition followed by recovery of renal function, further studies are needed. Available treatment options are corticosteroids, PUVA, immunomodulators, pentoxifylline, and extracorporeal photopheresis (ECP).

ECP is an immunomodulatory procedure in which a patient's leukocyte rich plasma is treated *ex vivo* with a photosensitizing agent and UV-A radiation followed by reinfusion of the treated blood product. Several case series have suggested the role of ECP in patients with NSF[33,34]. However, frequency and duration of ECP, other additional therapy, severity of the disease, and interpatient biological variability are some of the important factors speculated in determining the response to ECP. Common practice for using ECP is to begin with one cycle per week for 4 wk (*i.e.*, 8 ECP sessions over 4 wk), then taper down to once every 2 wk (4-5 cycles) and then monthly. The total number of sessions is determined by response and clinical recovery in the patient[35].

Kay *et al*[36] reported 2 patients with NSF who responded to imatinib mesylate therapy. Improvements in skin thickening and knee joint contractures were observed. The patients received 400 mg/day imatinib mesylate orally. Imatinib mesylate acts by blocking signal transduction *via* both the TGF β R and the PDGF-BB receptor.

Pentoxifylline improves red blood cell flexibility to improve circulation and is known for its antifibrotic activity. As thrombosis is speculated to be an inciting event in NSF, this mechanism could explain the improvements noted clinically with pentoxifylline[19].

Sodium thiosulfate is a crystalline substance that has antioxidant and chelating properties. The TGF- β /Smad signaling cascade is one of the pathways involved in the pathogenesis of both NSF and calciphylaxis. It is already used in calciphylaxis. There is a possibility that sodium thiosulfate acts through the same mechanism of action as calciphylaxis in NSF. However, more studies are required to establish this relationship. The most common side effects are nausea and vomiting and the dosage administered is 12.5 g to 25 g post-dialysis. Yerram *et al*[37] reported rapid improvement in NSF following intravenous sodium thiosulfate.

CONCLUSION

NSF is a progressive, severely disabling fibrotic condition, which develops in patients with impaired kidney function exposed to GBCAs. However, the occurrence of NSF with newer contrast agents has been questioned in recent times. Determination of the putative underlying mechanisms, etiological or triggering factors necessitates further

research and long-term data. Genetic predisposition may be a new revelation in future studies. Therapeutic approaches in the present literature are limited and have reduced benefit.

REFERENCES

- 1 **Cowper SE**, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. *Lancet* 2000; **356**: 1000-1001 [PMID: [11041404](#) DOI: [10.1016/S0140-6736\(00\)02694-5](#)]
- 2 **Cowper SE**, Bucala R, Leboit PE. Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis--setting the record straight. *Semin Arthritis Rheum* 2006; **35**: 208-210 [PMID: [16461067](#) DOI: [10.1016/j.semarthrit.2005.09.005](#)]
- 3 **Waikhom R**, Taraphder A. Nephrogenic systemic fibrosis: a brief review. *Indian J Dermatol* 2011; **56**: 54-58 [PMID: [21572794](#) DOI: [10.4103/0019-5154.77554](#)]
- 4 **Attari H**, Cao Y, Elmholt TR, Zhao Y, Prince MR. A Systematic Review of 639 Patients with Biopsy-confirmed Nephrogenic Systemic Fibrosis. *Radiology* 2019; **292**: 376-386 [PMID: [31264946](#) DOI: [10.1148/radiol.2019182916](#)]
- 5 **Cowper SE**. Nephrogenic fibrosing dermopathy: the first 6 years. *Curr Opin Rheumatol* 2003; **15**: 785-790 [PMID: [14569211](#) DOI: [10.1097/00002281-200311000-00017](#)]
- 6 **Mendoza FA**, Artlett CM, Sandorfi N, Latinis K, Piera-Velazquez S, Jimenez SA. Description of 12 cases of nephrogenic fibrosing dermopathy and review of the literature. *Semin Arthritis Rheum* 2006; **35**: 238-249 [PMID: [16461069](#) DOI: [10.1016/j.semarthrit.2005.08.002](#)]
- 7 **Schieren G**, Wirtz N, Altmeyer P, Rump LC, Weiner SM, Kreuter A. Nephrogenic systemic fibrosis--a rapidly progressive disabling disease with limited therapeutic options. *J Am Acad Dermatol* 2009; **61**: 868-874 [PMID: [19836645](#) DOI: [10.1016/j.jaad.2009.03.040](#)]
- 8 **Swartz RD**, Crofford LJ, Phan SH, Ike RW, Su LD. Nephrogenic fibrosing dermopathy: a novel cutaneous fibrosing disorder in patients with renal failure. *Am J Med* 2003; **114**: 563-572 [PMID: [12753880](#) DOI: [10.1016/s0002-9343\(03\)00085-8](#)]
- 9 **Barker-Griffith A**, Goldberg J, Abraham JL. Ocular pathologic features and gadolinium deposition in nephrogenic systemic fibrosis. *Arch Ophthalmol* 2011; **129**: 661-663 [PMID: [21555622](#) DOI: [10.1001/archophthalmol.2011.89](#)]
- 10 **Cowper SE**, Rabach M, Girardi M. Clinical and histological findings in nephrogenic systemic fibrosis. *Eur J Radiol* 2008; **66**: 191-199 [PMID: [18325705](#) DOI: [10.1016/j.ejrad.2008.01.016](#)]
- 11 **Aime S**, Caravan P. Biodistribution of gadolinium-based contrast agents, including gadolinium deposition. *J Magn Reson Imaging* 2009; **30**: 1259-1267 [PMID: [19938038](#) DOI: [10.1002/jmri.21969](#)]
- 12 **Perazella MA**. Current status of gadolinium toxicity in patients with kidney disease. *Clin J Am Soc Nephrol* 2009; **4**: 461-469 [PMID: [19201920](#) DOI: [10.2215/CJN.06011108](#)]
- 13 **FDA Drug Safety Communication**. FDA Drug Safety Communication: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings; 2018 [cited 4 October 2020]. In: FDA homepage [Internet] Available from: <https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm>
- 14 **American College of Radiology**. ACR Manual on Contrast Media, Version 10.3, ACR Committee on Drugs and Contrast Media. Reston, VA, American College of Radiology. 2017: 22-28 Available from: <https://xray.ufl.edu/files/2008/06/ACR-Manual-on-Contrast-Media-Version-10.3-2017.pdf>
- 15 **Shabana WM**, Cohan RH, Ellis JH, Hussain HK, Francis IR, Su LD, Mukherji SK, Swartz RD. Nephrogenic systemic fibrosis: a report of 29 cases. *AJR Am J Roentgenol* 2008; **190**: 736-741 [PMID: [18287446](#) DOI: [10.2214/AJR.07.3115](#)]
- 16 **Collidge TA**, Thomson PC, Mark PB, Traynor JP, Jardine AG, Morris ST, Simpson K, Roditi GH. Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: retrospective study of a renal replacement therapy cohort. *Radiology* 2007; **245**: 168-175 [PMID: [17704357](#) DOI: [10.1148/radiol.2451070353](#)]
- 17 **Prince MR**, Zhang H, Morris M, MacGregor JL, Grossman ME, Silberzweig J, DeLapaz RL, Lee HJ, Magro CM, Valeri AM. Incidence of nephrogenic systemic fibrosis at two large medical centers. *Radiology* 2008; **248**: 807-816 [PMID: [18710976](#) DOI: [10.1148/radiol.2483071863](#)]
- 18 **Kalb RE**, Helm TN, Sperry H, Thakral C, Abraham JL, Kanal E. Gadolinium-induced nephrogenic systemic fibrosis in a patient with an acute and transient kidney injury. *Br J Dermatol* 2008; **158**: 607-610 [PMID: [18076707](#) DOI: [10.1111/j.1365-2133.2007.08369.x](#)]
- 19 **Grobner T**. Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006; **21**: 1104-1108 [PMID: [16431890](#) DOI: [10.1093/ndt/gfk062](#)]
- 20 **Wahba IM**, Simpson EL, White K. Gadolinium is not the only trigger for nephrogenic systemic fibrosis: insights from two cases and review of the recent literature. *Am J Transplant* 2007; **7**: 2425-2432 [PMID: [17711550](#) DOI: [10.1111/j.1600-6143.2007.01941.x](#)]
- 21 **Peak AS**, Sheller A. Risk factors for developing gadolinium-induced nephrogenic systemic fibrosis. *Ann Pharmacother* 2007; **41**: 1481-1485 [PMID: [17684032](#) DOI: [10.1345/aph.1K295](#)]
- 22 **Abu-Alfa AK**. Nephrogenic systemic fibrosis and gadolinium-based contrast agents. *Adv Chronic*

- Kidney Dis* 2011; **18**: 188-198 [PMID: [21531325](#) DOI: [10.1053/j.ackd.2011.03.001](#)]
- 23 **Marckmann P**, Skov L, Rossen K, Dupont A, Damholt MB, Heaf JG, Thomsen HS. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol* 2006; **17**: 2359-2362 [PMID: [16885403](#) DOI: [10.1681/ASN.2006060601](#)]
- 24 **Morcos SK**, Haylor J. Pathophysiology of nephrogenic systemic fibrosis: A review of experimental data. *World J Radiol* 2010; **2**: 427-433 [PMID: [21179310](#) DOI: [10.4329/wjr.v2.i11.427](#)]
- 25 **Chopra T**, Kandukurti K, Shah S, Ahmed R, Panesar M. Understanding nephrogenic systemic fibrosis. *Int J Nephrol* 2012; **2012**: 912189 [PMID: [23193473](#) DOI: [10.1155/2012/912189](#)]
- 26 **High WA**, Ayers RA, Chandler J, Zito G, Cowper SE. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol* 2007; **56**: 21-26 [PMID: [17097388](#) DOI: [10.1016/j.jaad.2006.10.047](#)]
- 27 **Chrysochou C**, Power A, Shurrah AE, Husain S, Moser S, Lay J, Salama AD, Kalra PA. Low risk for nephrogenic systemic fibrosis in nondialysis patients who have chronic kidney disease and are investigated with gadolinium-enhanced magnetic resonance imaging. *Clin J Am Soc Nephrol* 2010; **5**: 484-489 [PMID: [20093350](#) DOI: [10.2215/CJN.06580909](#)]
- 28 **Altun E**, Semelka RC, Cakit C. Nephrogenic systemic fibrosis and management of high-risk patients. *Acad Radiol* 2009; **16**: 897-905 [PMID: [19375360](#) DOI: [10.1016/j.acra.2009.01.001](#)]
- 29 **Amet S**, Launay-Vacher V, Clément O, Frances C, Tricotel A, Stengel B, Gauvrit JY, Grenier N, Reinhardt G, Janus N, Choukroun G, Laville M, Deray G. Incidence of nephrogenic systemic fibrosis in patients undergoing dialysis after contrast-enhanced magnetic resonance imaging with gadolinium-based contrast agents: the Prospective Fibrose Néphrogénique Systémique study. *Invest Radiol* 2014; **49**: 109-115 [PMID: [24169070](#) DOI: [10.1097/RLI.0000000000000000](#)]
- 30 **Deray G**, Rouviere O, Bacigalupo L, Maes B, Hannedouche T, Vrtovnik F, Rigotherier C, Billioux JM, Campioni P, Ferreiros J, Devos D, Alison D, Glowacki F, Boffa JJ, Marti-Bonmati L. Safety of meglumine gadoterate (Gd-DOTA)-enhanced MRI compared to unenhanced MRI in patients with chronic kidney disease (RESCUE study). *Eur Radiol* 2013; **23**: 1250-1259 [PMID: [23212275](#) DOI: [10.1007/s00330-012-2705-x](#)]
- 31 **Soyer P**, Dohan A, Patkar D, Gottschalk A. Observational study on the safety profile of gadoterate meglumine in 35,499 patients: The SECURE study. *J Magn Reson Imaging* 2017; **45**: 988-997 [PMID: [27726239](#) DOI: [10.1002/jmri.25486](#)]
- 32 **Isaka Y**, Hayashi H, Aonuma K, Horio M, Terada Y, Doi K, Fujigaki Y, Yasuda H, Sato T, Fujikura T, Kuwatsuru R, Toei H, Murakami R, Saito Y, Hirayama A, Murohara T, Sato A, Ishii H, Takayama T, Watanabe M, Awai K, Oda S, Murakami T, Yagyu Y, Joki N, Komatsu Y, Miyauchi T, Ito Y, Miyazawa R, Kanno Y, Ogawa T, Koshi E, Kosugi T, Yasuda Y; Japanese Society of Nephrology, Japan Radiological Society; and Japanese Circulation Society Joint Working Group. Guideline on the use of iodinated contrast media in patients with kidney disease 2018. *Clin Exp Nephrol* 2020; **24**: 1-44 [PMID: [31709463](#) DOI: [10.1007/s10157-019-01750-5](#)]
- 33 **Richmond H**, Zwerner J, Kim Y, Fiorentino D. Nephrogenic systemic fibrosis: relationship to gadolinium and response to photopheresis. *Arch Dermatol* 2007; **143**: 1025-1030 [PMID: [17709661](#) DOI: [10.1001/archderm.143.8.1025](#)]
- 34 **Kafi R**, Fisher GJ, Quan T, Shao Y, Wang R, Voorhees JJ, Kang S. UV-A1 phototherapy improves nephrogenic fibrosing dermopathy. *Arch Dermatol* 2004; **140**: 1322-1324 [PMID: [15545539](#) DOI: [10.1001/archderm.140.11.1322](#)]
- 35 **Zhang R**, Rose WN. Photopheresis Provides Significant Long-Lasting Benefit in Nephrogenic Systemic Fibrosis. *Case Rep Dermatol Med* 2017; **2017**: 3240287 [PMID: [28695022](#) DOI: [10.1155/2017/3240287](#)]
- 36 **Kay J**, High WA. Imatinib mesylate treatment of nephrogenic systemic fibrosis. *Arthritis Rheum* 2008; **58**: 2543-2548 [PMID: [18668587](#) DOI: [10.1002/art.23696](#)]
- 37 **Yerram P**, Saab G, Karuparthi PR, Hayden MR, Khanna R. Nephrogenic systemic fibrosis: a mysterious disease in patients with renal failure--role of gadolinium-based contrast media in causation and the beneficial effect of intravenous sodium thiosulfate. *Clin J Am Soc Nephrol* 2007; **2**: 258-263 [PMID: [17699422](#) DOI: [10.2215/CJN.03250906](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>



World Journal of *Nephrology*

World J Nephrol 2021 July 25; 10(4): 37-75



MINIREVIEWS

- 37 Lower urinary tract dysfunction in pediatrics progress to kidney disease in adolescents: Toward precision medicine in treatment

Wishahi M

ORIGINAL ARTICLE**Retrospective Cohort Study**

- 47 Should pediatric idiopathic hypercalciuria be treated with hypocalciuric agents?

Penido MGMT, Tavares MS

SYSTEMATIC REVIEWS

- 59 Prediction of mortality among patients with chronic kidney disease: A systematic review

Hansrivijit P, Chen YJ, Lnu K, Trongtorsak A, Puthenpura MM, Thongprayoon C, Bathini T, Mao MA, Cheungpasitporn W

ABOUT COVER

Editorial Board Member of *World Journal of Nephrology*, Wisit Cheungpasitporn, FACP, FASN, FAST. Associate Professor, Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, United States. wcheungpasitporn@gmail.com

AIMS AND SCOPE

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

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc.*

INDEXING/ABSTRACTING

The WJN is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yan-Jie Ma*; Production Department Director: *Xiang Li*; Editorial Office Director: *Yan-Xia Xing*.

NAME OF JOURNAL

World Journal of Nephrology

ISSN

ISSN 2220-6124 (online)

LAUNCH DATE

February 6, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Li Zuo

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2220-6124/editorialboard.htm>

PUBLICATION DATE

July 25, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Lower urinary tract dysfunction in pediatrics progress to kidney disease in adolescents: Toward precision medicine in treatment

Mohamed Wishahi

ORCID number: Mohamed Wishahi
0000-0002-4559-619X.

Author contributions: Wishahi M designed the research study, performed the research, analyzed the data, wrote the manuscript and read and approved the final manuscript.

Conflict-of-interest statement:
There is no conflict of interest associated with the author of this manuscript.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Urology and nephrology

Country/Territory of origin: Egypt

Mohamed Wishahi, Department of Urology, Theodor Bilharz Research Institute, Cairo 12411, Egypt

Corresponding author: Mohamed Wishahi, MD, PhD, Professor, Department of Urology, Theodor Bilharz Research Institute, Embaba-Giza, Cairo 12411, Egypt.
moh.weshahy@gmail.com

Abstract

Newborn infants who had neurogenic bladder dysfunction (NBD) have a normal upper urinary tract at birth. Most of them will develop deterioration of renal function and chronic kidney disease if they do not receive proper management. Children with NBD can develop renal damage at adolescence or earlier, which is due to high detrusor pressures resulted from poor compliance of the bladder, detrusor overactivity against a closed sphincter or detrusor sphincter dyssynergia. To preserve renal function and prevent deterioration of the kidneys, NBD must be treated immediately after being diagnosed. Over the last few years there was great progress in the treatment of children with the NBD. We searched PubMed and the Cochrane Library for peer-reviewed articles published in any language up to March 10, 2021, using the search term "neurogenic bladder children." Our search excluded diagnosis, pathophysiology, surgical treatment of spinal cord injury and spina bifida. The research identified the effectiveness of treatment regimens targeting prevention of chronic kidney disease and the indications of kidney transplantation. The results of the research showed that NBD in children should be diagnosed early in life, and the child should receive the proper management. The literature search concluded that the management of NBD in children would be personalized for every case and could be changed according to response to treatment, side effects, child compliance, availability of treatment modality and costs of treatment. The objectives of the study are to present the different options of management of NBD in children and the selection of the proper method in a personalized manner.

Key Words: Neurogenic bladder dysfunction; Antimuscarinics; Onabotulinum toxin A; Neural stimulations; Renal transplantations

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Peer-review report's scientific quality classification

Grade A (Excellent): 0
 Grade B (Very good): 0
 Grade C (Good): C, C
 Grade D (Fair): 0
 Grade E (Poor): 0

Received: April 25, 2021

Peer-review started: April 25, 2021

First decision: June 6, 2021

Revised: June 16, 2021

Accepted: July 22, 2021

Article in press: July 22, 2021

Published online: July 25, 2021

P-Reviewer: Cabezuolo AS, Sakly A

S-Editor: Fan JR

L-Editor: Filipodia

P-Editor: Ma YJ



Core Tip: Neurogenic bladder dysfunction in children can lead to renal dysfunction and chronic kidney failure. This review reports treatment options including the latest modalities. The new anti-muscarinic drugs have minimal adverse effect, high tolerability, availability of solution form and dose adjustment. Children who develop adverse events from anti-muscarinics or non-compliant to clean intermittent catheterization would be candidate for detrusor muscle injection with onabotulinum toxin A, which proved to be safe with no adverse effects. Kidney transplantation would be the last resort for treatment after progressive deterioration of kidney function.

Citation: Wishahi M. Lower urinary tract dysfunction in pediatrics progress to kidney disease in adolescents: Toward precision medicine in treatment. *World J Nephrol* 2021; 10(4): 37-46

URL: <https://www.wjgnet.com/2220-6124/full/v10/i4/37.htm>

DOI: <https://dx.doi.org/10.5527/wjn.v10.i4.37>

INTRODUCTION

Newborn infants who had neurogenic bladder dysfunction (NBD) have a normal upper urinary tract. Most of them will develop deterioration of renal function if they do not receive proper management[1,2]. Renal damage is due to high detrusor pressures resulting from poor compliance of the bladder, detrusor overactivity against a closed sphincter or detrusor sphincter dyssynergia[3,4]. To preserve renal function and prevent deterioration of the kidneys, NBD must be treated immediately after being diagnosed. Over the last few years great progress in the treatment of children with the NBD has occurred.

NBD is classified to subcategories according to urodynamic findings: (1) sphincter overactivity combined with detrusor inactivity that results in incomplete bladder emptying; (2) sphincter overactivity during detrusor contraction that leads to affection and deterioration of upper tract; (3) incompetent sphincter associated with detrusor inactivity leading to large bladder capacity, urine leakage and incomplete emptying; and (4) detrusor hyper-reflexia and loss of bladder compliance[5-7].

Neglecting the case of NBD or improper management can end with deleterious effects on the upper tract that end with renal dysfunction and chronic kidney failure. Since the introduction of clean intermittent catheterization (CIC) for the treatment of NBD, a variety of medications and interventions were introduced. Children differ from adults in accepting certain treatment modalities, loss of compliance, and sensitivity to adverse effects. The variety of options made it possible to shift from one method to another seeking child acceptance, while aiming to avoid upper tract deterioration resulting from high pressure in the bladder. The objectives are to present different treatment options that have Food and Drug Administration and European Union approval for treatment of NBD in children. Each treatment modality has its advantage and limitations, and consequently the management can be personalized for every child.

SEARCH METHOD

We searched PubMed and the Cochrane Library for peer-reviewed articles published in any language up to March 10, 2021 using the search term “neurogenic bladder children.” It revealed 3143 articles, and 65 articles were fulfilling the criteria of the search. Articles that were excluded from the study were those dealing with diagnosis, urodynamic, pathophysiology, surgical treatment of spina bifida and spinal cord injury. The data collected ranged from standard methods of treatment of NBC to the newly introduced pharmacological product, minimally invasive interventions and the place of kidney transplantation in cases of renal failure. The different modalities were classified to (1) standard initial management; (2) pharmacological treatment; (3) botulism toxins; (4) neural stimulation; (5) vesicostomy; and (6) kidney transplantation. Every item presented for its mode of action, adverse effects, efficacy, availability and factors influencing the choice of management. The data are presented in the narrative review.

MANAGEMENT OF NBD IN CHILDREN

Different modalities are available for the personalized treatment of NBD in children to prevent renal deterioration. Every modality has a mode of action, adverse events, advantages and limitations. Different modalities are presented in [Table 1](#).

Standard initial management: CIC

CIC in combination with anticholinergics (oxybutynin) had been considered the standard therapy for children with NBD with detrusor hyperactivity[8,9]. This treatment is feasible and effective in developing countries, where untreated neuropathic bladder is an important cause of preventable chronic renal failure[10,11].

CIC enables complete bladder emptying and thus avoids bladder residual urine with its consequences of repeated urinary tract infection. Complete bladder emptying with CIC prevent the occurrence of high-pressure voiding that led to detriment for kidney function. CIC requires proper education and training and good patient compliance on a long-term basis. Patients and caregivers must learn how to catheterize properly. CIC by parents for newborns and infants would become a part of their everyday routine. CIC can be successfully taught to boys and girls around the age of 6 years. The required frequency of catheterization depends on several factors differs from one child to another. Most children are not able to perform CIC, where this task is taken by the mother who may not completely be dedicated to do this job, particularly working women.

Pharmacological treatments

Anti-muscarinics: (1) Oral oxybutynin suppresses detrusor hyper-reflexia and eliminates uninhibited detrusor contractions leading to urinary leakage. It prevents high-pressure bladder storage and high-pressure emptying. The frequent side effects (SEs) of oxybutynin is dry mouth, which leads most patients and particularly children to discontinue the treatment. There is cumulative evidence that prolonged use of bladder anti-muscarinic drugs would increase the risk to develop of dementia[12]; (2) Intravesical oxybutynin. Anti-muscarinic is considered the gold standard treatment for patients having overactive bladder (OAB). It is effective in most cases. Patients who developed SEs or reported no improvement discontinue the treatment[13,14]. Patients who experience intolerable SEs would benefit from intravesical oxybutynin chloride, which is an effective therapy for NBD[13,15,16]. The effect of intravesical oxybutynin is often transient. Supplementation of oxybutynin with hydroxypropyl cellulose (HPC), which adheres to the mucosal layer, reduces the absorption of oxybutynin from bladder mucosa and diminishes the systemic SEs. It is termed modified intravesical oxybutynin therapy, which proved to be safe and showed excellent efficacy[17,18]. It had been shown that children with NBD who had been treated with intravesical oxybutynin hydrochloride combined with HPC had superior efficacy over oxybutynin alone or oral anticholinergic drugs or children who showed intolerance to oral medications for NBD. Following catheterizing of the bladder and emptying it, the modified oxybutynin chloride solution was instilled into the bladder at a dosage of 5 mL each time and remained until the next catheterization. This procedure would be repeated twice daily. Intravesical oxybutynin chloride is an effective method with fewer SEs than oral medication. The modified oxybutynin chloride solution is injected into the bladder at a dose of 5 mL twice daily; follow-up at 6 mo showed favorable effects with no side effect[19,20]. Intravesical oxybutynin hydrochloride in a daily dose of 2.5 mg combined with HPC was safe with effective outcome in long-term treatment for children with NBD. The modified intravesical oxybutynin treatment for children with NBD offers a new option for improving continence and bladder compliance[21]; and (3) New anti-muscarinic drugs. These newly introduced anti-muscarinic drugs antagonize the muscarinic receptors in detrusor muscle and consequently decrease intravesical pressure and the uninhibited bladder overactivity. The pediatric population with OAB NBD had limited treatment options. Formerly the only widely available anti-muscarinic was oxybutynin, which had many SEs that are not tolerated by the children. The main SEs are dry mouth, headache, blurred vision, flushing and cognitive impairment. The newly developed anti-muscarinic drugs overcame most adverse effects of oxybutynin[22-24].

Solifenacin: Controlled studies suggest that solifenacin may be useful for pediatric NBD. It is available in the form of oral suspension that is given to children as once daily with possibility of dose adjustment[25-28]. Once-daily oral suspension of solifenacin is available that allows greater dosing flexibility in all patients[25-28]. Once daily oral suspension demonstrated superiority over placebo for the change from

Table 1 Management of neurogenic bladder dysfunction to prevent upper tract deterioration

Management of neurogenic bladder dysfunction in children		
Ref.	Mode of action and advantages	Limitations
CIC[8-11]	Enable complete bladder emptying and prevent high bladder pressure and urinary tract infection	Required proper education and compliance, pediatrics and some children are not able to perform CIC
Oral oxybutynin[12]	Antimuscarinic, suppress detrusor hyper-reflexia, prevent high pressure	Dry mouth, abdominal pain that leads to discontinuation of treatment. Limited availability of liquid oxybutynin for children. Risk to develop dementia
Intravesical oxybutynin[13-21]	Intravesical oxybutynin chloride combined with hydroxypropyl cellulose leads to mucosal adhesion and minimal side effects	Administered with urethral catheter twice daily
Solifenacin succinate [22-31]	Works against muscarine receptors in detrusor muscles, relaxes it and decreases intravesical pressure. It is a competitive muscarinic receptor antagonist. Available as one daily oral suspension and is used in pediatric population	Minimal adverse effects
Tolterodine[32]	Antimuscarinic and calcium channel modulating properties. Available for children as a solution or as tablet. Oral solution is available for children from 5-16 yr	Low incidence of adverse effects (1.5%)
Propiverine hydrochlorid[33,34]	Antimuscarinic and calcium channel modulating properties. Low incidence of adverse events. Superior tolerability over oxybutynin	Minimal adverse effects
Trospium chloride [35,36]	Antimuscarinic and calcium channel modulating properties. Dosage 10-45 mg administered three times per day. Is tolerated by children	Minimal adverse effects
Mirabegron	β_3 -adrenoceptor agonist, demonstrated to be effective in adults with overactive bladder	Still not approved for children
Onabotulinum toxin A (Botox—BTX-A) [45-48]	Is injected in the detrusor muscle, leading to fits relaxation. The dose should not exceed 6 U/kg, ranging from 50, 100 and 200 U. 200 U are a well-tolerated and effective treatment for children aged 5-17 yr with NBD. Patients may be considered for reinjection when the clinical effect of the previous injection diminishes (median 6-12 mo in most children)	Repeated injections are safe and effective in children
Neural stimulations [49-54]	Sensory fibers in the pudendal nerve (afferents) innervates the urethra sensation of urine flow. This will lead to reflex generation of positive feedback to enhance bladder contraction in amplitude and duration and inhibit contraction of the external urethral sphincter. Electrical activation of pudendal nerve afferents provides a new approach to restore efficient bladder emptying. Long-term outcome in children showed good results maintained for 2 yr	Maintenance treatment was necessary in 29% of children. Cost-effective as a primary treatment
Vesicostomy[55-62]	Patients with impaired renal function before kidney transplantation would improve or stabilize kidney function after vesicostomy. The long-term outcomes of vesicostomy in NBD patients are effective in reversing the deleterious consequences when conservative treatment fails	Vesicostomy is an incontinent abdominal stoma. The child will have a social embarrassment
Renal transplantations[63-65]	Children with renal insufficiency due to NBD can receive a renal allograft and achieve good long-term results. Correction of structural urogenital abnormalities and optimization of emptying and storage functions of the bladder has to be achieved before renal transplantation	There is no one technique for the urinary drainage of the lower urinary tract, it should be individualized for each case

CIC: Clean intermittent catheterization; NBD: Neurogenic bladder dysfunction.

baseline to normality. It was well tolerated in children aged 5-12 years, adolescents aged 12-18 years and in pediatric populations[29-31].

Tolterodine is available as an oral solution. A dose of 0.2–2.0 mg twice daily was described for pediatric age group 4 mo to 4 years. For older children, 5–10 years, the dose is solution of 0.5–4.0 mg twice daily. At adolescence, the dosage is oral capsules or tablets 4–6 mg once daily[32].

Propiverine hydrochloride: It has a low incidence rate of SEs (less than 1.5%). Recommended dose is 0.7–0.8 mg/kg body weight/day. It was shown that it has superior tolerability over oxybutynin[33,34].

Trospium: Dosage of 10 mg and up to 25 mg for children with bladder overactivity showed good response and was well tolerated with minimal adverse effects[35]. A dose of 15–45 mg administered three times per day showed a significant increase in bladder capacity that was tested with a urodynamic study[36].

Anticholinergic agents: Mirabegron, a β_3 -adrenoceptor agonist, was approved by the Food and Drug Administration for adults and children. It is safe and effective in children.

Onabotulinum toxin A (Botox—BTX-A)

Intradetrusor injection has been proven to be an effective and safe long-term therapy for the management neurogenic detrusor overactivity (NDO), which is defined as detrusor hyper-reflexia leading to involuntary detrusor contractions during the bladder filling leading to incontinence, reflux and consequently deterioration of renal bladder function. The case is due to the interruption of the signaling pathways that control bladder function.

Neurological causes of NDO include spinal cord injury, multiple sclerosis, myelomeningocele, spina bifida occulta, split cord malformation, lipomyelomeningocele and tethered spinal cord[37,38]. Children with NBD whose urodynamic investigation shows detrusor pressure of 40 cm H₂O or higher, are at risk of upper tract deterioration and renal failure. The target of treatment of NDO in children is to keep low detrusor pressure and adequate storage[39]. Early treatment with CIC for children with NDO is recommended by European Association of Urology and European Society for Pediatric Urology[40].

CIC combined with oral anticholinergic is recommended by the International Children's Continence Society[41]. Children who do not respond to these regimens of treatment are more than 15%, in addition to the reported SEs[42-44].

Onabotulinum toxin A 200 U is effective and tolerated treatment option for adults with NDO who were not well controlled with anticholinergic therapy[45]. Onabotulinum toxin A showed positive efficacy and safety in children at doses up to 360 U. It was shown that 32%–100% of children achieved continence, detrusor pressure was reduced by 32% to 54%, and the maximum pressure was below the 40 cm H₂O threshold[46].

The dose should not exceed 6 U/kg, ranging from 50, 100 and 200 U treatment for children aged 5–17 years who were inadequately managed with other therapies. Onabotulinum toxin A 200 U is well-tolerated and effective. The 200 U dose demonstrated objective and clinically subjective significant greater improvement; urodynamic assessment showed increases in functional bladder capacity. Repeat treatment with onabotulinum toxin A showed continued safety and efficacy[47].

Patients may be considered to receive second injection in case the clinical effect of the previous one gets diminished, which was observed after 6-12 mo in most patients. Repeat injections of botulinum toxin A have been shown to be safe, and do not lead to increased risk of fibrosis in the bladder wall. It is safe and effective in children with NBD with a positive effect on their dryness, quality of life and protection of the upper tract[48].

Neural stimulations

NBD leads to urinary retention due to bladder hypocontractility and/or increases in the outlet resistance. Chronic urinary retention led to reflux, upper urinary tract deterioration, urinary tract infection and incontinence. Children who are not compliant to CIC or refractory to pharmacologic approaches would benefit from percutaneous tibial nerve stimulation (PTNS).

The scientific background is that pudendal afferent sensory fibers innervate the urethra sensation of passage of urine. This will lead to reflex generation of positive feedback to stimulating the bladder to contract in amplitude and duration. Another sequence is to relax the external urethral sphincter. Electrical stimulation of pudendal nerve afferents significantly improves voiding efficiency. Pudendal sensory has an important feedback role in an efficient bladder emptying. Activation of afferents of the pudendal restore efficient bladder emptying[49].

Sacral nerve stimulation is becoming the latest advancement in treatment of NBD after technical development and showed successful results in clinical studies[50-52]. Long-term outcome in children treated with PTNS for dysfunctional voiding and OAB showed good results and remained stable after 2 years[53].

Neural stimulation improved both storage and voiding and functions of the bladder in about 60% of the patients. Neural stimulation has its limitation for cost-effective compared to anti-muscarinics. Neural stimulation is the ideal option in refractory OAB or when the child does not tolerate anti-muscarinics[54].

Vesicostomy

The aim of urological treatment and follow-up in children with NBD is to avoid upper tract deterioration[55]. Early diagnosis and establishment of proper treatment would minimize the consequences of dysfunction of bladder. Lower urinary tract dysfunction in childhood will affect bladder function at puberty in both storage and emptying functions that will precipitate renal failure[56].

Vesicostomy could be the best treatment for the hostile bladder in myelodysplastic [57]. Vesicostomy is a temporary procedure to maintain low detrusor pressure and to stabilize renal function in children not responding to anticholinergics and CIC. It can be reversed at any age. Vesicostomy provided overall resolution, improvement or stabilization of the preoperative parameters. Hydronephrosis would achieve complete resolution or stabilization of the renal function. Patients with impaired renal function before surgery would improve or stabilize kidney function after vesicostomy.

Vesicostomy would be closed at any age. Children who will be candidates for kidney transplantation would have an additional procedure during closure that could be anti-reflux procedure for the refluxing ureters or augmentation cystoplasty. At the time of closure, a bladder capacity of > 300 mL would not need augmentation cystoplasty.

Vesicostomy could be considered an emergency option when the child presents with renal failure, and the aim is to stabilize renal function and reverse the deleterious consequences of NBD, aiming at preparing the patient for definitive treatment[58-62].

Renal transplantations

Children who developed renal failure secondary to lower urinary tract dysfunction are treated with regular ambulatory hemodialysis that will be followed with renal transplantation. Optimization of bladder function before transplantation will ensure the safety and survival of the allograft. The technique and therapeutic option are personalized and differ from one case to another[63-65]. The decision for kidney transplantation would be considered early in life when measures to control NBD are not satisfactory and the kidney shows progressive deterioration.

RESULTS

Innovations in the treatment of NBD in children solved the dilemma of the ideal treatment. There are many options that would be used in treatment of NBD and guard against upper tract deterioration. Newly introduced drug delivery systems using intravesical oxybutynin chloride solution supplemented with HPC, which is a mucosal adhesive substance, reduced systemic SEs and proved to be safe and showed excellent efficacy[17,18].

Drug delivery systems using fluid suspension of the newly introduced anti-muscarinics made it possible to treat pediatric population without the need for clean intermittent catheterization. These drugs included: solifenacin[30,31], tolterodine[32], propiverine[33,34] and trospium[35]. Studies demonstrated the superior tolerability of these drugs over oxybutynin, with higher efficacy and minimal SEs.

Onabotulinum toxin A (Botox – BTX-A) intradetrusor injection has been proven to be an effective and safe long-term therapy for the management of NDO and NBD. It prevents incontinence and reflux and consequently deterioration of renal function. It can be repeated without causing fibrosis of the detrusor muscle.

Neural stimulation with PTNS or sacral nerve stimulation for children who are not compliant to CIC or refractory to pharmacologic approaches would benefit from the progressive improvements in these modalities. PTNS can modulate the voiding and storage function of the bladder leading to an overall subjective improvement of symptoms in about 60% of the patients and 47%-56% improvement of filling and voiding function parameters[53,54]. Children with renal insufficiency due to NBD can receive a renal allograft and achieve good long-term results. Correction of structural urogenital abnormalities and optimization of emptying and storage functions of the bladder has to be achieved before renal transplantation[63-65]. Urinary diversion or vesicostomy are resorted to before transplantation to stabilize and improve kidney function. Availability of different effective and safe treatment modalities made it unacceptable for a child with NBD to develop renal impairment. The variety of options facilitates safe and effective control of the deleterious effect of NBD on the upper tract.

CONCLUSION

NBD in children can end with deleterious effects on the upper tract that end with renal dysfunction and chronic kidney failure. This would indicate dialysis or kidney transplantation. Choice of proper management will differ from one child to another, where the management would be personalized. CIC combined with oral oxybutynin is

the basic and standard treatment. Children who receive oxybutynin and develop adverse effects that lead to discontinuation of treatment would shift intravesical oxybutynin. The new anti-muscarinic drugs have minimal adverse effects, high tolerability, availability of solution form and dose adjustment. Mirabegron is a β_3 -adrenoceptor agonist that is a promising drug for children with NBD. Children who develop adverse events from anti-muscarinics, β_3 -adrenergic agonist drugs or are non-compliant to CIC would be candidates for detrusor muscle injection with onabotulinum toxin A, which proved to be safe with no adverse effects.

PTNS is an emerging modality for treatment of NBD in children. It has no adverse effects, which is accepted by the child and parents. Kidney transplantation would be the last resort for treatment of NBD in children when they have progressive deterioration of kidney function and the child did not respond to other treatments. The type of management for NBD in children would be personalized for every case and could be changed accordingly.

REFERENCES

- 1 **Kari JA.** Neuropathic bladder as a cause of chronic renal failure in children in developing countries. *Pediatr Nephrol* 2006; **21**: 517-520 [PMID: [16511684](#) DOI: [10.1007/s00467-006-0034-5](#)]
- 2 **Filler G,** Gharib M, Casier S, Lödige P, Ehrich JH, Dave S. Prevention of chronic kidney disease in spina bifida. *Int Urol Nephrol* 2012; **44**: 817-827 [PMID: [21229390](#) DOI: [10.1007/s11255-010-9894-5](#)]
- 3 **Amarante MA,** Shrensel JA, Tomei KL, Carmel PW, Gandhi CD. Management of urological dysfunction in pediatric patients with spinal dysraphism: review of the literature. *Neurosurg Focus* 2012; **33**: E4 [PMID: [23025445](#) DOI: [10.3171/2012.7.FOCUS12232](#)]
- 4 **Bauer SB.** Neurogenic bladder: etiology and assessment. *Pediatr Nephrol* 2008; **23**: 541-551 [PMID: [18270749](#) DOI: [10.1007/s00467-008-0764-7](#)]
- 5 **Kumar A,** Goel A, Paul S. Re: urodynamic testing-is it a useful tool in the management of children with cutaneous stigmata of occult spinal dysraphism? *J Urol* 2013; **190**: 812-813 [PMID: [23485506](#) DOI: [10.1016/j.juro.2013.02.076](#)]
- 6 **Drzewiecki BA,** Bauer SB. Urodynamic testing in children: indications, technique, interpretation and significance. *J Urol* 2011; **186**: 1190-1197 [PMID: [21849190](#) DOI: [10.1016/j.juro.2011.02.2692](#)]
- 7 **Bauer SB,** Hallett M, Khoshbin S, Lebowitz RL, Winston KR, Gibson S, Colodny AH, Retik AB. Predictive value of urodynamic evaluation in newborns with myelodysplasia. *JAMA* 1984; **252**: 650-652 [PMID: [6737668](#)]
- 8 **Baskin LS,** Kogan BA, Benard F. Treatment of infants with neurogenic bladder dysfunction using anticholinergic drugs and intermittent catheterisation. *Br J Urol* 1990; **66**: 532-534 [PMID: [2249125](#) DOI: [10.1111/j.1464-410x.1990.tb15004.x](#)]
- 9 **Fernandes ET,** Reinberg Y, Vernier R, Gonzalez R. Neurogenic bladder dysfunction in children: review of pathophysiology and current management. *J Pediatr* 1994; **124**: 1-7 [PMID: [8283355](#) DOI: [10.1016/s0022-3476\(94\)70245-4](#)]
- 10 **Stein R,** Bogaert G, Dogan HS, Hoen L, Kocvara R, Nijman RJM, Quadackers JSLT, Rawashdeh YF, Silay MS, Tekgul S, Radmayr C. EAU/ESPU guidelines on the management of neurogenic bladder in children and adolescent part I diagnostics and conservative treatment. *Neurourol Urodyn* 2020; **39**: 45-57 [PMID: [31724222](#) DOI: [10.1002/nau.24211](#)]
- 11 **Penna FJ,** Elder JS. CKD and bladder problems in children. *Adv Chronic Kidney Dis* 2011; **18**: 362-369 [PMID: [21896378](#) DOI: [10.1053/j.ackd.2011.08.001](#)]
- 12 **Coupland CAC,** Hill T, Denning T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study. *JAMA Intern Med* 2019; **179**: 1084-1093 [PMID: [31233095](#) DOI: [10.1001/jamainternmed.2019.0677](#)]
- 13 **Schröder A,** Albrecht U, Schnitker J, Reitz A, Stein R. Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: A randomized, prospective, controlled multi-center trial. *Neurourol Urodyn* 2016; **35**: 582-588 [PMID: [25754454](#) DOI: [10.1002/nau.22755](#)]
- 14 **Lehtoranta K,** Tainio H, Lukkari-Lax E, Hakonen T, Tammela TL. Pharmacokinetics, efficacy, and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. *Scand J Urol Nephrol* 2002; **36**: 18-24 [PMID: [12002352](#) DOI: [10.1080/003655902317259319](#)]
- 15 **Guerra LA,** Moher D, Sampson M, Barrowman N, Pike J, Leonard M. Intravesical oxybutynin for children with poorly compliant neurogenic bladder: a systematic review. *J Urol* 2008; **180**: 1091-1097 [PMID: [18639290](#) DOI: [10.1016/j.juro.2008.05.056](#)]
- 16 **Lazarus J.** Intravesical oxybutynin in the pediatric neurogenic bladder. *Nat Rev Urol* 2009; **6**: 671-674 [PMID: [19901914](#) DOI: [10.1038/nrurol.2009.214](#)]
- 17 **Saito M,** Watanabe T, Tabuchi F, Otsubo K, Satoh K, Miyagawa I. Urodynamic effects and safety of modified intravesical oxybutynin chloride in patients with neurogenic detrusor overactivity: 3 years experience. *Int J Urol* 2004; **11**: 592-596 [PMID: [15285747](#) DOI: [10.1111/j.1442-2042.2004.00871.x](#)]

- 18 **Hayashi A**, Saito M, Okada S, Hanada T, Watanabe T, Satoh K, Kanzaki S. Treatment with modified intravesical oxybutynin chloride for neurogenic bladder in children. *J Pediatr Urol* 2007; **3**: 438-442 [PMID: 18947791 DOI: 10.1016/j.jpuro.2007.05.007]
- 19 **Inoue S**, Saito M, Honda M, Dimitriadis F, Takenaka A. Intravesical Oxybutynin for Neurogenic Bladder in Children. *Pediat Therapeut* 2012; **2**: 138 [DOI: 10.4172/2161-0665.1000138]
- 20 **Mizunaga M**, Miyata M, Kaneko S, Yachiku S, Chiba K. Intravesical instillation of oxybutynin hydrochloride therapy for patients with a neuropathic bladder. *Paraplegia* 1994; **32**: 25-29 [PMID: 8015832 DOI: 10.1038/sc.1994.5]
- 21 **Honda M**, Kimura Y, Tsounapi P, Hikita K, Saito M, Takenaka A. Long-Term Efficacy, Safety, and Tolerability of Modified Intravesical Oxybutynin Chloride for Neurogenic Bladder in Children. *J Clin Med Res* 2019; **11**: 256-260 [PMID: 30937115 DOI: 10.14740/jocmr3752]
- 22 **Alloussi S**, Mürtz G, Braun R, Gerhardt U, Heinrich M, Hellmis E, Horn W, Marschall-Kehrel D, Niklas K, Raabe M, Rössler T, Seibt B, Siemer S, Schultz-Lampel D, Walter H, Wiedeking B, Alloussi S, Bock P, Strugala G, Madersbacher H. Efficacy, tolerability and safety of propiverine hydrochloride in comparison to oxybutynin in children with urge incontinence due to overactive bladder: Results of a multicentre observational cohort study. *BJU Int* 2010; **106**: 550-556 [PMID: 20002668 DOI: 10.1111/j.1464-410X.2009.09129.x]
- 23 **Ferrara P**, D'Aleo CM, Tarquini E, Salvatore S, Salvaggio E. Side-effects of oral or intravesical oxybutynin chloride in children with spina bifida. *BJU Int* 2001; **87**: 674-678 [PMID: 11350411 DOI: 10.1046/j.1464-410x.2001.02152.x]
- 24 **Katz IR**, Sands LP, Bilker W, DiFilippo S, Boyce A, D'Angelo K. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc* 1998; **46**: 8-13 [PMID: 9434659 DOI: 10.1111/j.1532-5415.1998.tb01006.x]
- 25 **Kay G**, Crook T, Rekeda L, Lima R, Ebinger U, Arguinzoniz M, Steel M. Differential effects of the antimuscarinic agents darifenacin and oxybutynin ER on memory in older subjects. *Eur Urol* 2006; **50**: 317-326 [PMID: 16687205 DOI: 10.1016/j.eururo.2006.03.057]
- 26 **Bolduc S**, Moore K, Nadeau G, Lebel S, Lamontagne P, Hamel M. Prospective open label study of solifenacin for overactive bladder in children. *J Urol* 2010; **184**: 1668-1673 [PMID: 20728124 DOI: 10.1016/j.juro.2010.03.124]
- 27 **Hoebeke P**, De Pooter J, De Caestecker K, Raes A, Dehoorne J, Van Laecke E, Vande Walle J. Solifenacin for therapy resistant overactive bladder. *J Urol* 2009; **182**: 2040-2044 [PMID: 19695608 DOI: 10.1016/j.juro.2009.05.100]
- 28 **Nadeau G**, Schröder A, Moore K, Genois L, Lamontagne P, Hamel M, Pellerin E, Bolduc S. Long-term use of solifenacin in pediatric patients with overactive bladder: Extension of a prospective open-label study. *Can Urol Assoc J* 2014; **8**: 118-123 [PMID: 24839481 DOI: 10.5489/cuaj.1356]
- 29 **Park SJ**, Pai KS, Kim JM, Park K, Kim KS, Song SH, Park S, Kim SO, Ryu DS, Baek M, Lee SD, Lee JW, Im YJ, Han SW, Chung JM, Cho MH, Ha TS, Cho WY, Suh HJ; Korean Children's Continence and Enuresis Society. Efficacy and tolerability of anticholinergics in Korean children with overactive bladder: a multicenter retrospective study. *J Korean Med Sci* 2014; **29**: 1550-1554 [PMID: 25408588 DOI: 10.3346/jkms.2014.29.11.1550]
- 30 **Newgreen D**, Bosman B, Hollestein-Havelaar A, Dahler E, Besuyen R, Sawyer W, Bolduc S, Rittig S. Solifenacin in Children and Adolescents with Overactive Bladder: Results of a Phase 3 Randomised Clinical Trial. *Eur Urol* 2017; **71**: 483-490 [PMID: 27687820 DOI: 10.1016/j.eururo.2016.08.061]
- 31 **Tannenbaum S**, den Adel M, Krauwinkel W, Meijer J, Hollestein-Havelaar A, Verheggen F, Newgreen D. Pharmacokinetics of solifenacin in pediatric populations with overactive bladder or neurogenic detrusor overactivity. *Pharmacol Res Perspect* 2020; **8**: e00684 [PMID: 33231929 DOI: 10.1002/prp2.684]
- 32 **Reddy PP**, Borgstein NG, Nijman RJ, Ellsworth PI. Long-term efficacy and safety of tolterodine in children with neurogenic detrusor overactivity. *J Pediatr Urol* 2008; **4**: 428-433 [PMID: 19013412 DOI: 10.1016/j.jpuro.2008.05.003]
- 33 **Grigoleit U**, Mürtz G, Laschke S, Schuldt M, Goepel M, Kramer G, Stöhrer M. Efficacy, tolerability and safety of propiverine hydrochloride in children and adolescents with congenital or traumatic neurogenic detrusor overactivity--a retrospective study. *Eur Urol* 2006; **49**: 1114-20; discussion 1120 [PMID: 16542772 DOI: 10.1016/j.eururo.2006.02.026]
- 34 **Schulte-Baukloh H**, Mürtz G, Heine G, Austin P, Miller K, Michael T, Strugala G, Knispel HH. Urodynamic effects of propiverine in children and adolescents with neurogenic bladder: results of a prospective long-term study. *J Pediatr Urol* 2012; **8**: 386-392 [PMID: 21907623 DOI: 10.1016/j.jpuro.2011.07.014]
- 35 **Lopez Pereira P**, Miguelez C, Caffarati J, Estornell F, Anguera A. Trospium chloride for the treatment of detrusor instability in children. *J Urol* 2003; **170**: 1978-1981 [PMID: 14532838 DOI: 10.1097/01.ju.0000085667.05190.ad]
- 36 **Bürst M**, Wolf A. Efficacy and safety of trospium chloride use in children with idiopathic and neurogenic detrusor overactivity: an overview of available data. *Urotoday Int J* 201; **4**: art17 [DOI: 10.3834/uij.1944-5784.2011.02.17]
- 37 **Guys JM**, Hery G, Haddad M, Borronne C. Neurogenic bladder in children: basic principles, new therapeutic trends. *Scand J Surg* 2011; **100**: 256-263 [PMID: 22182847 DOI: 10.1177/145749691110000405]
- 38 **Venkataramana NK**. Spinal dysraphism. *J Pediatr Neurosci* 2011; **6**: S31-S40 [PMID: 22069428]

- DOI: [10.4103/1817-1745.85707](https://doi.org/10.4103/1817-1745.85707)]
- 39 **Snodgrass WT**, Gargollo PC. Urologic care of the neurogenic bladder in children. *Urol Clin North Am* 2010; **37**: 207-214 [PMID: [20569799](https://pubmed.ncbi.nlm.nih.gov/20569799/) DOI: [10.1016/j.ucl.2010.03.004](https://doi.org/10.1016/j.ucl.2010.03.004)]
 - 40 **Bauer SB**, Austin PF, Rawashdeh YF, de Jong TP, Franco I, Siggard C, Jorgensen TM; International Children's Continence Society. International Children's Continence Society's recommendations for initial diagnostic evaluation and follow-up in congenital neuropathic bladder and bowel dysfunction in children. *Neurourol Urodyn* 2012; **31**: 610-614 [PMID: [22532312](https://pubmed.ncbi.nlm.nih.gov/22532312/) DOI: [10.1002/nau.22247](https://doi.org/10.1002/nau.22247)]
 - 41 **Gish P**, Mosholder AD, Truffa M, Johann-Liang R. Spectrum of central anticholinergic adverse effects associated with oxybutynin: comparison of pediatric and adult cases. *J Pediatr* 2009; **155**: 432-434 [PMID: [19732583](https://pubmed.ncbi.nlm.nih.gov/19732583/) DOI: [10.1016/j.jpeds.2009.01.074](https://doi.org/10.1016/j.jpeds.2009.01.074)]
 - 42 **Greer T**, Abbott J, Breytenbach W, McGuane D, Barker A, Khosa J, Samnakay N. Ten years of experience with intravesical and intrasphincteric onabotulinumtoxinA in children. *J Pediatr Urol* 2016; **12**: 94.e1-94.e6 [PMID: [26472538](https://pubmed.ncbi.nlm.nih.gov/26472538/) DOI: [10.1016/j.jpuro.2015.06.019](https://doi.org/10.1016/j.jpuro.2015.06.019)]
 - 43 **Hernandez RD**, Hurwitz RS, Foote JE, Zimmern PE, Leach GE. Nonsurgical management of threatened upper urinary tracts and incontinence in children with myelomeningocele. *J Urol* 1994; **152**: 1582-1585 [PMID: [7933209](https://pubmed.ncbi.nlm.nih.gov/7933209/) DOI: [10.1016/s0022-5347\(17\)32480-1](https://doi.org/10.1016/s0022-5347(17)32480-1)]
 - 44 **Hamid R**, Lorenzo-Gomez MF, Schulte-Baukloh H, Boroujerdi A, Patel A, Farrelly E. OnabotulinumtoxinA is a well tolerated and effective treatment for refractory overactive bladder in real-world practice. *Int Urogynecol J* 2021; **32**: 65-74 [PMID: [32719964](https://pubmed.ncbi.nlm.nih.gov/32719964/) DOI: [10.1007/s00192-020-04423-0](https://doi.org/10.1007/s00192-020-04423-0)]
 - 45 **Hascoet J**, Manunta A, Brochard C, Arnaud A, Damphousse M, Menard H, Kerdraon J, Journal H, Bonan I, Odent S, Fremont B, Siproudhis L, Gamé X, Peyronnet B; French Referral Network of Spina Bifida. Outcomes of intra-detrusor injections of botulinum toxin in patients with spina bifida: A systematic review. *Neurourol Urodyn* 2017; **36**: 557-564 [PMID: [27187872](https://pubmed.ncbi.nlm.nih.gov/27187872/) DOI: [10.1002/nau.23025](https://doi.org/10.1002/nau.23025)]
 - 46 **Austin PF**, Franco I, Dobremez E, Kroll P, Titanji W, Geib T, Jenkins B, Hoebeke PB. OnabotulinumtoxinA for the treatment of neurogenic detrusor overactivity in children. *Neurourol Urodyn* 2021; **40**: 493-501 [PMID: [33305474](https://pubmed.ncbi.nlm.nih.gov/33305474/) DOI: [10.1002/nau.24588](https://doi.org/10.1002/nau.24588)]
 - 47 **Riccabona M**, Koen M, Schindler M, Goedeke B, Pycha A, Lusuadi L, Bauer SB. Botulinum-A toxin injection into the detrusor: a safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflexia. *J Urol* 2004; **171**: 845-8; discussion 848 [PMID: [14713840](https://pubmed.ncbi.nlm.nih.gov/14713840/) DOI: [10.1097/01.ju.0000108892.35041.2d](https://doi.org/10.1097/01.ju.0000108892.35041.2d)]
 - 48 **Marte A**. Onabotulinumtoxin A for treating overactive/poor compliant bladders in children and adolescents with neurogenic bladder secondary to myelomeningocele. *Toxins (Basel)* 2012; **5**: 16-24 [PMID: [23274271](https://pubmed.ncbi.nlm.nih.gov/23274271/) DOI: [10.3390/toxins5010016](https://doi.org/10.3390/toxins5010016)]
 - 49 **Peng CW**, Chen JJ, Cheng CL, Grill WM. Improved bladder emptying in urinary retention by electrical stimulation of pudendal afferents. *J Neural Eng* 2008; **5**: 144-154 [PMID: [18430976](https://pubmed.ncbi.nlm.nih.gov/18430976/) DOI: [10.1088/1741-2560/5/2/005](https://doi.org/10.1088/1741-2560/5/2/005)]
 - 50 **Peh WYX**, Mogan R, Thow XY, Chua SM, Rusly A, Thakor NV, Yen SC. Novel Neurostimulation of Autonomic Pelvic Nerves Overcomes Bladder-Sphincter Dyssynergia. *Front Neurosci* 2018; **12**: 186 [PMID: [29618971](https://pubmed.ncbi.nlm.nih.gov/29618971/) DOI: [10.3389/fnins.2018.00186](https://doi.org/10.3389/fnins.2018.00186)]
 - 51 **Lee S**, Peh WYX, Wang J, Yang F, Ho JS, Thakor NV, Yen SC, Lee C. Toward Bioelectronic Medicine-Neuromodulation of Small Peripheral Nerves Using Flexible Neural Clip. *Adv Sci (Weinh)* 2017; **4**: 1700149 [PMID: [29201608](https://pubmed.ncbi.nlm.nih.gov/29201608/) DOI: [10.1002/advs.201700149](https://doi.org/10.1002/advs.201700149)]
 - 52 **Lissandrello CA**, Gillis WF, Shen J, Pearre BW, Vitale F, Pasquali M, Holinski BJ, Chew DJ, White AE, Gardner TJ. A micro-scale printable nanoclip for electrical stimulation and recording in small nerves. *J Neural Eng* 2017; **14**: 036006 [PMID: [28323640](https://pubmed.ncbi.nlm.nih.gov/28323640/) DOI: [10.1088/1741-2552/aa5a5b](https://doi.org/10.1088/1741-2552/aa5a5b)]
 - 53 **Capitanucci ML**, Camanni D, Demelas F, Mosiello G, Zaccara A, De Gennaro M. Long-term efficacy of percutaneous tibial nerve stimulation for different types of lower urinary tract dysfunction in children. *J Urol* 2009; **182**: 2056-2061 [PMID: [19695611](https://pubmed.ncbi.nlm.nih.gov/19695611/) DOI: [10.1016/j.juro.2009.03.007](https://doi.org/10.1016/j.juro.2009.03.007)]
 - 54 **de Wall LL**, Heesakkers JP. Effectiveness of percutaneous tibial nerve stimulation in the treatment of overactive bladder syndrome. *Res Rep Urol* 2017; **9**: 145-157 [PMID: [28861404](https://pubmed.ncbi.nlm.nih.gov/28861404/) DOI: [10.2147/RRU.S124981](https://doi.org/10.2147/RRU.S124981)]
 - 55 **Kaefer M**, Pabby A, Kelly M, Darbey M, Bauer SB. Improved bladder function after prophylactic treatment of the high risk neurogenic bladder in newborns with myelomeningocele. *J Urol* 1999; **162**: 1068-1071 [PMID: [10458433](https://pubmed.ncbi.nlm.nih.gov/10458433/) DOI: [10.1097/00005392-199909000-00031](https://doi.org/10.1097/00005392-199909000-00031)]
 - 56 **Hutcheson JC**, Cooper CS, Canning DA, Zderic SA, Snyder HM 3rd. The use of vesicostomy as permanent urinary diversion in the child with myelomeningocele. *J Urol* 2001; **166**: 2351-2353 [PMID: [11696783](https://pubmed.ncbi.nlm.nih.gov/11696783/)]
 - 57 **Morrisroe SN**, O'Connor RC, Nanigian DK, Kurzrock EA, Stone AR. Vesicostomy revisited: the best treatment for the hostile bladder in myelodysplastic children? *BJU Int* 2005; **96**: 397-400 [PMID: [16042737](https://pubmed.ncbi.nlm.nih.gov/16042737/) DOI: [10.1111/j.1464-410X.2005.05638.x](https://doi.org/10.1111/j.1464-410X.2005.05638.x)]
 - 58 **Cohen JS**, Harbach LB, Kaplan GW. Cutaneous vesicostomy for temporary urinary diversion in infants with neurogenic bladder dysfunction. *J Urol* 1978; **119**: 120-121 [PMID: [621794](https://pubmed.ncbi.nlm.nih.gov/621794/) DOI: [10.1016/s0022-5347\(17\)57401-7](https://doi.org/10.1016/s0022-5347(17)57401-7)]
 - 59 **Sonda LP**, Solomon MH. Twenty-year outcome of cutaneous vesicostomy. *J Urol* 1980; **124**: 326-328 [PMID: [7431495](https://pubmed.ncbi.nlm.nih.gov/7431495/) DOI: [10.1016/s0022-5347\(17\)55432-4](https://doi.org/10.1016/s0022-5347(17)55432-4)]
 - 60 **Allen TD**. Vesicostomy for the temporary diversion of the urine in small children. *J Urol* 1980; **123**: 929-931 [PMID: [6445989](https://pubmed.ncbi.nlm.nih.gov/6445989/) DOI: [10.1016/s0022-5347\(17\)56198-4](https://doi.org/10.1016/s0022-5347(17)56198-4)]
 - 61 **Mandell J**, Bauer SB, Colodny AH, Retik AB. Cutaneous vesicostomy in infancy. *J Urol* 1981; **126**:

- 92-93 [PMID: 7253086 DOI: 10.1016/s0022-5347(17)54396-7]
- 62 **Bruce RR**, Gonzales ET Jr. Cutaneous vesicostomy: a useful form of temporary diversion in children. *J Urol* 1980; **123**: 927-928 [PMID: 7382012 DOI: 10.1016/s0022-5347(17)56196-0]
- 63 **Broyer M**, Le Bihan C, Charbit M, Guest G, Tete MJ, Gagnadoux MF, Niaudet P. Long-term social outcome of children after kidney transplantation. *Transplantation* 2004; **77**: 1033-1037 [PMID: 15087767 DOI: 10.1097/01.tp.0000120947.75697.8b]
- 64 **Koo HP**, Bunchman TE, Flynn JT, Punch JD, Schwartz AC, Bloom DA. Renal transplantation in children with severe lower urinary tract dysfunction. *J Urol* 1999; **161**: 240-245 [PMID: 10037414]
- 65 **Adams J**, Mehls O, Wiesel M. Pediatric renal transplantation and the dysfunctional bladder. *Transpl Int* 2004; **17**: 596-602 [PMID: 15517166 DOI: 10.1007/s00147-004-0784-6]



Retrospective Cohort Study

Should pediatric idiopathic hypercalciuria be treated with hypocalciuric agents?

Maria Goretti Moreira Guimarães Penido, Marcelo de Sousa Tavares

ORCID number: Maria Goretti Moreira Guimarães Penido 0000-0002-1534-3861; Marcelo de Sousa Tavares 0000-0002-9766-9354.

Author contributions: Penido MGMG and Tavares MS contributed equally to the conception and design of the study, the acquisition, analysis and interpretation of data, and the drafting and critical revision of the final article.

Institutional review board statement: The study was approved by the institutional review board of the Clinics Hospital of the Federal University of Minas Gerais, Brazil (ETIC 0479.0.203.000-10, December 01, 2010) and by the Research Ethics Committee of Santa Casa de Belo Horizonte. It was conducted in accordance with the ethical standards laid down in 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: The authors declare no conflict of interest.

Data sharing statement: Technical

Maria Goretti Moreira Guimarães Penido, Marcelo de Sousa Tavares, Pediatric Nephrology Unit, Nephrology Center of Santa Casa de Belo Horizonte, Belo Horizonte 30150320, Minas Gerais, Brazil

Maria Goretti Moreira Guimarães Penido, Federal University of Minas Gerais, Faculty of Medicine, Department of Pediatrics, Pediatric Nephrology Unit, Belo Horizonte 30130100, Minas Gerais, Brazil

Corresponding author: Maria Goretti Moreira Guimarães Penido, FRCP (Hon), MD, PhD, Associate Professor, Chief Doctor, Professor, Pediatric Nephrology Unit, Nephrology Center of Santa Casa de Belo Horizonte, Rua Piauí 420, Santa Efigênia, Belo Horizonte 30150320, Minas Gerais, Brazil. mariagorettipenido@yahoo.com.br

Abstract

BACKGROUND

Hypercalciuria is the most common metabolic risk factor for calcium urolithiasis and is associated with bone loss in adult patients. Reduced bone mineral density (BMD) was already described in idiopathic hypercalciuria (IH) children, but the precise mechanisms of bone loss or inadequate bone mass gain remain unknown. Life-long hypercalciuria might be considered a risk to change bone structure and determine low bone mass throughout life. The peak of bone mass should occur without interferences. A beneficial effect of citrate formulations and thiazides on bone mass in adult and pediatric patients with IH have been shown.

AIM

To evaluate whether pharmacological therapy has a beneficial effect on bone mass in children and adolescents with IH.

METHODS

This retrospective cohort study evaluated 40 hypercalciuric children non-responsive to lifestyle and diet changes. After a 2-mo run-in period of citrate formulation (Kcitrate) usage, the first bone densitometry (DXA) was ordered. In patients with sustained hypercalciuria, a thiazide diuretic was prescribed. The second DXA was performed after 12 mo. Bone densitometry was performed by DXA at lumbar spine (L2-L4). A 24-h urine (calcium, citrate, creatinine) and blood samples (urea, creatinine, uric acid, calcium, phosphorus, magnesium, chloride, hemoglobin) were obtained. Clinical data included age, gender, weight, height and body mass index.

appendix, statistical code, and dataset available from the corresponding author at: mariagorettipenido@yahoo.com.br. Participants gave informed consent for data sharing. Data are anonymized and there were no risk of identification.

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.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Urology and nephrology

Country/Territory of origin: Brazil

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 30, 2021

Peer-review started: April 1, 2021

First decision: July 8, 2021

Revised: July 18, 2021

Accepted: July 22, 2021

Article in press: July 22, 2021

Published online: July 25, 2021

P-Reviewer: Bilic Curcic I

S-Editor: Gao CC

L-Editor: Filipodia

P-Editor: Ma YJ

RESULTS

Forty IH children; median age 10.5 year and median time follow-up 6.0 year were evaluated. Nine patients were treated with Kcitrates (G1) and 31 with Kcitrates + thiazide (G2). There were no differences in age, gender, body mass index z-score and biochemical parameters between G1 and G2. There were no increases in total cholesterol, kalemia and magnesemia. Calciuria decreased in both groups after treatment. Lumbar spine BMD z-score increased after thiazide treatment in G2. There was no improvement in G1.

CONCLUSION

Results point to a beneficial effect of thiazide on lumbar spine BMD z-score in children with IH. Further studies are necessary to confirm the results of the present study.

Key Words: Children; Adolescent; Hypercalciuria; Bone mineral density; Thiazides; Citrate

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Should pediatric idiopathic hypercalciuria be treated with hypocalciuric agents? Reduction in bone mass has already been described in hypercalciuric pediatric patients, and the precise mechanisms of bone loss or failure to achieve adequate bone mass remain unknown. Initial recommendations for the treatment of hypercalciuric pediatric patients consist of lifestyle changes and adequate diet. Children rarely comply with those recommendations and require potassium citrate supplementation or thiazides to reduce calciuria. However, anticalciuric therapy in children and adolescents is not based on strong clinical evidences. We speculate if the anticalciuric effect of pharmacologic therapy has a beneficial role on bone mass in pediatric idiopathic hypercalciuria and compromised bone mass in adulthood.

Citation: Penido MGMG, Tavares MS. Should pediatric idiopathic hypercalciuria be treated with hypocalciuric agents? *World J Nephrol* 2021; 10(4): 47-58

URL: <https://www.wjnet.com/2220-6124/full/v10/i4/47.htm>

DOI: <https://dx.doi.org/10.5527/wjn.v10.i4.47>

INTRODUCTION

Idiopathic hypercalciuria (IH) is the leading metabolic risk factor of pediatric urolithiasis (UL) and has high morbidity with or without UL. This morbidity is related to hematuria, renal colic, abdominal pain, urinary tract infection, voiding dysfunction symptoms and bone mass reduction[1]. Studies have showed a decrease in bone mineral density (BMD), especially at the lumbar spine, in idiopathic hypercalciuria children and adolescents[2-10]. García-Nieto *et al*[4] in 1997 showed the BMD reduction in 30% of their pediatric patients with IH. In sequence, Freundlich *et al*[10], Penido *et al*[2] and Schwaderer *et al*[9], demonstrated that 38%, 35% and 47% of their pediatric hypercalciuric patients also had significant reduction in BMD.

We all know that the highest accumulation of bone mass occurs during childhood and adolescence. The peak of bone mass is reached at the end of the second decade of life[11]. A current understanding is that the persistent hypercalciuria would be an important contributor to diminished bone mass. Thus, the peak bone mass should occur without interference in order to prevent the possibility of osteopenia, osteoporosis and fractures during adulthood[11,12]. The mechanisms of bone loss or failure of adequate bone mass gain is not completely understood. However, it is a consensus that bone mass acquired during childhood and adolescence is one of the major determinants of adult bone health[11,12]. The investigation on bone metabolism in pediatric IH is necessary to prevent the potential harmful consequences of this metabolic disorder.



In children with IH, the need for hypocalciuric therapy and its nature and duration remains to be determined. At present, anticalciuric therapy in pediatric hypercalciuria is not based on strong clinical evidence but more on clinical observation. This treatment may be required not only to protect against stone formation but also against low bone density.

The initial approach to pediatric IH consists in dietary modification with high fluid intake, low sodium and the Recommended Dietary Allowances[13] of protein and calcium. However, children do not comply with these recommendations, and frequently require anticalciuric therapy. If dietary recommendations fail, pharmacological therapy should be considered[12,13].

A beneficial effect of citrate formulations [particularly potassium citrate (Kcitra)] on bone mass in adult patients with IH has been shown since the 1990s[14-19]. Recently, it has been described that supplementation with alkaline potassium salts leads to reduction in urinary calcium excretion and reduction in bone resorption[20]. Nevertheless, some authors pointed out that the current evidence is still heterogeneous [21].

In pediatric patients, Kcitra has been shown to decrease the recurrence of new stones and the growth of residual stone fragments following lithotripsy[22,23]. However, until now there is no study confirming the beneficial effect of Kcitra on bone mass in children and adolescents.

Studies *in vitro* have suggested that thiazides reduce osteoclastic activity[24] and stimulate osteoblast differentiation and bone mineral formation[25]. Bolland *et al*[26] demonstrated in 122 postmenopausal women that hydrochlorothiazide produces small positive benefits on cortical bone density. LaCroix *et al*[27] demonstrated in a randomized, double-blind, placebo controlled study that low-dose hydrochlorothiazide could preserve BMD in older adults. As for Kcitra, up to now there is no study confirming the beneficial effect of thiazides on bone mass in pediatric patients. In this sense, the aim of this study was to examine whether pharmacological therapy has a beneficial effect on bone mass in children and adolescents with IH.

MATERIALS AND METHODS

Design

This is a retrospective cohort study with 40 children and adolescents diagnosed with IH. The study protocol is represented in Figure 1.

Patients and treatment

All 40 pediatric patients were evaluated and regularly followed at the Pediatric Nephrology Unit of the Nephrology Center of Santa Casa de Belo Horizonte, Belo Horizonte and the Pediatric Nephrology Unit of Clinic Hospital, School of Medicine of Federal University of Minas Gerais, in State of Minas Gerais, Brazil, between 1990 and November 2018. Inclusion criteria included no previous treatment of IH, no history of drug use with possible actions on calcium metabolism during the preceding year before diagnosis, diurnal and nocturnal continency, symptomatic (defined as lumbar and/or abdominal pain, voiding dysfunction or gross hematuria) and urinary calcium excretion ≥ 4 mg/kg per 24 h or an increased calcium/creatinine ratios, according to age[28-31]. Exclusion criteria included: Patients older than 18 years of age at initial evaluation, patients with chronic immobilization, physically impaired, nephrocalcinosis, hypercalcemia, defects of the lumbar spine, history of malignancy, hyperuricemia, excessive oral ingestion of calcium or vitamin D, tubular defects, long-term steroid treatment and concurrent conditions associated with metabolic bone disease. Patients were kept on a usual diet, water intake, physical exercise and sun exposure. All parents/caregivers were asked in detail about the dietary habits. All 40 patients had a complete evaluation at 4-mo intervals during the entire follow-up period, and all clinical and laboratory data were recorded.

Initial approach was high fluid intake and dietary modifications: Calcium and protein according to Recommended Dietary Allowances[13], sodium restriction (2.0-2.4 g/d) and potassium supplementation (3.0-3.5 g/d) with fruits and vegetables. However, none achieved a normal calciuria level. Kcitra (0.5-1.0 mEq/kg per day) was added to the treatment for 2 mo, and the first bone densitometry was done, according to the protocol study. If no normalization of calciuria occurred after 2 mo on Kcitra or if signs and symptoms continued (chronic abdominal pain or prolonged gross hematuria)[12], a diuretic thiazide (0.5-1.0 mg/kg per day) was added. After 12 mo on Kcitra alone or Kcitra and thiazide treatment, the second bone densitometry

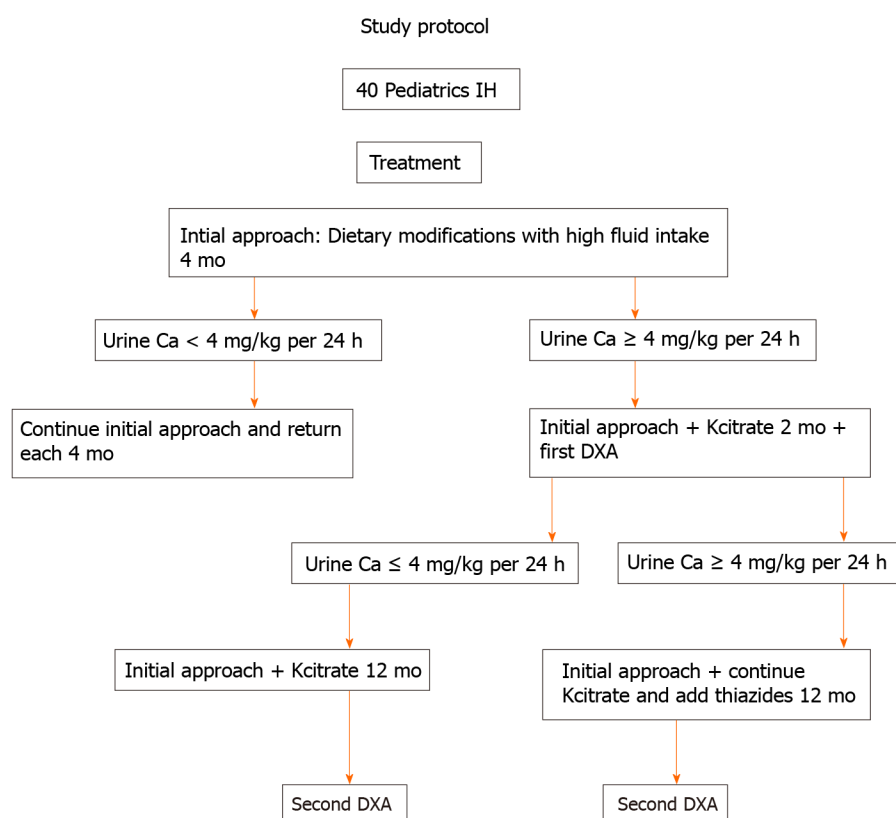


Figure 1 Study protocol for children and adolescents with idiopathic hypercalciuria. IH: Idiopathic hypercalciuria.

was done. Patients took Kcitrates or Kcitrates in combination with thiazides for at least 1 year. Nine patients were treated with Kcitrates alone and were called Group 1 (G1). Thirty-one patients were treated with Kcitrates + thiazide and were called Group 2 (G2).

Bone densitometry

Bone densitometry was performed by dual-energy X-ray absorptiometry (DEXA) using a Lunar DPX-IQ 2516 device. The exposure to radiation was 0.96 mrem for the lumbar spine.

A 76-KeV X-ray source of energy was used and the accuracy of this test was 0.1%. BMD was measured in the lumbar spine between L1-L4 and was also corrected for volume of the vertebra, as described by Kröger[32] and Gordon *et al*[33]. Lumbar spine BMD Z scores were calculated in relation to individuals of the same gender and age range and corrected for height according to the literature[34,35].

Laboratory and clinical data

Two 24-h urine samples were obtained, followed by a two single fasting urine samples (were kept refrigerated). A venous blood sample was drawn after the collection of the urine samples. Blood samples were analyzed for creatinine, urea, uric acid, calcium, phosphorus, magnesium, chloride, sodium, potassium, pH, bicarbonate, parathyroid hormone, alkaline phosphatase, hematocrit and hemoglobin. The 24-h urine samples analysis included calcium and creatinine. A complete urinalysis was performed on the two single fasting urine samples, and the pH determined. Clinical data included patient age, gender, weight, height and body mass index (BMI).

Statistical analysis

Clinical, laboratory and bone densitometry data are expressed as median, minimum and maximum values. The normality of data distribution was analyzed using the Shapiro-Wilk's test. In the case of non-normal distributions, non-parametric tests were chosen and data represented as medians, first and third quartiles and/or range. The following tests were used for comparison between groups: The Mann-Whitney *U* test and *T* test for unpaired samples when normality conditions were fulfilled and the Wilcoxon test when they were not. The statistical analysis was conducted with SPSS

ver. 18.0 (SPSS, Chicago, IL, United States). Anthropometric data were analyzed with AnthroPlus software[36]. The significance level was set at 5%. The comparison between lumbar BMD z-scores before and after treatment were analyzed by the Wilcoxon paired test. The statistical review of the study was performed by a biomedical statistician.

Ethical aspects

The study was approved by the institutional review board of the Clinics Hospital of the Federal University of Minas Gerais, Brazil (ETIC 0479.0.203.000-10, December 01, 2010) and by the Research Ethics Committee of Santa Casa de Belo Horizonte. It was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The participants and/or their guardians were adequately informed about the study and signed informed consent forms.

RESULTS

Study group characteristics

The group of study contained 40 pediatric patients, of whom 22 (55%) were males and 18 (45%) were females (1.2:1.0, male/female ratio). The mean age of clinical presentation was 10.5 ± 3.5 (3.2-19.6) years. The children and adolescents were regularly followed for a median time of 6.0 (range 4.5-8.3) years. All patients had normal physical examination, including blood pressure evaluation. Blood levels of hematocrit, hemoglobin, bicarbonate, pH, creatinine, urea, phosphorus, calcium, parathyroid hormone, alkaline phosphatase, sodium, potassium, magnesium, uric acid and chloride were all within the normal range. In the same way, the 24-h urine sample was collected properly, and its volume evaluated according to Tiselius[37] and Hellerstein *et al*[38]. No patient showed clinical signs of malnutrition or had proteinuria and urinary infection during the sample collection. There were no differences in BMI z-score and age between G1 and G2 before and after treatment (Table 1). No increase in total cholesterol or low-density lipoprotein-cholesterol as well as no hypokalemia nor hypomagnesemia were observed with pharmacologic treatment (Kcitrate or thiazides).

As already mentioned, the study sample was divided into two groups: G1 composed of 9 patients treated with Kcitrate alone and G2 composed of 31 patients treated with Kcitrate + thiazide. The mean urinary calcium excretion in G1 before and after the treatment were 5.12 ± 0.84 and 2.57 ± 0.82 mg/kg per 24 h, respectively ($P = 0.0004$). The median urinary calcium excretion in G2 before and after the treatment were 5.2 (4.3-7.0) and 2.9 (2.0-4.3) mg/kg per 24 h, respectively (0.001) (Table 2).

BMD

All patients underwent bone densitometry, and all had BMD z-score of the lumbar spine (L1-L4) < -1 . The interval between BMD measurements was 1 year. BMD z-score of the lumbar spine (L1-L4) increased significantly after the treatment in G2 (from -1.7 to -1.4; $P = 0.04$; *U*-Test Mann-Whitney), and there was no improvement in G1 (from -1.3 to -1.6; $P = 0.16$; *U*-Test Mann-Whitney) (Figure 2).

DISCUSSION

The acquisition of bone mass occurs during childhood and adolescence. The maximum peak of bone mass is reached at the end of the second decade of life. It is known that bone mass acquired during childhood and adolescence is the major determinant of adult bone health. Several studies have already demonstrated reduced BMD in hypercalciuric pediatric patients[1-6,9,10]. If reduced BMD in childhood can compromise adult peak bone mass, therapeutic strategies to optimize bone mass in pediatric IH should be considered. Considering that the chronic loss of calcium in the urine is a risk factor for the reduction of BMD and may therefore compromise the final bone mass in adulthood, there is a question that is not yet answered: "should pediatric idiopathic hypercalciuria be treated with hypocalciuric agents?" This study evaluated the BMD of pediatric patients with IH before and after treatment with Kcitrate and thiazides in order to examine whether pharmacological therapy has a beneficial effect on its bone mass.

Table 1 Demographic variables in G1 and G2

	Age (yr), mean $\pm$ SD	Gender, M/F	BMiz-score before, mean $\pm$ SD	BMiz-score after, mean $\pm$ SD
G1 (<i>n</i> = 9)	9.11 $\pm$ 2.57	4/5	-0.74 $\pm$ 0.76	-0.80 $\pm$ 0.76
G2 (<i>n</i> = 31)	10.09 $\pm$ 3.65	18/13	-0.82 $\pm$ 2.06	-0.63 $\pm$ 1.15
<i>P</i> value	NS	NS	¹ 0.72	¹ 0.80

¹*T* test. There were no differences in age, gender, body mass index z-score, and biochemical parameters between G1 and G2. There were no increases in total cholesterol and in low-density lipoprotein-cholesterol as well as hypokalemia and hypomagnesemia. BMI: Body mass index; F: Female; M: Male.

Table 2 Biochemical variables in G1 and G2

	Calciuria before (mg/kg per 24 h)	Calciuria after (mg/kg per 24 h)	<i>P</i> value
G1 (<i>n</i> = 9), mean $\pm$ SD	5.12 $\pm$ 0.84	2.57 $\pm$ 0.82	¹ 0.0004
G2 (<i>n</i> = 31), median (Min-Max)	5.2 (4.3-7.0)	2.9 (2.0-4.3)	² 0.001

¹*T* test (normal distribution).

²Wilcoxon test (abnormal distribution). Calciuria was significantly lower after treatment in G1 as well as in G2.

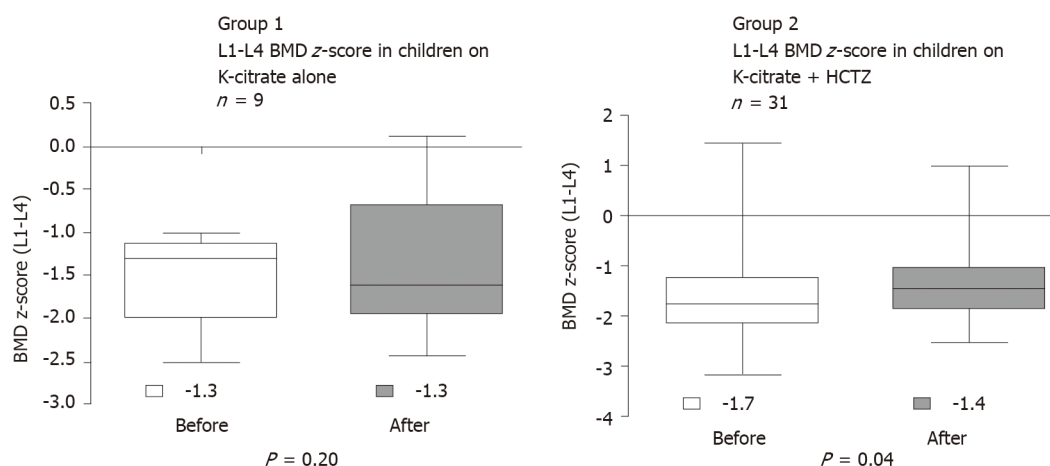


Figure 2 Comparison of the lumbar spine bone mineral density z-score between Group 1 and Group 2 before and after treatment. Test: *U*-test Mann-Whitney. BMD: Bone mineral density; HCTZ: Hydrochlorothiazide.

Study group characteristics

The male/female ratio of our patients was 1.2:1.0, and the mean age at onset of clinical presentation was 10.5 years, in accordance with other studies[9,39]. As shown in Table 1, there were no differences in BMI z-score and age between G1 and G2 before and after treatment. It should be noted that BMI must not be different in the two groups evaluated (G1 and G2). According to García-Nieto *et al*[40], there is a correlation between the improvements in the BMI and BMD values, indicating that the BMI is a decisive factor to increase the BMD. Schwaderer *et al*[9] found a negative correlation between BMD and BMI. However, there are some studies reporting the opposite. Both weight gain[41] and exercise[42-45] lead to an increase in BMD. A Brazilian study showed that the lean body mass is the main predictor of bone mass at the end of adolescence in healthy individuals[43]. Inomoto[44] evaluated the effects of physical exercise (moderate exercise activities for 2 h) in Japanese children and concluded that the observed increase in BMD was associated with an increase in overall muscle quantity. In the same way, Sardinha *et al*[45] reported that daily vigorous physical activity for 25 min a day seems to improve femoral neck bone health in children. These recommendations should be given to all children and adolescents.

Laboratorial data and treatment

No increase in total cholesterol, low-density lipoprotein-cholesterol, hypokalemia and hypomagnesemia were observed with thiazide use. It is known that diuretics, especially thiazides, have a significant effect on lipid profiles. However, Akhtar *et al* [46] in a meta-analysis of randomized controlled trials concluded that further research is needed because this conclusion is supported by a low number of studies. Hollifield [47] showed that the undesirable effects of hypokalemia and hypomagnesemia are associated with increasing doses of hydrochlorothiazide. In the present study, the thiazide dose was low (0.5-1.0 mg/kg per day), and no changes were seen in cholesterol, potassium and magnesium levels.

In the two studied groups (G1 and G2), a significant reduction in urinary calcium excretion after treatment with Kcitate and/or thiazides was observed, in accordance with García-Nieto *et al* [40] and Moreira Guimarães Penido *et al* [3]. There were no differences in biochemical and mineral parameters between G1 and G2 before and after treatment, as previously demonstrated [3,40].

BMD

BMD z-score of the lumbar spine (L1-L4) increased significantly after the treatment in G2, and there was no improvement in G1 (Figure 2). G1 was treated with Kcitate alone and G2 was treated with Kcitate and thiazides. Our results continued pointing to a beneficial effect of thiazide on BMD z-score in children with IH. However, pharmacological treatment of children and adolescents with IH is not yet based on strong scientific evidence. Usually, this treatment is initiated in patients who do not improve calciuria or maintain signs and symptoms with non-pharmacological treatment, which includes modification of dietary habits with high water intake.

In IH adult patients a beneficial effect of Kcitate on bone mass was observed. Pak *et al* [15] treated their adult patients with Kcitate and observed that spinal bone density increased in most of them. Marangella *et al* [17] suggested that treatment with an alkaline salt, such as potassium citrate, can reduce bone resorption. Vescini *et al* [18] showed that long-term treatment with Kcitate increases forearm BMD in idiopathic calcium stone formers. Recently, Lambert *et al* [20], based on the role of acid-base homeostasis as a determinant of bone health and the contribution of supplemental alkali in promoting skeletal integrity, performed a meta-analysis study. The authors confirmed that supplementation with alkaline potassium salts determined a significant reduction in urinary calcium excretion and reduction in bone resorption. Granchi *et al* [21] highlighted the main functions of citrate, focusing especially on its role in the pathophysiology of metabolic bone diseases. However, the authors believe that current evidence is still very heterogeneous. In a model of hypercalciuria, Krieger *et al* [48] demonstrated that Kcitate significantly raises urine citrate levels and lowers urinary calcium. However, the increases in phosphate, oxalate, and pH levels would lead to increase calcium oxalate and calcium phosphate supersaturation. The authors pointed that Kcitate may not be beneficial in preventing calcium phosphate stone formation because it can induce complex changes in urinary chemical constitution [48].

In pediatric patients, there is no study confirming the beneficial effect of Kcitate on bone mass. The mechanism of the association between the use of Kcitate and interruption of bone mass loss can occur through the reduction of endogenous acid production with a consequent decrease in urinary calcium excretion [49]. In a study involving dietary load of Kcitate in prepubescent girls, there was no change in urinary calcium excretion, although net acid excretion decreased [50]. In the same way, rats also did not decrease urinary calcium excretion after a load of alkaline potassium [51]. The differences observed in bone metabolism between children and adults (bone modeling *vs* remodeling) may be involved in the difference in calciuric response to alkaline potassium in these two groups. Jones *et al* [49] concluded in a cross-sectional study of 330 boys and girls that urinary potassium was associated with BMD independently of lean body mass in these well-nourished, calcium-replete children. The authors also suggested that these findings should be confirmed in longitudinal studies. According to Perez-Suarez *et al* [8] and others, the indiscriminate use of Kcitate and thiazides indefinitely is not advisable [3,8,52-54]. Pharmacological treatment should be reserved in three situations: When there are marked clinical complaints as sustained dysuria, frequent macroscopic hematuria, or recurrent renal colic; when ultrasonography shows stones or nephrocalcinosis or in case of repeated fractures [3,9,52].

The effect of diuretic thiazides on the bone may extend beyond its anticalciuric actions and probably is related to the stimulation of osteoblastic bone formation [55]. Studies have shown that the mitogenic action of the thiazide diuretic may be partly

due to the increased proliferation of osteoblastic cells associated with the inhibition of osteoclastic bone resorption due to the reduction in osteoclastic cell differentiation, which is mediated by the direct inhibition of hematopoietic precursors[55,56]. Data in the literature suggest a protective effect of thiazide diuretic treatment on bone health by increasing BMD. In fact, thiazides increase renal calcium reabsorption by inhibiting the sodium chloride cotransporter in the distal tubule. This action favors an increase in sodium urinary excretion and decrease in urinary calcium excretion[57]. Spivacow *et al* [58] evaluated retrospectively BMD and biochemical markers of bone turnover in response to thiazide therapy in 52 adult female patients with IH and nephrolithiasis (25 were pre-menopausal G1, and 27 were postmenopausal G2). The authors concluded that correction of hypercalciuria with long term treatment with low-dose hydrochlorothiazide/amiloride prevented bone loss. Patients with osteoporosis had a significant increase in BMD at the lumbar spine[58]. A systematic review and meta-analysis evaluated the effectiveness of thiazides on serum and urinary calcium levels and BMD in adult patients with osteoporosis. The authors concluded that thiazides might play a role in preserving bone mass and be effective in the prevention and treatment of osteoporosis[59]. Recently, van der Burgh *et al*[60] in a cross-sectional analysis of the Rotterdam Study concluded that the decrease in fracture risk in patients who used thiazide diuretics is explained by the increase in bone mass and not by the improvement in bone microarchitecture[60]. The Rotterdam Study is an ongoing prospective population-based cohort study with Dutch citizens and was designed to investigate chronic diseases in the elderly.

The administration of thiazides is considered to be an appropriate treatment for hypercalciuria in adult patients with IH, however, only a few published articles have reported on children with IH treated with thiazides. According to García-Nieto *et al* [40], these studies have been cross-sectional and were controversial in relation to the used technology to measured bone mass. Although there is evidence showing the ability of thiazide to control calciuria, little is known on its impact on BMD, especially in children.

Reusz *et al*[61] showed in their 18 pediatric patients with IH a positive effect of thiazides on BMD and an important reduction in urinary calcium excretion. Schwaderer *et al*[9] recommended the pharmacological treatment (Kcitate and/or thiazide) if a decreased in BMD is observed, even if modifications in life habits have improved the clinical presentation of the metabolic change. Srivastava and Schwaderer [12] believe that the use of drug therapy should be reserved for children with symptomatic IH and/or rare monogenic disorders. Moreira Guimarães Penido *et al*[3] showed that the BMD of the lumbar spine (L1-L4) and its respective z-scores increased significantly after treatment with Kcitate or Kcitate and thiazides. The authors suggested a possible beneficial effect of this treatment on bone mass and pointed out that a normal calciuria with a persistent positive calcium balance could impact and contribute to an ideal peak in bone mass and/or an adequate bone mass acquisition over the years. García-Nieto *et al*[40] studied 22 children with IH and bone mass reduction who had received thiazides for 2.4 years and compared them with a group of 32 IH children also with bone mass reduction, who had not received thiazide treatment. The authors concluded that thiazide treatment does not improve the BMD z-score in children with IH. They also concluded that more than half of the hypercalciuric children showed a spontaneous improvement in their bone mass, suggesting that there is a tendency for the spontaneous improvement of BMD, which is associated with increased body mass[40]. The same Spanish group (2020) evaluate BMD evolution in 34 IH patients through three bone densitometry studies during over 20 years. They concluded that improved BMD may be related to female sex, increment of body mass, and reduction in bone resorption. No relationship with the use of thiazide diuretics was mentioned by the authors[8].

The weaknesses of our study were the fact of being retrospective, the small number of patients, especially in the K-citrate only group, the lack of long-term follow-up, and the fact that the thiazide treated patients received also K-citrate, which may have protected from hypokalemia and hypomagnesemia. Further prospective longitudinal studies with two subgroups of symptomatic hypercalciuric children (thiazides group *vs* no treatment group) are necessary.

CONCLUSION

BMD should be considered in the management of pediatric patients with IH. The diagnosis and prevention of bone mass reduction should be detected in these patients

because they are considered to be at risk of reduced bone mass. Low BMD with subsequent osteopenia, osteoporosis, and increased fracture risk can have a considerable impact on the health system and in patient quality of life.

Some authors believe that hypercalciuria is not a disease but the physiology of people who occupy one extreme of a continuous spectrum of urine calcium excretion rates[52]. However, if this spectrum of high calcium excretion can cause harmful consequences and diseases in adulthood, it could be considered as a disease in pediatric patients. In fact, in most cases, it is simply a benign metabolic abnormality and as such should be conducted. However, it is known that reduced BMD is reported in pediatric hypercalciuria and can impact the health of adult bone.

Studies with IH pediatric patients indicated that citrate or thiazide diuretic treatment may improve BMD[3,61]. However, the treatment with these medications has very well-defined indications for use. As aforementioned, the initial approach of IH consists of dietary modifications and high fluid intake. In case of no normalization of calcium excretion with the dietary modifications and high fluid intake, hypocalciuric agents are considered. The first line of hypocalciuric agents is Kcitrate. Thiazide should be initiated combined with potassium citrate only if there is low BMD and/or fractures, and no improvement of calciuria levels and symptoms was obtained[3,4,6,12,13]. Controlled studies in the future will be able to define if children and adolescents with IH should or should not be treated.

In conclusion, we continue to speculate if thiazide has a role in bone mass and if steady positive calcium balance could impact on the achievement of optimal peak bone mass. However, we do believe that prospective randomized controlled studies are the key to test the effectiveness of pharmacological therapy in children with IH and if it prevents impairment of bone mass in adulthood.

ARTICLE HIGHLIGHTS

Research background

Idiopathic hypercalciuria (IH) is the leading metabolic risk factor for pediatric urolithiasis. The reduction in bone mass has already been described in hypercalciuric children. Life-long hypercalciuria might be considered a risk to change bone structure and determine low bone mass throughout life. A beneficial effect of citrate formulations and thiazides on bone mass in adult and pediatric patients with IH have been shown.

Research motivation

Considering that HI can cause a reduction in mineral bone density in children and adolescents and lead to osteopenia, osteoporosis, and an increased risk of fractures in adulthood, it would be important to know how to diagnose and treat this metabolic disorder.

Research objectives

Evaluated whether pharmacological therapy has a beneficial effect on bone mass in children and adolescents with IH.

Research methods

This is a retrospective cohort study that evaluated hypercalciuric children non-responsive to lifestyle and diet changes. They were treated with potassium Kcitrate or with Kcitrate combined to thiazides. Before and after treatment they underwent bone densitometry.

Research results

Forty IH children, median age 10.5 years and median time follow-up 6.0 years, were evaluated. Nine patients were treated with Kcitrate (G1) and 31 with Kcitrate + thiazide (G2). Calciuria decreased in both groups after treatment. Lumbar spine bone mineral density z-score increased after thiazide treatment in G2. There was no improvement in G1.

Research conclusions

Results point to a beneficial effect of thiazide on lumbar spine bone mineral density z-score in children with IH.

Research perspectives

Future perspectives are to understand better the pathogenesis of HI in order to treat children and adolescents, preventing bone mass reduction.

ACKNOWLEDGEMENTS

We thank the special collaboration of all children, adolescents, and their families involved in this study.

REFERENCES

- 1 **Pavlou M**, Giapros V, Challa A, Chaliasos N, Siomou E. Does idiopathic hypercalciuria affect bone metabolism during childhood? *Pediatr Nephrol* 2018; **33**: 2321-2328 [PMID: [30043116](#) DOI: [10.1007/s00467-018-4027-y](#)]
- 2 **Penido MG**, Lima EM, Marino VS, Tupinambá AL, França A, Souto MF. Bone alterations in children with idiopathic hypercalciuria at the time of diagnosis. *Pediatr Nephrol* 2003; **18**: 133-139 [PMID: [12579402](#) DOI: [10.1007/s00467-002-1036-6](#)]
- 3 **Moreira Guimarães Penido MG**, de Sousa Tavares M, Campos Linhares M, Silva Barbosa AC, Cunha M. Longitudinal study of bone mineral density in children with idiopathic hypercalciuria. *Pediatr Nephrol* 2012; **27**: 123-130 [PMID: [21779854](#) DOI: [10.1007/s00467-011-1952-4](#)]
- 4 **García-Nieto V**, Ferrández C, Monge M, de Sequera M, Rodrigo MD. Bone mineral density in pediatric patients with idiopathic hypercalciuria. *Pediatr Nephrol* 1997; **11**: 578-583 [PMID: [9323283](#) DOI: [10.1007/s004670050341](#)]
- 5 **Skalova S**, Palicka V, Kutilek S. Bone mineral density and urinary N-acetyl-beta-D-glucosaminidase activity in paediatric patients with idiopathic hypercalciuria. *Nephrology (Carlton)* 2005; **10**: 99-102 [PMID: [15877664](#) DOI: [10.1111/j.1440-1797.2005.00381.x](#)]
- 6 **García-Nieto V**, Sánchez Almeida E, Monge M, Luis Yanes MI, Hernández González MJ, Ibáñez A. Longitudinal study, bone mineral density in children diagnosed with idiopathic hypercalciuria (IH). *Pediatr Nephrol* 2009; **24**: 2083
- 7 **Kusumi K**, Schwaderer AL, Clark C, Budge K, Hussein N, Raina R, Denburg M, Safadi F. Bone mineral density in adolescent urinary stone formers: is sex important? *Urolithiasis* 2020; **48**: 329-335 [PMID: [32236650](#) DOI: [10.1007/s00240-020-01183-w](#)]
- 8 **Perez-Suarez G**, Yanes MIL, de Basoa MCMF, Almeida ES, García Nieto VM. Evolution of bone mineral density in patients with idiopathic hypercalciuria: a 20-year longitudinal study. *Pediatr Nephrol* 2021; **36**: 661-667 [PMID: [32980941](#) DOI: [10.1007/s00467-020-04754-6](#)]
- 9 **Schwaderer AL**, Cronin R, Mahan JD, Bates CM. Low bone density in children with hypercalciuria and/or nephrolithiasis. *Pediatr Nephrol* 2008; **23**: 2209-2214 [PMID: [18696122](#) DOI: [10.1007/s00467-008-0929-4](#)]
- 10 **Freundlich M**, Alonzo E, Bellorin-Font E, Weisinger JR. Reduced bone mass in children with idiopathic hypercalciuria and in their asymptomatic mothers. *Nephrol Dial Transplant* 2002; **17**: 1396-1401 [PMID: [12147785](#) DOI: [10.1093/ndt/17.8.1396](#)]
- 11 **Carrié Fässler AL**, Bonjour JP. Osteoporosis as a pediatric problem. *Pediatr Clin North Am* 1995; **42**: 811-824 [PMID: [7610014](#) DOI: [10.1016/S0031-3955\(16\)39018-6](#)]
- 12 **Srivastava T**, Schwaderer A. Diagnosis and management of hypercalciuria in children. *Curr Opin Pediatr* 2009; **21**: 214-219 [PMID: [19307900](#) DOI: [10.1097/MOP.0b013e3283223db7](#)]
- 13 **Subcommittee of the Tenth Edition of the RDAs**, Food and Nutrition Board, Commission on Life Sciences, National Research Council. FNB recommended dietary allowances, 10th ed. National Academy Press, Washington, 1989
- 14 **Sellmeyer DE**, Schloetter M, Sebastian A. Potassium citrate prevents increased urine calcium excretion and bone resorption induced by a high sodium chloride diet. *J Clin Endocrinol Metab* 2002; **87**: 2008-2012 [PMID: [11994333](#) DOI: [10.1210/jcem.87.5.8470](#)]
- 15 **Pak CY**, Peterson RD, Poindexter J. Prevention of spinal bone loss by potassium citrate in cases of calcium urolithiasis. *J Urol* 2002; **168**: 31-34 [PMID: [12050486](#)]
- 16 **Caudarella R**, Vescini F, Buffa A, Stefoni S. Citrate and mineral metabolism: kidney stones and bone disease. *Front Biosci* 2003; **8**: s1084-s1106 [PMID: [12957820](#) DOI: [10.2741/1119](#)]
- 17 **Marangella M**, Di Stefano M, Casalis S, Berutti S, D'Amelio P, Isaia GC. Effects of potassium citrate supplementation on bone metabolism. *Calcif Tissue Int* 2004; **74**: 330-335 [PMID: [15255069](#) DOI: [10.1007/s00223-003-0091-8](#)]
- 18 **Vescini F**, Buffa A, La Manna G, Ciavatti A, Rizzoli E, Bottura A, Stefoni S, Caudarella R. Long-term potassium citrate therapy and bone mineral density in idiopathic calcium stone formers. *J Endocrinol Invest* 2005; **28**: 218-222 [PMID: [15952405](#) DOI: [10.1007/BF03345376](#)]
- 19 **Dawson-Hughes B**, Harris SS, Palermo NJ, Castaneda-Sceppa C, Rasmussen HM, Dallal GE. Treatment with potassium bicarbonate lowers calcium excretion and bone resorption in older men and women. *J Clin Endocrinol Metab* 2009; **94**: 96-102 [PMID: [18940881](#) DOI: [10.1210/jc.2008-1662](#)]

- 20 **Lambert H**, Frassetto L, Moore JB, Torgerson D, Gannon R, Burckhardt P, Lanham-New S. The effect of supplementation with alkaline potassium salts on bone metabolism: a meta-analysis. *Osteoporos Int* 2015; **26**: 1311-1318 [PMID: 25572045 DOI: 10.1007/s00198-014-3006-9]
- 21 **Granchi D**, Baldini N, Olivieri FM, Caudarella R. Role of Citrate in Pathophysiology and Medical Management of Bone Diseases. *Nutrients* 2019; **11** [PMID: 31731473 DOI: 10.3390/nu11112576]
- 22 **Tekin A**, Tekgul S, Atsu N, Bakkaloglu M, Kendi S. Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. *J Urol* 2002; **168**: 2572-2574 [PMID: 12441986]
- 23 **Sarica K**, Erturhan S, Yurtseven C, Yagci F. Effect of potassium citrate therapy on stone recurrence and regrowth after extracorporeal shockwave lithotripsy in children. *J Endourol* 2006; **20**: 875-879 [PMID: 17144854 DOI: 10.1089/end.2006.20.875]
- 24 **Lalande A**, Roux S, Denne MA, Stanley ER, Schiavi P, Guez D, De Vernejoul MC. Indapamide, a thiazide-like diuretic, decreases bone resorption in vitro. *J Bone Miner Res* 2001; **16**: 361-370 [PMID: 11204436 DOI: 10.1359/jbmr.2001.16.2.361]
- 25 **Dvorak MM**, De Jossineau C, Carter DH, Pisitkun T, Knepper MA, Gamba G, Kemp PJ, Riccardi D. Thiazide diuretics directly induce osteoblast differentiation and mineralized nodule formation by interacting with a sodium chloride co-transporter in bone. *J Am Soc Nephrol* 2007; **18**: 2509-2516 [PMID: 17656470 DOI: 10.1681/ASN.2007030348]
- 26 **Bolland MJ**, Ames RW, Horne AM, Orr-Walker BJ, Gamble GD, Reid IR. The effect of treatment with a thiazide diuretic for 4 years on bone density in normal postmenopausal women. *Osteoporos Int* 2007; **18**: 479-486 [PMID: 17120180 DOI: 10.1007/s00198-006-0259-y]
- 27 **LaCroix AZ**, Ott SM, Ichikawa L, Scholes D, Barlow WE. Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; **133**: 516-526 [PMID: 11015164 DOI: 10.7326/0003-4819-133-7-200010030-00010]
- 28 **Penido MG**, Diniz JS, Guimarães MM, Cardoso RB, Souto MF, Penido MG. [Urinary excretion of calcium, uric acid and citrate in healthy children and adolescents]. *J Pediatr (Rio J)* 2002; **78**: 153-160 [PMID: 14647798]
- 29 **Sargent JD**, Stukel TA, Kresel J, Klein RZ. Normal values for random urinary calcium to creatinine ratios in infancy. *J Pediatr* 1993; **123**: 393-397 [PMID: 8355114 DOI: 10.1016/s0022-3476(05)81738-x]
- 30 **Stapleton FB**. Hematuria associated with hypercalciuria and hyperuricosuria: a practical approach. *Pediatr Nephrol* 1994; **8**: 756-761 [PMID: 7696121 DOI: 10.1007/BF00869114]
- 31 **Chen YH**, Lee AJ, Chen CH, Chesney RW, Stapleton FB, Roy S 3rd. Urinary mineral excretion among normal Taiwanese children. *Pediatr Nephrol* 1994; **8**: 36-39 [PMID: 8142222 DOI: 10.1007/BF00868256]
- 32 **Kröger HPJ**. Measurement of bone mass and density in children. In: Schönau E. Paediatric osteology: new developments in diagnostics and therapy. Elsevier Science, Amsterdam, 1996: 103-108
- 33 **Gordon CM**, Bachrach LK, Carpenter TO, Crabtree N, El-Hajj Fuleihan G, Kutilek S, Lorenc RS, Tosi LL, Ward KA, Ward LM, Kalkwarf HJ. Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions. *J Clin Densitom* 2008; **11**: 43-58 [PMID: 18442752 DOI: 10.1016/j.jocd.2007.12.005]
- 34 **del Rio L**, Carrascosa A, Pons F, Gusinyé M, Yeste D, Domenech FM. Bone mineral density of the lumbar spine in white Mediterranean Spanish children and adolescents: changes related to age, sex, and puberty. *Pediatr Res* 1994; **35**: 362-366 [PMID: 8190528 DOI: 10.1203/00006450-199403000-00018]
- 35 **Thomas KA**, Cook SD, Bennett JT, Whitecloud TS 3rd, Rice JC. Femoral neck and lumbar spine bone mineral densities in a normal population 3-20 years of age. *J Pediatr Orthop* 1991; **11**: 48-58 [PMID: 1988478 DOI: 10.1097/01241398-199101000-00011]
- 36 **World Health Organization**. Anthroplus software. [cited 15 June 2020]. In: World Health Organization [Internet]. Available from: <http://www.who.int/growthref/tools/en/>
- 37 **Tiselius HG**. Practical aspects of the handling of samples and evaluation of laboratory data. *Scand J Urol Nephrol Suppl* 1980; **53**: 105-108 [PMID: 6937986]
- 38 **Hellerstein S**, Simon SD, Berenbom M, Erwin P, Nickell E. Creatinine excretion rates for renal clearance studies. *Pediatr Nephrol* 2001; **16**: 637-643 [PMID: 11519893 DOI: 10.1007/s004670100622]
- 39 **Spivacow FR**, Negri AL, del Valle EE, Calviño I, Fradinger E, Zanchetta JR. Metabolic risk factors in children with kidney stone disease. *Pediatr Nephrol* 2008; **23**: 1129-1133 [PMID: 18324422 DOI: 10.1007/s00467-008-0769-2]
- 40 **García-Nieto V**, Monge-Zamorano M, González-García M, Luis-Yanes MI. Effect of thiazides on bone mineral density in children with idiopathic hypercalciuria. *Pediatr Nephrol* 2012; **27**: 261-268 [PMID: 21874585 DOI: 10.1007/s00467-011-1987-6]
- 41 **El Hage R**, Jacob C, Moussa E, Groussard C, Pineau JC, Benhamou CL, Jaffré C. Influence of the weight status on bone mineral content and bone mineral density in a group of Lebanese adolescent girls. *Joint Bone Spine* 2009; **76**: 680-684 [PMID: 19945325 DOI: 10.1016/j.jbspin.2009.10.004]
- 42 **Eliakim A**, Raisz LG, Brasel JA, Cooper DM. Evidence for increased bone formation following a brief endurance-type training intervention in adolescent males. *J Bone Miner Res* 1997; **12**: 1708-1713 [PMID: 9333132 DOI: 10.1359/jbmr.1997.12.10.1708]
- 43 **Fonseca RM**, de França NM, Van Praagh E. Relationship between indicators of fitness and bone

- density in adolescent Brazilian children. *Pediatr Exerc Sci* 2008; **20**: 40-49 [PMID: [18364533](#) DOI: [10.1123/pes.20.1.40](#)]
- 44 **Inomoto T.** [Physical activity/sports and bone mineral density]. *Clin Calcium* 2008; **18**: 1339-1348 [PMID: [18758041](#)]
- 45 **Sardinha LB**, Baptista F, Ekelund U. Objectively measured physical activity and bone strength in 9-year-old boys and girls. *Pediatrics* 2008; **122**: e728-e736 [PMID: [18762509](#) DOI: [10.1542/peds.2007-2573](#)]
- 46 **Akhtar F**, Khalid F, Wang H, Zhang D, Gong X. The Effect of Thiazide Diuretics on Blood Lipid Profile in Hypertensive Adults: A Meta-analysis of Randomized Controlled Trials. *Cureus* 2018; **10**: e2651 [PMID: [30034973](#) DOI: [10.7759/cureus.2651](#)]
- 47 **Hollifield JW.** Thiazide treatment of hypertension. Effects of thiazide diuretics on serum potassium, magnesium, and ventricular ectopy. *Am J Med* 1986; **80**: 8-12 [PMID: [3706351](#) DOI: [10.1016/0002-9343\(86\)90335-9](#)]
- 48 **Krieger NS**, Asplin JR, Frick KK, Granja I, Culbertson CD, Ng A, Grynpsas MD, Bushinsky DA. Effect of Potassium Citrate on Calcium Phosphate Stones in a Model of Hypercalciuria. *J Am Soc Nephrol* 2015; **26**: 3001-3008 [PMID: [25855777](#) DOI: [10.1681/ASN.2014121223](#)]
- 49 **Jones G**, Riley MD, Whiting S. Association between urinary potassium, urinary sodium, current diet, and bone density in prepubertal children. *Am J Clin Nutr* 2001; **73**: 839-844 [PMID: [11273862](#) DOI: [10.1093/ajcn/73.4.839](#)]
- 50 **Duff TL**, Whiting SJ. Calciuric effects of short-term dietary loading of protein, sodium chloride and potassium citrate in prepubescent girls. *J Am Coll Nutr* 1998; **17**: 148-154 [PMID: [9550458](#) DOI: [10.1080/07315724.1998.10718740](#)]
- 51 **Greger JL**, Kaup SM, Behling AR. Calcium, magnesium and phosphorus utilization by rats fed sodium and potassium salts of various inorganic anions. *J Nutr* 1991; **121**: 1382-1388 [PMID: [1880616](#) DOI: [10.1093/jn/121.9.1382](#)]
- 52 **García Nieto VM**, Luis Yanes MI, Tejera Carreño P, Perez Suarez G, Moraleda Mesa T. The idiopathic hypercalciuria reviewed. Metabolic abnormality or disease? *Nefrología (Engl Ed)* 2019; **39**: 592-602 [PMID: [31160051](#) DOI: [10.1016/j.nefro.2019.02.011](#)]
- 53 **Alon US**, Zimmerman H, Alon M. Evaluation and treatment of pediatric idiopathic urolithiasis-revisited. *Pediatr Nephrol* 2004; **19**: 516-520 [PMID: [15015063](#) DOI: [10.1007/s00467-004-1422-3](#)]
- 54 **Spivacow FR**, Pailler M, Martínez P. [Idiopathic hypercalciuria: can the diuretics be avoided? *Medicina (B Aires)* 2019; **79**: 477-482 [PMID: [31829950](#)]
- 55 **Sakhaee K**, Maalouf NM, Kumar R, Pasch A, Moe OW. Nephrolithiasis-associated bone disease: pathogenesis and treatment options. *Kidney Int* 2011; **79**: 393-403 [PMID: [21124301](#) DOI: [10.1038/ki.2010.473](#)]
- 56 **Hall TJ**, Schaeuble M. Hydrochlorothiazide inhibits osteoclastic bone resorption in vitro. *Calcif Tissue Int* 1994; **55**: 266-268 [PMID: [7820777](#) DOI: [10.1007/BF00310404](#)]
- 57 **Caudarella R**, Vescini R, Rizzol E, Olivieri FM. The effect of Thiazides on Bone Markers, Bone Mineral Density and Fractures. *Clinic Rev Bone Miner Metab* 2015; **13**: 173-184 [DOI: [10.1007/s12018-015-9190-0](#)]
- 58 **Spivacow FR**, Negri AL, del Valle EE. Long Term Effect of Thiazides on Bone Mass in Women with Hypercalciuric Nephrolithiasis. *Nefrología Diálisis y Trasplante* 2013; **33**: 180-187
- 59 **Cheng L**, Zhang K, Zhang Z. Effectiveness of thiazides on serum and urinary calcium levels and bone mineral density in patients with osteoporosis: a systematic review and meta-analysis. *Drug Des Devel Ther* 2018; **12**: 3929-3935 [PMID: [30532521](#) DOI: [10.2147/DDDT.S179568](#)]
- 60 **van der Burgh AC**, Oliai Araghi S, Zillikens MC, Koromani F, Rivadeneira F, van der Velde N, Hoorn EJ, Uitterlinden AG, Ikram MA, Stricker BH. The impact of thiazide diuretics on bone mineral density and the trabecular bone score: the Rotterdam Study. *Bone* 2020; **138**: 115475 [PMID: [32531338](#) DOI: [10.1016/j.bone.2020.115475](#)]
- 61 **Reusz GS**, Dobos M, Vársárhelyi B, Sallay P, Szabó A, Horváth C, Byrd DJ, Thole HH, Tulassay T. Sodium transport and bone mineral density in hypercalciuria with thiazide treatment. *Pediatr Nephrol* 1998; **12**: 30-34 [PMID: [9502564](#) DOI: [10.1007/s004670050398](#)]

Prediction of mortality among patients with chronic kidney disease: A systematic review

Panupong Hansrivijit, Yi-Ju Chen, Kriti Lnu, Angkawipa Trongtorsak, Max M Puthenpura, Charat Thongprayoon, Tarun Bathini, Michael A Mao, Wisit Cheungpasitporn

ORCID number: Panupong Hansrivijit 0000-0002-5041-4290; Yi-Ju Chen 0000-0002-4367-5724; Kriti Lnu 0000-0001-5753-8301; Angkawipa Trongtorsak 0000-0003-1855-029X; Max M Puthenpura 0000-0002-3821-1095; Charat Thongprayoon 0000-0002-8313-3604; Tarun Bathini 0000-0002-3775-8689; Michael A Mao 0000-0003-1814-7003; Wisit Cheungpasitporn 0000-0001-9954-9711.

Author contributions: Hansrivijit P contributed to acquisition of data, analysis, and interpretation of data, drafting the article, and final approval; Chen YJ, Lnu K and Trongtorsak A contributed to acquisition of data, analysis of data, and drafting the article; Puthenpura MM contributed to acquisition of data and drafting the article; Thongprayoon C and Bathini T contributed to acquisition of data and final approval; Mao MA and Cheungpasitporn W contributed to interpretation of data, revising the article, and final approval.

Conflict-of-interest statement: The authors have declared no potential conflicts of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised

Panupong Hansrivijit, Yi-Ju Chen, Kriti Lnu, Department of Internal Medicine, UPMC Pinnacle, Harrisburg, PA 17104, United States

Angkawipa Trongtorsak, Department of Internal Medicine, Amita Health Saint Francis Hospital, Evanston, IL 60202, United States

Max M Puthenpura, Department of Medicine, Drexel University College of Medicine, Philadelphia, PA 19129, United States

Charat Thongprayoon, Wisit Cheungpasitporn, Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN 55905, United States

Tarun Bathini, Department of Internal Medicine, University of Arizona, Tucson, AZ 85721, United States

Michael A Mao, Division of Nephrology and Hypertension, Mayo Clinic, Jacksonville, FL 32224, United States

Corresponding author: Wisit Cheungpasitporn, FACP, FASN, FAST, Associate Professor, Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, United States. wcheungpasitporn@gmail.com

Abstract

BACKGROUND

Chronic kidney disease (CKD) is a common medical condition that is increasing in prevalence. Existing published evidence has revealed through regression analyses that several clinical characteristics are associated with mortality in CKD patients. However, the predictive accuracies of these risk factors for mortality have not been clearly demonstrated.

AIM

To demonstrate the accuracy of mortality predictive factors in CKD patients by utilizing the area under the receiver operating characteristic (ROC) curve (AUC) analysis.

METHODS

We searched Ovid MEDLINE, EMBASE, and the Cochrane Library for eligible articles through January 2021. Studies were included based on the following

according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Urology and nephrology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 21, 2021

Peer-review started: March 21, 2021

First decision: May 6, 2021

Revised: May 11, 2021

Accepted: July 23, 2021

Article in press: July 23, 2021

Published online: July 25, 2021

P-Reviewer: Liu JM, Patel J

S-Editor: Gao CC

L-Editor: Filipodia

P-Editor: Ma YJ



criteria: (1) Study nature was observational or conference abstract; (2) Study populations involved patients with non-transplant CKD at any CKD stage severity; and (3) Predictive factors for mortality were presented with AUC analysis and its associated 95% confidence interval (CI). AUC of 0.70-0.79 is considered acceptable, 0.80-0.89 is considered excellent, and more than 0.90 is considered outstanding.

RESULTS

Of 1759 citations, a total of 18 studies ($n = 14579$) were included in this systematic review. Eight hundred thirty two patients had non-dialysis CKD, and 13747 patients had dialysis-dependent CKD (2160 patients on hemodialysis, 370 patients on peritoneal dialysis, and 11217 patients on non-differentiated dialysis modality). Of 24 mortality predictive factors, none were deemed outstanding for mortality prediction. A total of seven predictive factors [N-terminal pro-brain natriuretic peptide (NT-proBNP), BNP, soluble urokinase plasminogen activator receptor (suPAR), augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure] were identified as excellent. Seventeen predictive factors were in the acceptable range, which we classified into the following subgroups: predictors for the non-dialysis population, echocardiographic factors, comorbidities, and miscellaneous.

CONCLUSION

Several factors were found to predict mortality in CKD patients. Echocardiography is an important tool for mortality prognostication in CKD patients by evaluating left atrial reservoir strain, systolic pulmonary artery pressure, diastolic function, and left ventricular mass index.

Key Words: Chronic kidney disease; End stage kidney disease; End stage renal disease; Dialysis; Mortality; Death; Predictors

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Although the current evidence has shown that several clinical factors are associated with mortality in chronic kidney disease (CKD), the accuracy of mortality prediction has not been clearly demonstrated. Our systematic review of studies that reported prognostic mortality factors using area under the receiver operating characteristic curve analysis in CKD patients provides an accuracy measurement. A total of 18 studies were identified. Eight hundred thirty two patients had non-dialysis CKD, and 13747 patients had end-stage kidney disease. Of 24 predictive factors, none were considered outstanding for mortality prediction. A total of seven predictive factors were identified as excellent. Our review summarizes the current accuracy of prognostic factors for CKD mortality.

Citation: Hansrivijit P, Chen YJ, Lnu K, Trongtorsak A, Puthenpura MM, Thongprayoon C, Bathini T, Mao MA, Cheungpasitporn W. Prediction of mortality among patients with chronic kidney disease: A systematic review. *World J Nephrol* 2021; 10(4): 59-75

URL: <https://www.wjgnet.com/2220-6124/full/v10/i4/59.htm>

DOI: <https://dx.doi.org/10.5527/wjn.v10.i4.59>

INTRODUCTION

Chronic kidney disease (CKD) is defined by the presence of kidney damage (such as hematuria or structural abnormalities), an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m², or albuminuria of greater than 30 mg in 24 h with duration of more than 3 mo[1]. The prevalence of CKD ranges from 8% to 16% of the population worldwide[2,3]. CKD is more prevalent in low- and middle-income countries compared with high-income countries[4]. With the increasing prevalence of hypertension and diabetes, it is projected that CKD prevalence in adults over 30-years-old will increase from 14.4% in 2020 to 16.7% in 2030[5]. Moreover, in the general

population of the United States, the average GFR decline rate is approximately 1 mL/min per 1.73 m² per year[6,7] with a lifetime risk of developing CKD (as defined by eGFR less than 60 mL/min per 1.73 m²) of more than 50%[8].

Progression of CKD has been associated with significantly increased adverse clinical outcomes, such as end-stage kidney disease (ESKD), dialysis dependence, cardiovascular events, and all-cause mortality[9,10]. Tonelli *et al*[11] conducted a meta-analysis of 38 studies that included over 1.3 million participants. They showed that the absolute risk for death increased exponentially with decreasing kidney function[11]. Several risk factors have been identified to predict mortality in CKD patients. One meta-analysis demonstrated that age, diabetes, previous cardiovascular disease, adiponectin, and C-reactive protein are all risk factors for mortality in dialysis patients [12]. Alternatively, an analysis of the Cleveland Clinic CKD Registry of 621 CKD patients with age > 65 years showed that increasing age, congestive heart failure, absence of arteriovenous fistula, and lack of nephrology care prior to dialysis initiation were significant risk factors for increased 1-year mortality after dialysis initiation[13]. However, data on mortality risk factors for non-dialysis dependent CKD patients are limited.

Nearly all of the available evidence has reported their findings using regression analysis. Thus, the accuracy of mortality prediction has not been clearly demonstrated. In this study, we conducted a systematic review of studies that utilized associated area under the receiver operating characteristic (ROC) curve (AUC) analysis to report predictive factors for mortality in CKD patients. This method allows the reader to assess the predictive accuracy of distributional models in comparison with regression analyses[14]. Our findings would help guide the future design of an accurate mortality risk calculator for CKD patients.

MATERIALS AND METHODS

Search strategy

This manuscript follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis)[15] statement as well as MOOSE (Meta-analysis of Observational Studies in Epidemiology)[16] guidelines. A systematic search was conducted through Ovid MEDLINE, EMBASE, and the Cochrane Library from each respective database inception to January 2021. The domain for the systematic search on Cochrane Library included PubMed, EMBASE, ClinicalTrials.gov, and International Clinical Trial Registry Platform (ICTRP). The following search terms were used: ("chronic kidney disease" OR "CKD" OR "end-stage kidney disease" OR "ESKD" OR "end-stage renal disease" OR "ESRD") AND ("mortality" OR "death" OR "survival") AND ("area under curve" OR "AUC"). The detailed search strategy for each database is summarized in [Supplementary material](#), Appendix 1. No language restrictions were applied during the systematic search.

Inclusion criteria

The eligibility of each study was determined by the following inclusion criteria: (1) The study nature was observational or conference abstract; (2) Study populations involved patients with non-transplant CKD at any CKD stage severity; and (3) Predictive factors for mortality were presented with AUC analysis and its associated 95% confidence interval (CI). Case reports, case series, review articles, or articles concerning pediatric patients were excluded. Study eligibility was independently evaluated by two investigators (Hansrivijit P and Chen YJ). Disagreements were resolved by mutual consensus among all authors. The quality of each study was appraised using the Newcastle-Ottawa quality scale which assesses six components: (1) representativeness of the subjects, (2) ascertainment of the exposure, (3) demonstration of the outcome of interest was not present at the start of study, (4) assessment of outcome, (5) follow-up duration period was long enough for the outcome to occur, and (6) adequate follow-up duration.

Review process and data extraction

The titles and abstracts of all references were screened (Hansrivijit P and Chen YJ) prior to proceeding with full-text review. The full-text of the selected screened articles were then reviewed to determine their eligibility for inclusion into the systematic review. A standardized data collection form was invented to extract the following information from included study: first author's name, year of publication, country of origin, study design, subject(s), sample size, age, male sex, AUC and its 95%CI, and

follow-up duration. Full articles or conference abstracts that reported the AUC without 95%CI were excluded. An AUC of 1.0 represents the ideal predictor with a 100% sensitivity and 0% false positive rate. Thus, in this mortality model, factors with AUC closer to 1.0 represented a better predictor for mortality, with AUC of 0.70-0.79 considered acceptable, 0.80-0.89 considered excellent, and more than 0.90 considered outstanding[17,18].

RESULTS

Study characteristics

A total of 1759 citations underwent three passes of article screening. After duplicates were removed, another 1665 irrelevant articles were excluded after the title and abstract were screened. The methods and results of the remaining 94 articles were then evaluated for eligibility in accordance with the inclusion criteria. Only 31 articles passed this stage to undergo full-text review. A final total of 18 studies from 2004 to 2021 consisting of 14579 subjects were included in this systematic review. **Figure 1** provides a flowchart of the literature search and study selection. All studies were observational in nature (retrospective in 33.3% and prospective in 66.7%). The median age was 62.0 ($\pm$ 4.1) years, and 57.3% were male. The median duration of follow-up was 2.0 ($\pm$ 1.1) years. **Table 1** describes the included study characteristics and results. The risk of bias assessment is shown in **Supplementary Table 1**.

Study population

Of 14579 patients from 18 studies, 832 patients had non-dialysis CKD, and 13,747 patients had dialysis-dependent CKD. Among studies that included dialysis-dependent CKD patients, 2160 patients required hemodialysis (HD) and 370 patients required peritoneal dialysis (PD). The remaining 11217 patients (from four studies) had been composed of a non-differentiated mixed population of HD and PD patients. **Figure 2** illustrates the study population classification.

Predictive factors for mortality

A total of 24 predictive factors for mortality were identified. We classified these factors into three categories depending on their AUCs. None had an AUC greater than 0.90, which is considered outstanding for mortality prediction. The majority ($n = 17$) were in the acceptable range (AUCs 0.70-0.79). A total of seven predictive factors were identified as excellent (AUCs 0.80-0.89). **Table 2** shows the predictive factors for mortality based on the population studied.

DISCUSSION

Excellent predictors (AUC 0.80-0.89)

N-terminal pro-brain natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP) were found to be excellent predictors of mortality in dialysis patients[22,24]. In the general population, numerous factors such as age, female sex, and obesity can influence NT-proBNP level separate from heart failure[37]. BNP is eliminated by three main mechanisms: enzymatic metabolism, clearance through receptors, and urinary excretion[22]. Both BNP and NT-proBNP can be elevated in dialysis patients due to poor renal clearance, concomitant heart disease, heart failure, and volume expansion [38,39]. The mechanisms underlying the link between elevated BNP and NT-proBNP with increased mortality have not been fully established. One study suggested that chronic HD induces recurrent transient episodes of myocardial ischemia that result in myocardial stunning, hibernation, and remodeling[40]. Burton *et al*[40] described in this study that the decline in cardiac function and cardiac stunning were correlated with increasing BNP levels. These myocardial changes likely have a causative pathophysiologic role in the high cardiovascular complication rates and deaths in HD patients.

Soluble urokinase plasminogen activator receptor (suPAR) and C-reactive protein (CRP) were also excellent predictors for mortality in dialysis patients[29,36]. SuPAR is a proteolytic cleavage product of the glycosyl-phosphatidylinositol anchor of the urokinase plasminogen activator receptor expressed on immune and endothelial cells [41]. The concentration of suPAR is low in healthy individuals, but it becomes elevated in the presence of infection or inflammatory diseases[41]. Observational studies of

Table 1 Study characteristics

Ref.	Country	Study type	n	Subject	Age, yr	Male, %	AUC for mortality (95%CI)	Follow-up
Dara <i>et al</i> [19], 2004	United States	Retrospective	476	HD patients	66	58	APACHE III on hospital mortality 0.76 (0.66-0.84) and 30-d mortality 0.78 (0.68-0.86); SOFA score on hospital mortality 0.65 (0.55-0.75) and 30-d mortality 0.66 (0.55-0.76)	-
Miskulin <i>et al</i> [20], 2004	United States	Prospective	1779	Outpatient dialysis patients	62	53	ICED 0.72 (0.69-0.75); CCI 0.67 (0.65-0.70); Wright- Khan indices 0.68 (0.65-0.70); Davies indices 0.68 (0.65-0.70)	1 yr
Wang <i>et al</i> [21], 2007	Hong Kong	Prospective	238	ESRD on continuous PD	55.7	51.3	cTnT 0.774 (0.706-0.841); High sensitivity CRP 0.691 (0.614-0.768)	3 yr
Sun <i>et al</i> [22], 2008	China	Prospective	217	HD patients	65.4	62.2	BNP on CV events 0.61 (0.57-0.70); NT-proBNP on CV events 0.83 (0.75-0.91)	2 yr
Selim <i>et al</i> [23], 2010	Macedonia	Prospective	125	HD patients	48.8	-	BNP > 1200 pg/mL on CV mortality 0.612 (0.473-0.750); NT-proBNP > 10000 pg/mL on CV mortality 0.747 (0.677-0.816)	2 yr
Breidthardt <i>et al</i> [24], 2011	Switzerland	Retrospective	113	HD patients	67.9	60	BNP: all-cause mortality 0.70 (0.60-0.81); BNP: CV mortality 0.82 (0.73-0.90)	735 d
Tomaszuk-Kazberuk <i>et al</i> [25], 2011	Poland	Prospective	39	HD patients	59	63.8	Perfusion defects on MCE for death 0.752 (0.582-0.878)	3 yr
Chiang <i>et al</i> [26], 2016	Taiwan	Prospective	132	ESRD patients on PD	53.7	47.0	Short-term detrended fluctuation analysis (DFA α 1) < 0.95-0.761 (0.617-0.905)	34 mo
Sato <i>et al</i> [27], 2017	Japan	Retrospective	302	HD patients	63.4	65.4	Neutrophil-lymphocyte ratio for 1-yr mortality 0.791 (0.602-0.980)	1 yr
Wang <i>et al</i> [28], 2018	China	Prospective	300	CKD 3-5	60	53.6	UPCR for mortality 0.78 (0.72-0.84); eGFR for mortality 0.75 (0.69-0.81); Mitral E/E' ratio for mortality 0.74 (0.67-0.80); LV mass index for mortality 0.72 (0.65-0.79); LVEF for mortality 0.50 (0.42-0.58)	68 mo
Wlazeł <i>et al</i> [29], 2018	Poland	Prospective	64	HD patients	66	66	SuPAR 0.84 (0.7-0.94)	3 yr
Danial <i>et al</i> [30], 2019	Malaysia	Retrospective	160	CKD 3-5 with adverse drug reaction	-	57.5	Mortality risk score model 0.789 (0.700-0.878)	Few weeks (until end date of ADRs)
Jagadeswaran <i>et al</i> [31], 2019	India	Prospective	129	Pre-dialysis CKD 3-5	50.6	51.2	Malnutrition inflammation score for mortality 0.709 (0.604-0.815)	36 mo
Mukai <i>et al</i> [32], 2019	Sweden	Prospective	261	CKD 5 (both dialysis and non-dialysis)	56	66	Skin autofluorescence for all-cause mortality 0.78 (0.71-0.86); Augmentation index for all-cause mortality 0.81 (0.75-0.87)	25 mo
Pladys <i>et al</i> [33], 2020	France	Retrospective	9052	ESRD on dialysis	68.4	-	Rennes score model 1(REIN and SNDS data) 0.789 (0.761-0.816); Model 2 (REIN data only) 0.794 (0.768-0.821); Wright classification 0.631 (0.621-0.639); Modified CCI 0.703 (0.689-0.716)	1 yr
Shahidi <i>et al</i> [34], 2020	Iran	Retrospective	824	HD patients	57.9	61.8	Hemoglobin change on mortality 0.61 (0.56-0.65)	24.08 mo
Gan <i>et al</i> [35], 2021	Australia	Prospective	243	CKD 3-4	65.6	62.6	Left atrial reservoir strain for CV death 0.84 (0.76-0.90)	3.9 yr
Rroji <i>et al</i> [36], 2021	Albania	Prospective	125	ESRD on dialysis	52.4	60.0	CRP on CV mortality 0.80 (0.73-0.92); Left ventricular mass index on CV mortality 0.76 (0.65-0.88); Ratio of early mitral inflow velocity/annular diastolic velocity	2 yr

(E/E') on CV mortality 0.75 (0.64-0.86); Systolic pulmonary artery pressure on CV mortality 0.80 (0.68-0.92); Pulse pressure on CV mortality 0.72 (0.60-0.84)

APACHE: Acute physiology and chronic health evaluation; AUC: Area under receiver operating characteristic curve; BMI: Body mass index; BNP: Brain natriuretic peptide; CAPD: Continuous ambulatory peritoneal dialysis; CCI: Charlson Comorbidity Index; CKD: Chronic kidney disease; CRP: C-reactive protein; CI: Confidence interval; cTnT: Cardiac troponin T; CV: Cardiovascular; E/E': Ratio of early inflow velocity/annular diastolic velocity; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; HD: Hemodialysis; ICED: Index of coexisting disease; LV: Left ventricular; MCE: Myocardial contrast echocardiography; ND: Non-dialysis; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAP: Pulmonary artery pressure; PD: Peritoneal dialysis; REIN: Renal epidemiology and information network; SOFA: Sequential organ failure assessment; SNDS: French national health insurance information system; SuPAR: Soluble urokinase plasminogen activator receptor; UPCr: Urine protein creatinine ratio.

dialysis patients have shown that higher suPAR levels are detected in patients that have severe angiographic coronary artery disease[29,42] or after cardiovascular events, both of which are associated with significantly increased cardiovascular death[43]. Increased suPAR levels are also associated with end-organ fibrosis, such as cirrhosis [44,45] and focal segmental glomerulosclerosis[46]. Similarly, CRP is a nonspecific acute phase reactant that can be elevated in the setting of infection or inflammatory processes[47]. Higher CRP levels are associated with pulmonary hypertension, which could represent crosstalk between inflammatory cells and pulmonary wall components[36,48,49]. Moreover, a population-based study demonstrated that CRP is independently associated with elevated parathyroid hormone levels (PTH) and increased mortality[50]. Elevated PTH in CKD patients can lead to renal osteodystrophy and accelerated vascular calcification. The associations between suPAR, CRP, and increased death suggest that these markers show promise for use as standard CKD mortality predictors in the future.

Echocardiography has been shown as a useful tool in the assessment of mortality risk in CKD patients. Gan *et al*[35] have demonstrated that impaired left atrial reservoir strain (LASr) is the best predictor of adverse cardiovascular outcomes in CKD stage 3-4 patients. In this assessment, the left atrium is divided into a total of 12 segments: six segments each from the apical four- and two-chamber views. LASr is measured from the average peak systolic strain from the 12 segments[35]. Impaired LASr is defined as $\leq 23\%$, based on a previously reported lower limit of reference value[51]. A few hypotheses have been postulated to link impaired LASr and mortality in the CKD population. First, the left atrium may be more predictive for mortality because it is a thin-walled chamber and may exhibit earlier alterations before the left ventricle[51]. Second, alterations of LASr irrespective of left ventricular (LV) function have been noted in heart failure with preserved ejection fraction[52], further highlighting it as a more sensitive marker. The underlying mechanisms for reduced LASr are believed to be a consequence of atrial fibrosis, which could be accelerated in the setting of CKD due to the attendant high systemic inflammatory state[53,54]. These potential pathophysiologic mechanisms may explain the significance of reduced LASr as an early indicator for poor outcomes in non-dialysis CKD patients.

Roji *et al*[36] added that systolic pulmonary artery pressure (PAP) is predictive for mortality in dialysis patients. Other studies have concordantly shown that pulmonary hypertension (PH) confers a significant mortality risk in dialysis patients[55,56]. The prevalence of PH increases with CKD severity[55], and several studies have proposed mechanisms for the association between PH and CKD for both non-dialysis and dialysis patients. Arteriovenous fistulas for dialysis access and exposure to bio-incompatible dialysis membranes are a few of these factors that could increase the risk for PH in CKD patients[48,57]. The latter causes neutrophil activation that subsequently migrates to the lungs, resulting in increased pulmonary inflammation and vascular resistance[57]. For non-dialysis CKD patients, CKD itself can pathophysiologically directly incite pulmonary circulatory dysfunction and remodeling through uremic toxins, systemic inflammation, altered vasoregulation and endothelial dysfunction[48]. Altogether, prompt detection of PH *via* measurement of the systolic PAP could result in earlier intervention in order to prevent excess mortality in CKD patients.

Augmentation index (AIx) was predictive of mortality in CKD patients[32]. AIx was derived from the arterial pulse wave analysis using a tonometry-based SphygmoCor device[32]. Augmentation pressure (AP) is defined as the maximum systolic pressure subtracted from the inflection point pressure (the merging of incident and the reflected wave). AIx is defined as AP divided by pulse pressure (PP), presented as a percentage.

Table 2 Predictive factors for mortality in chronic kidney disease patients

AUC range	Interpretation	Predictive factors (AUC)	Subjects	Ref.
≥ 0.90	Outstanding	-	-	-
0.80-0.89	Excellent	NT-proBNP (0.83)	HD	Sun <i>et al</i> [22]
		BNP (0.82)	HD	Breidthardt <i>et al</i> [24]
		SuPAR (0.84)	HD	Wlazeł <i>et al</i> [29]
		Augmentation index (0.81)	ND, HD, PD	Mukai <i>et al</i> [32]
		Left atrial reservoir strain (0.84)	ND	Gan <i>et al</i> [35]
		CRP (0.80)	HD, PD	Rroji <i>et al</i> [36]
		Systolic PAP (0.80)	HD, PD	Rroji <i>et al</i> [36]
0.70-0.79	Acceptable	APACHE III (0.76)	HD	Dara <i>et al</i> [19]
		ICED (0.72)	HD, PD	Miskulin <i>et al</i> [20]
		cTnT (0.77)	PD	Wang <i>et al</i> [21],
		NT-proBNP > 10000 pg/mL (0.75)	HD	Sun <i>et al</i> [22]
		MCE perfusion defect (0.75)	HD	Tomaszuk-Kazberuk <i>et al</i> [25]
		DFA1 < 0.95 (0.76)	PD	Chiang <i>et al</i> [26]
		Neutrophil/lymphocyte ratio (0.79)	HD	Sato <i>et al</i> [27]
		UPCR (0.78)	ND	Wang <i>et al</i> [28]
		eGFR (0.75)	ND	Wang <i>et al</i> [28]
		Mitral E/E' ratio (0.74, 0.75)	ND, HD, PD	Wang <i>et al</i> [28] and Rroji <i>et al</i> [36]
		LV mass index (0.72, 0.76)	ND, HD, PD	Wang <i>et al</i> [28] and Rroji <i>et al</i> [36]
		Mortality risk score (0.79)	ND	Danial <i>et al</i> [30]
		Malnutrition inflammation score (0.71)	ND	Jagadeswaran <i>et al</i> [31]
		Skin autofluorescence (0.78)	ND, HD, PD	Mukai <i>et al</i> [32]
		Rennes score (0.79)	HD, PD	Pladys <i>et al</i> [33]
		Modified CCI (0.70)	HD, PD	Pladys <i>et al</i> [33]
		Pulse pressure (0.72)	HD, PD	Rroji <i>et al</i> [36]

APACHE: Acute physiology and chronic health evaluation; AUC: Area under receiver operating characteristic curve; BMI: Body mass index; BNP: Brain natriuretic peptide; CAPD: Continuous ambulatory peritoneal dialysis; CCI: Charlson Comorbidity Index; CKD: Chronic kidney disease; CRP: C-reactive protein; CI: Confidence interval; cTnT: Cardiac troponin T; CV: Cardiovascular; E/E': Ratio of early inflow velocity/annular diastolic velocity; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; HD: Hemodialysis; ICED: Index of coexisting disease; LV: Left ventricular; MCE: Myocardial contrast echocardiography; ND: Non-dialysis; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAP: Pulmonary artery pressure; PD: Peritoneal dialysis; REIN: Renal epidemiology and information network; SOFA: Sequential organ failure assessment; SNDS: French national health insurance information system; SuPAR: Soluble urokinase plasminogen activator receptor; UPCR: Urine protein creatinine ratio.

This index represents arterial stiffness, which could be a result of various patho-physiologic mechanisms. For example, fibrosis, disruption of elastin fibers, calcification, or diffusion of macromolecules within arterial walls are potential contributors [32]. Although AIx is useful in predicting mortality in CKD patients, given the invasive nature of this procedure, the clinical use of this parameter to monitor and prognosticate outcomes in the ambulatory setting is limited.

Acceptable predictors (AUC 0.70-0.79)

Non-dialysis population: Several predictive factors for mortality have been identified among non-dialysis CKD participants. Urine protein creatinine ratio (UPCR), eGFR, mortality risk score and malnutrition inflammation score (MIS) have been demonstrated to be predictive of mortality in this patient population[28,30,31]. It is thus not surprising that Wang *et al*[21] reported that UPCR and eGFR are predictive of

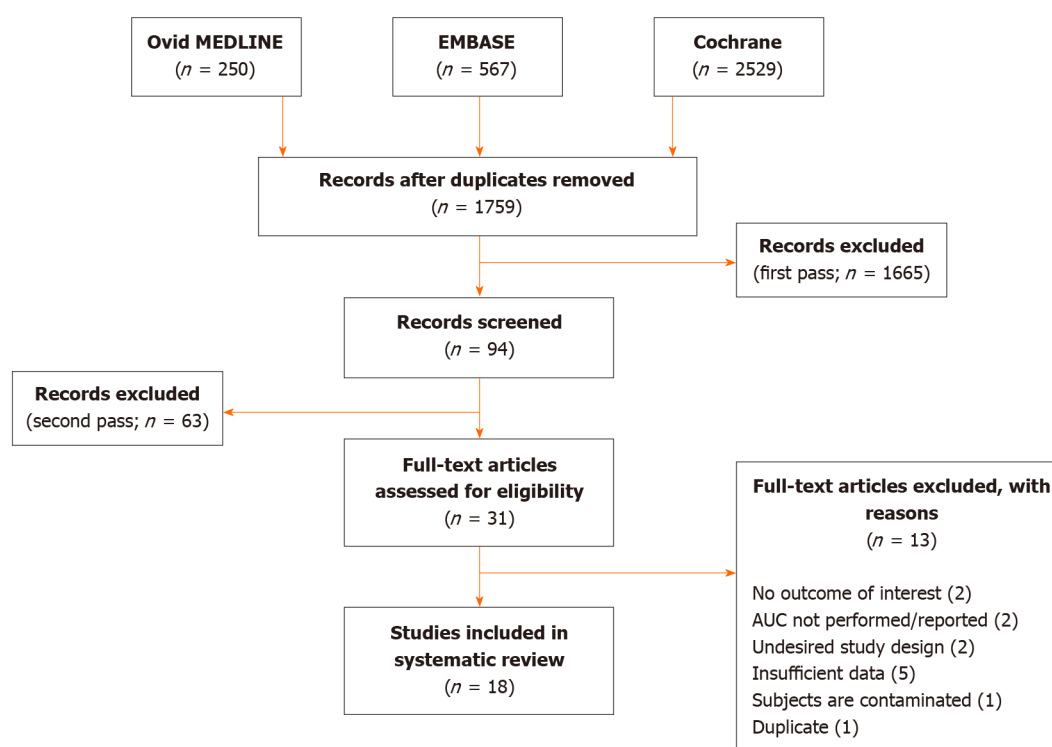


Figure 1 Flowchart of the literature search and study selection. “Undesired study design” includes non-human studies ($n = 2$); “Insufficient data” includes conference abstracts that reported only area under the receiver operating characteristic curve (AUC) without 95% confidence interval ($n = 5$); “Subjects are contaminated” refers to a study that has mixed chronic kidney disease (CKD) and non-CKD subjects ($n = 1$).

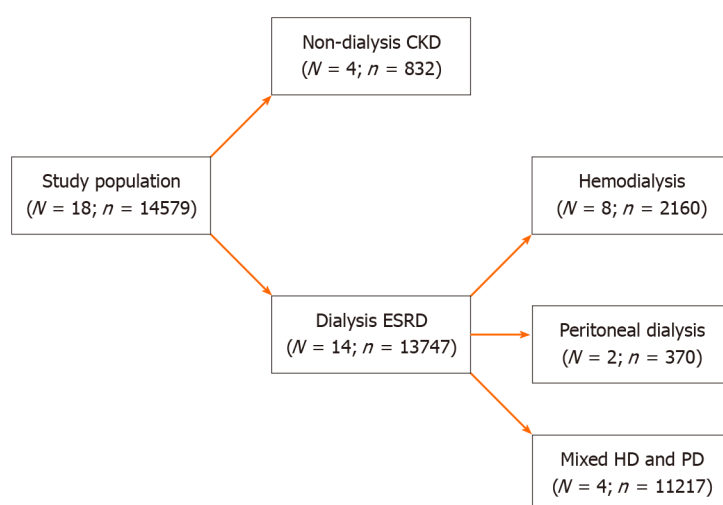


Figure 2 Algorithm of study population classification. CKD: Chronic kidney disease; ESRD: End-stage renal disease; HD: Hemodialysis; N: Number of population classification; PD: Peritoneal dialysis.

mortality among CKD patients. The presence of proteinuria in CKD patients has been widely associated with an increased risk of CKD progression and death[58]. Similarly, eGFR decline represents progression of CKD severity, which independently confers a significantly increased mortality risk[59,60]. Renal interstitial fibrosis/scarring and tubular atrophy are consistent with GFR decline and degree of proteinuria[58]. Along with these changes, the tubular epithelial cells are stimulated to synthesize reactive oxygen species, which further attracts inflammatory cells and interstitial myofibroblasts, leading to more fibrosis and scarring[58]. These interstitial changes are associated with CKD progression, which could indirectly increase mortality[58]. Thus, early interventions aiming to prevent proteinuria and CKD progression are essential for reducing mortality in CKD patients.

In 2019, Danial *et al*[30] developed a mortality risk score for CKD patients. In this study, the authors investigated mortality from adverse drug reactions (ADRs) that specifically occurred in CKD patients. The mortality risk prediction model included the following variables: (1) History of heart disease; (2) Dyslipidemia; (3) Electrolyte imbalance; (4) Psychotic agents; (5) Creatine kinase; (6) Total number of medications; and (7) Conservative management (how the treatment was provided to subjects with ADR)[30]. The authors noted that these clinical factors are easily obtained in clinical practice, and this score allowed preemptive identification of CKD patients at risk of ADR-associated mortality. These patients may thus have a significant benefit with early clinical intervention and medication adjustment. However, this model has not been proven to be predictive of mortality outside the scope of ADR, and consequently, its applicability in general CKD patients may be limited.

MIS is another mortality risk predictor tool for both pre-dialysis and dialysis-dependent CKD patients. The MIS consists of ten elements obtained from the past medical history, physical examination, body mass index, and laboratory indices[61]. In 2001, Kalantar-Zadeh *et al*[61] demonstrated that the MIS correlated with morbidity and mortality in maintenance HD patients. Later, Jagadeswaran *et al*[31] applied MIS to a pre-dialysis Indian population and found that MIS had a 56.5% sensitivity and 81% specificity (AUC 0.709; 95%CI: 0.604-0.815) for mortality prediction during a 36-mo follow-up. The mortality risk increased by 13.7% for each additional point in the MIS. These studies demonstrate the importance of malnutrition prevention for both pre-dialysis and dialysis-dependent CKD patients.

Echocardiographic factors: The ratios of early inflow velocity/annular diastolic velocity (E/E') through the mitral valve and the LV mass index are predictive of mortality in CKD patients, regardless of dialysis status[28,36]. Mitral E/E' ratio may be a marker of LV diastolic dysfunction[62] or a predictor of pulmonary hypertension [36]. Diastolic dysfunction has been associated with increased mortality in various CKD and non-CKD patient populations[63-65]. Similarly, an increased LV mass index represents LV hypertrophy, a well-established predictor for heart failure and death in CKD patients[66]. The 2013 European Society of Hypertension/European Society of Cardiology guidelines recommend performing echocardiography to refine cardiovascular risk assessment in hypertensive patients[67]. However, there are no recommendations specifically for CKD patients, despite studies showing an increased prevalence of LV hypertrophy with advancing CKD[68]. Our study further adds to the available evidence supporting echocardiography for mortality risk stratification in CKD patients. It should be highlighted that a combination of echocardiographic findings should be utilized to predict mortality in CKD patients, rather than isolated findings. This concept is supported by Tripepi *et al*[69] where the measurement of LV mass index in isolation does not provide significant prognostic value for CKD patients.

Real-time myocardial contrast echocardiography (MCE) is a non-invasive tool for assessment of myocardial ischemia in HD patients[70]. During this procedure, intravenous contrast is utilized to assess myocardial perfusion adequacy, which is defined as homogenous enhancement in > 50% of myocardial wall thickness for each segment[25]. One study showed that MCE and coronary angiography resulted in equal accuracy for anticipating combined cardiovascular endpoints and death[25]. The authors concluded that MCE is a safe and uncomplicated test that can aid in the selection of candidates for coronary revascularization. However, this data was limited to only HD patients. The utility of MCE should be confirmed in large multi-center studies of non-dialysis CKD patients.

Comorbidities: Comorbidities may serve as significant predictors for mortality in dialysis patients. Miskulin *et al*[20] investigated the index of coexisting disease (ICED) as an accurate mortality predictor in dialysis patients. In this study, ICED had greater discriminatory ability than other instruments. ICED is comprised of 19 medical conditions and 11 physical impairments; these are classified into four and three severity levels, respectively[20]. Another unique feature of ICED is the assessment of physical limitations, which has been shown as a strong prognostic factor in dialysis patients[71].

The Rennes comorbidity score and modified Charlson Comorbidity Index (CCI) have also been demonstrated to be predictive for mortality among dialysis patients [33]. The Rennes comorbidity score consists of seven components: Age, albumin level, cardiac, respiratory, and hepatic diseases, active malignancy, and walking disability [33]. Similarly, the modified CCI consists of 16 matrices composed of a wide range of medical comorbidities found in the original CCI plus patient's age[33]. Pladys *et al*[33] found that the original CCI (without including patient's age) had a low ability to

predict 1-year mortality. Surprisingly, the Rennes score resulted in a very impressive ability to predict 1-year mortality among dialysis patients despite its inclusion of only seven variables[33]. Altogether, we conclude that specific comorbidities are crucial in determining mortality risk among dialysis patients. Not unexpectedly, accuracy is improved by the consideration of several high-yield comorbidities rather than relying solely on one particular comorbidity.

Miscellaneous: Acute physiologic assessment and chronic health evaluation (APACHE) III is an acceptable predictor for hospital, and 30-d mortality among HD patients admitted to the intensive care unit (ICU)[19]. The APACHE III prognostic system was invented in 1991 and has been validated in several patient populations [72]. The APACHE III is calculated from clinical data obtained during the first 24 h of ICU admission. It consists of several components, including the primary reason for ICU admission, age, sex, race, preexisting comorbidities, and location prior to ICU admission[72]. Although several modifications have been made to the original APACHE score, only APACHE III has confirmed accuracy for mortality prediction in critically ill HD patients. Dara *et al*[19] compared the performance of APACHE III with the SOFA score. They found that APACHE III outperformed SOFA score for mortality prediction in critically ill HD patients. In our systematic review, this was the only study that focused on ICU patients.

The prognostic value of serological biomarkers, such as cardiac troponin T (cTnT) and NT-proBNP, for mortality in dialysis patients has been shown in observational studies[21,22]. As noted earlier, these biomarkers highlight the association between cardiac remodeling and death in dialysis patients. cTnT has been shown to predict mortality in PD patients independent of inflammation, residual renal function, and cardiac hypertrophy[21]. This was supported by the recent Netherland Cooperative Study on the Adequacy of Dialysis report, where the predictive power of cTnT for mortality is superior to other risk factors in a mixed population of HD and PD patients [73]. We suggest the use of cTnT for its prognostic value in at least PD patients due to its ease of testing.

Pre-dialysis neutrophil-lymphocyte ratio (NLR) is a novel and strong short-term predictor for all-cause mortality in HD patients[27]. NLR has been shown to have predictive utility in numerous disease states, including acute myocardial infarction and autoimmune disease[74,75]. NLR represents systemic inflammation, nutritional status, and atherosclerosis, which are all prevalent in CKD patients[76,77]. One single-center Japanese cohort revealed that NLR is superior to other generic biomarkers for 1-year survival among patients with ESKD due to diabetic nephropathy[27]. Although the usefulness of NLR has been widely studied in CKD patients, more data on its accuracy in diverse CKD patients are needed.

Skin autofluorescence (SAF) has been studied in healthy and uremic individuals[78-80]. SAF is predictive of microvascular disease progression, cardiovascular events, and nonspecific adverse clinical outcomes in diabetic and CKD patients regardless of dialysis status[79,81-84]. SAF is measured by illuminating approximately 1 cm² of skin surface with a 300-420 nm light source. SAF is calculated as the ratio between the emission light and reflected excitation light, multiplied by 100[32]. It is speculated that SAF represents the accumulation of advanced glycation end-products that cause collagen and elastin cross-linking, which can translate into increased arterial stiffness [85-87]. In 2019, Mukai *et al*[32] found that SAF in CKD patients is predictive of adverse clinical outcomes, including death. This study supports the association between SAF, arterial stiffness, and increased mortality in CKD patients.

PP is the difference between systolic and diastolic blood pressure. Rroji *et al*[36] demonstrated that PP has a significant impact on dialysis patient survival. In their study, patients with pulmonary hypertension had significantly higher PP compared with patients without pulmonary hypertension. The underlying mechanism between increased PP and death in CKD is not fully understood. However, we postulate that increased PP, either from a reduction of diastolic blood pressure or increase of systolic pressure, could increase morbidity and mortality due to reduced coronary perfusion pressure, elevated systemic vascular resistance, or decreased vascular compliance[88]. However, the predictive value of PP in CKD patients needs to be demonstrated in a larger study.

Detrended fluctuation analysis (DFA) of heart rate dynamics is another prognostic marker for PD patients. In recent years, heart rate variability derived from beat-to-beat heart rate dynamic monitors has been used as a surrogate marker of autonomic modulation in an effort to predict patient outcomes[89-91]. DFA is a scaling analysis method to represent the correlation properties of a signal[92]. This form of analysis permits the detection of long-range correlation embedded in non-stationary time series

[93]. To date, a few studies have demonstrated that DFA provides significant information on risk of cardiovascular events in heart failure and acute coronary syndrome patients[94,95]. In 2016, Chiang and colleagues showed that lower short-term DFA was predictive of total mortality in PD patients (median follow-up duration of 34 mo)[26]. They were the first study to measure and associate autonomic dysregulation with clinical outcomes in ESRD patients. Subsequent studies have shown consistent data obtained from the general population, where reduced DFA was associated with increased mortality *via* sudden cardiac death[96]. DFA shows potential promise in CKD patients since ESRD is associated with an overactive sympathetic nervous system[97]. This dysregulation results in an amplification of intracellular cyclic AMP (cAMP), which leads to an increase of the action potentials in the sinoatrial node[98]. These pathophysiological changes can be detected in the altered beat-to-beat variability[99]. However, DFA is a relatively new method of clinical analysis, and its application in other patient populations such as HD and non-dialysis CKD remains to be elucidated.

Limitations

Our study has several limitations that should be considered. First, the predictive factors reported in each study were not homogenous. They varied from each study due to study design and patient population. Because of this limitation, a meta-analysis, subgroup analysis, and test of homogeneity could not be performed. Second, all included studies were observational in nature, making them susceptible to selection bias. However, we minimized this bias by conducting the risk of bias assessment. Third, the pooled sample size for PD patients remained relatively small compared to non-dialysis CKD and HD patients. Generalization of our research findings to the PD population should be cautiously performed. Nonetheless, the findings from our research could be applied towards the design of future prospective studies with the goal of developing a prognostication scoring system for mortality in CKD patients. To date, the outstanding factors (defined by $AUC \geq 0.90$) for mortality prediction in CKD patients have yet to be discovered.

CONCLUSION

Several factors were identified to provide accurate predictions of mortality in CKD patients. Echocardiography is an important tool for mortality prognostication in CKD patients by evaluating LAsr, systolic PAP, mitral E/E' ratio, and LV mass index. NT-proBNP, BNP, suPAR, CRP, and AIX are excellent factors in mortality prediction among CKD patients.

ARTICLE HIGHLIGHTS

Research background

Chronic kidney disease (CKD) is a common medical condition that is increasing in prevalence. Understanding the accuracy of mortality risk factors in CKD patients could mitigate death.

Research motivation

Evidence has shown that several clinical factors are associated with mortality in CKD patients using regression analyses. However, the accuracy of these mortality predictive factors has not been clearly demonstrated.

Research objectives

To establish the accuracy of mortality predictive factors among CKD patients by utilizing the area under the receiver operating characteristic curve (AUC) analysis.

Research methods

Ovid MEDLINE, EMBASE, and the Cochrane Library were searched for eligible articles through January 2021. Only studies that reported their mortality predictive factors with AUC and 95% confidence interval were included. These factors were classified as acceptable, excellent, or outstanding based on their AUC.

Research results

Of 1759 citations, a total of 18 studies ($n = 14579$) were included in the systematic review. Eight hundred thirty two patients had non-dialysis CKD, and 13747 patients had dialysis-dependent CKD (2160 hemodialysis, 370 peritoneal dialysis, and 11217 undifferentiated modalities of dialysis). Of 24 predictive factors, none were considered outstanding for mortality prediction. A total of seven predictive factors (N-terminal pro-brain natriuretic peptide, brain natriuretic peptide, soluble urokinase plasminogen activator receptor, augmentation index, left atrial reservoir strain, C-reactive protein, and systolic pulmonary artery pressure) were identified as excellent. Seventeen predictive factors were in the acceptable range, which we classified into the following subgroups: predictors for the non-dialysis population, echocardiographic factors, comorbidities, and miscellaneous.

Research conclusions

This study determined several mortality risk factors for CKD patients that were deemed acceptable or excellent. Echocardiography is an important tool for mortality prognostication in CKD patients.

Research perspectives

The results of this study provide a preliminary perspective on the importance of identifying better prognostic factors for mortality in CKD patients. There is a lack of predictive risk factors with an AUC greater than 0.90. Currently identified mortality risk factors can be combined to create a risk calculator for CKD patients, which could be subsequently validated in future research.

REFERENCES

- 1 Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl.* 2017;7:1-59. *Kidney Int Suppl* (2011) 2017; 7: e1 [PMID: 30681074 DOI: 10.1016/j.kisu.2017.10.001]
- 2 Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; 298: 2038-2047 [PMID: 17986697 DOI: 10.1001/jama.298.17.2038]
- 3 Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW. Chronic kidney disease: global dimension and perspectives. *Lancet* 2013; 382: 260-272 [PMID: 23727169 DOI: 10.1016/S0140-6736(13)60687-X]
- 4 Mills KT, Xu Y, Zhang W, Bundy JD, Chen CS, Kelly TN, Chen J, He J. A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010. *Kidney Int* 2015; 88: 950-957 [PMID: 26221752 DOI: 10.1038/ki.2015.230]
- 5 Hoerger TJ, Simpson SA, Yarnoff BO, Pavkov ME, Rios Burrows N, Saydah SH, Williams DE, Zhuo X. The future burden of CKD in the United States: a simulation model for the CDC CKD Initiative. *Am J Kidney Dis* 2015; 65: 403-411 [PMID: 25468386 DOI: 10.1053/j.ajkd.2014.09.023]
- 6 Peralta CA, Vittinghoff E, Bansal N, Jacobs D Jr, Muntner P, Kestenbaum B, Lewis C, Siscovick D, Kramer H, Shlipak M, Bibbins-Domingo K. Trajectories of kidney function decline in young black and white adults with preserved GFR: results from the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Kidney Dis* 2013; 62: 261-266 [PMID: 23473985 DOI: 10.1053/j.ajkd.2013.01.012]
- 7 Grams ME, Rebholz CM, Chen Y, Rawlings AM, Estrella MM, Selvin E, Appel LJ, Tin A, Coresh J. Race, APOL1 Risk, and eGFR Decline in the General Population. *J Am Soc Nephrol* 2016; 27: 2842-2850 [PMID: 26966015 DOI: 10.1681/ASN.2015070763]
- 8 Grams ME, Chow EK, Segev DL, Coresh J. Lifetime incidence of CKD stages 3-5 in the United States. *Am J Kidney Dis* 2013; 62: 245-252 [PMID: 23566637 DOI: 10.1053/j.ajkd.2013.03.009]
- 9 van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, de Jong P, Gansevoort RT; Chronic Kidney Disease Prognosis Consortium, van der Velde M, Levey AS, de Jong PE, El-Nahas M, Eckardt KU, Kasiske BL, Ninomiya T, Chalmers J, Macmahon S, Tonelli M, Hemmelgarn B, Sacks F, Curhan G, Collins AJ, Li S, Chen SC, Hawaii Cohort KP, Lee BJ, Ishani A, Neaton J, Svendsen K, Mann JF, Yusuf S, Teo KK, Gao P, Nelson RG, Knowler WC, Bilo HJ, Joosten H, Kleefstra N, Groenier KH, Auguste P, Veldhuis K, Wang Y, Camarata L, Thomas B, Manley T. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int* 2011; 79: 1341-1352 [PMID: 21307840 DOI: 10.1038/ki.2010.536]
- 10 Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GW, Muntner P, Roderick P, Sairenchi T, Schöttker B, Shankar A, Shlipak M, Tonelli M, Townsend J, van Zuilen A, Yamagishi K, Yamashita K, Gansevoort R, Sarnak M, Warnock DG, Woodward M, Ärnlöv

- J; CKD Prognosis Consortium. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2015; **3**: 514-525 [PMID: 26028594 DOI: 10.1016/S2213-8587(15)00040-6]
- 11 **Tonelli M**, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006; **17**: 2034-2047 [PMID: 16738019 DOI: 10.1681/ASN.2005101085]
 - 12 **Ma L**, Zhao S. Risk factors for mortality in patients undergoing hemodialysis: A systematic review and meta-analysis. *Int J Cardiol* 2017; **238**: 151-158 [PMID: 28341375 DOI: 10.1016/j.ijcard.2017.02.095]
 - 13 **Saeed F**, Arrigain S, Schold JD, Nally JV Jr, Navaneethan SD. What are the Risk Factors for One-Year Mortality in Older Patients with Chronic Kidney Disease? *Nephron* 2019; **141**: 98-104 [PMID: 30463082 DOI: 10.1159/000494298]
 - 14 **Grund B**, Sabin C. Analysis of biomarker data: logs, odds ratios, and receiver operating characteristic curves. *Curr Opin HIV AIDS* 2010; **5**: 473-479 [PMID: 20978390 DOI: 10.1097/COH.0b013e32833ed742]
 - 15 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]
 - 16 **Stroup DF**, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: 10789670 DOI: 10.1001/jama.283.15.2008]
 - 17 **Mandrekar JN**. Receiver operating characteristic curve in diagnostic test assessment. *J Thorac Oncol* 2010; **5**: 1315-1316 [PMID: 20736804 DOI: 10.1097/JTO.0b013e3181ee173d]
 - 18 **Hosmer Jr DW**, Lemeshow S, Sturdivant RX. Applied Logistic Regression, Third Edition. John Wiley & Sons, 2013
 - 19 **Dara SI**, Afessa B, Bajwa AA, Albright RC. Outcome of patients with end-stage renal disease admitted to the intensive care unit. *Mayo Clin Proc* 2004; **79**: 1385-1390 [PMID: 15544016 DOI: 10.4065/79.11.1385]
 - 20 **Miskulin DC**, Martin AA, Brown R, Fink NE, Coresh J, Powe NR, Zager PG, Meyer KB, Levey AS; Medical Directors, Dialysis Clinic, Inc. Predicting 1 year mortality in an outpatient haemodialysis population: a comparison of comorbidity instruments. *Nephrol Dial Transplant* 2004; **19**: 413-420 [PMID: 14736967 DOI: 10.1093/ndt/gfg571]
 - 21 **Wang AY**, Lam CW, Wang M, Chan IH, Goggins WB, Yu CM, Lui SF, Sanderson JE. Prognostic value of cardiac troponin T is independent of inflammation, residual renal function, and cardiac hypertrophy and dysfunction in peritoneal dialysis patients. *Clin Chem* 2007; **53**: 882-889 [PMID: 17395709 DOI: 10.1373/clinchem.2006.078378]
 - 22 **Sun L**, Sun Y, Zhao X, Xu C, Chen D, Li L, Ma Y, Rong S, Mei C. Predictive role of BNP and NT-proBNP in hemodialysis patients. *Nephron Clin Pract* 2008; **110**: c178-c184 [PMID: 18957868 DOI: 10.1159/000167270]
 - 23 **Selim G**, Stojceva-Taneva O, Gelev S, Stojcev N, Dzekova P, Trajcevska L, Asani A, Busletic I, Pavleska S, Sikole A. A multi-biomarker approach for the prediction of cardiovascular mortality in hemodialysis patients. International Journal of Artificial Organs. Conference: 37th Annual European Society for Artificial Organs, ESAO Congress. Skopje Macedonia. 72/74 via Friuli, 20135 Milan, Italy: Wichtig editore, 2010
 - 24 **Breidthardt T**, Kalbermatter S, Socrates T, Noveanu M, Klima T, Mebazaa A, Mueller C, Kiss D. Increasing B-type natriuretic peptide levels predict mortality in unselected haemodialysis patients. *Eur J Heart Fail* 2011; **13**: 860-867 [PMID: 21628312 DOI: 10.1093/eurjhf/hfr057]
 - 25 **Tomaszuk-Kazberuk A**, Sobkowicz B, Malyszko J, Malyszko JS, Hirnle T, Dobrzycki S, Mysliwiec M, Musial WJ. Real-time myocardial contrast echocardiography as a useful tool to select candidates for coronary revascularization among patients with end-stage renal disease - a 3-year follow-up study. *Adv Med Sci* 2011; **56**: 207-214 [PMID: 22112432 DOI: 10.2478/v10039-011-0050-y]
 - 26 **Chiang JY**, Huang JW, Lin LY, Chang CH, Chu FY, Lin YH, Wu CK, Lee JK, Hwang JJ, Lin JL, Chiang FT. Detrended Fluctuation Analysis of Heart Rate Dynamics Is an Important Prognostic Factor in Patients with End-Stage Renal Disease Receiving Peritoneal Dialysis. *PLoS One* 2016; **11**: e0147282 [PMID: 26828209 DOI: 10.1371/journal.pone.0147282]
 - 27 **Sato H**, Takeuchi Y, Matsuda K, Kagaya S, Saito A, Fukami H, Ojima Y, Nagasawa T. Pre-Dialysis Neutrophil-Lymphocyte Ratio, a Novel and Strong Short-Term Predictor of All-Cause Mortality in Patients With Diabetic Nephropathy: Results From a Single-Center Study. *Ther Apher Dial* 2017; **21**: 370-377 [PMID: 28665535 DOI: 10.1111/1744-9987.12533]
 - 28 **Wang AYM**, Wu HH, Cai Q, Wong HKS, Lu X. Kidney and cardiac parameters-which are more important in predicting circulatory congestion and mortality risk in CKD Insights from a 5-year prospective analysis. *J Am Soc Nephrol* 2018; **29**: 416-417
 - 29 **Wlazel RN**, Szadkowska I, Bartnicki P, Rośniak-Bąk K, Rysz J. Clinical and prognostic usefulness of soluble urokinase plasminogen activator receptor in hemodialysis patients. *Int Urol Nephrol* 2018; **50**: 339-345 [PMID: 29313168 DOI: 10.1007/s11255-017-1778-5]
 - 30 **Danial M**, Hassali MA, Meng OL, Kin YC, Khan AH. Development of a mortality score to assess risk of adverse drug reactions among hospitalized patients with moderate to severe chronic kidney disease. *BMC Pharmacol Toxicol* 2019; **20**: 41 [PMID: 31287030 DOI: 10.1186/s40360-019-0318-6]

- 31 **Jagadeswaran D**, Indhumathi E, Hemamalini AJ, Sivakumar V, Soundararajan P, Jayakumar M. Inflammation and nutritional status assessment by malnutrition inflammation score and its outcome in pre-dialysis chronic kidney disease patients. *Clin Nutr* 2019; **38**: 341-347 [PMID: [29398341](#) DOI: [10.1016/j.clnu.2018.01.001](#)]
- 32 **Mukai H**, Svedberg O, Lindholm B, Dai L, Heimbürger O, Barany P, Anderstam B, Stenvinkel P, Qureshi AR. Skin autofluorescence, arterial stiffness and Framingham risk score as predictors of clinical outcome in chronic kidney disease patients: a cohort study. *Nephrol Dial Transplant* 2019; **34**: 442-448 [PMID: [29378035](#) DOI: [10.1093/ndt/gfx371](#)]
- 33 **Pladys A**, Vigneau C, Raffray M, Sautenet B, Gentile S, Couchoud C, Bayat S. Contribution of medico-administrative data to the development of a comorbidity score to predict mortality in End-Stage Renal Disease patients. *Sci Rep* 2020; **10**: 8582 [PMID: [32444698](#) DOI: [10.1038/s41598-020-65612-x](#)]
- 34 **Shahidi S**, Amooshahi M, Shekl Abadi E, Shekl Abadi R, Faghih N, Feizi A. SAT-221 Association of blood cell count, iron indices and hemoglobin level with mortality in hemodialysis patients. *Kidney Int Rep* 2020; **5**: S94-S95 [DOI: [10.1016/j.ekir.2020.02.236](#)]
- 35 **Gan GCH**, Kadappu KK, Bhat A, Fernandez F, Gu KH, Cai L, Byth K, Eshoo S, Thomas L. Left Atrial Strain Is the Best Predictor of Adverse Cardiovascular Outcomes in Patients with Chronic Kidney Disease. *J Am Soc Echocardiogr* 2021; **34**: 166-175 [PMID: [33223356](#) DOI: [10.1016/j.echo.2020.09.015](#)]
- 36 **Rroji M**, Cafka M, Seferi S, Seiti J, Barbullushi M, Goda A. The potential effect of cardiac function on pulmonary hypertension, other risk factors, and its impact on survival in dialysis patients. *Int Urol Nephrol* 2021; **53**: 343-351 [PMID: [33389501](#) DOI: [10.1007/s11255-020-02655-z](#)]
- 37 **Costello-Boerrigter LC**, Boerrigter G, Redfield MM, Rodeheffer RJ, Urban LH, Mahoney DW, Jacobsen SJ, Heublein DM, Burnett JC Jr. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. *J Am Coll Cardiol* 2006; **47**: 345-353 [PMID: [16412859](#) DOI: [10.1016/j.jacc.2005.09.025](#)]
- 38 **Goetze JP**, Jensen G, Møller S, Bendtsen F, Rehfeld JF, Henriksen JH. BNP and N-terminal proBNP are both extracted in the normal kidney. *Eur J Clin Invest* 2006; **36**: 8-15 [PMID: [16403004](#) DOI: [10.1111/j.1365-2362.2006.01594.x](#)]
- 39 **Haller C**, Zehelein J, Remppis A, Müller-Bardorff M, Katus HA. Cardiac troponin T in patients with end-stage renal disease: absence of expression in truncal skeletal muscle. *Clin Chem* 1998; **44**: 930-938 [PMID: [9590364](#)]
- 40 **Burton JO**, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol* 2009; **4**: 914-920 [PMID: [19357245](#) DOI: [10.2215/CJN.03900808](#)]
- 41 **Thuno M**, Macho B, Eugen-Olsen J. suPAR: the molecular crystal ball. *Dis Markers* 2009; **27**: 157-172 [PMID: [19893210](#) DOI: [10.3233/DMA-2009-0657](#)]
- 42 **Eapen DJ**, Manocha P, Ghasemzadeh N, Patel RS, Al Kassem H, Hammadah M, Veledar E, Le NA, Pielak T, Thorball CW, Velegraki A, Kremastinos DT, Lerakis S, Sperling L, Quyyumi AA. Soluble urokinase plasminogen activator receptor level is an independent predictor of the presence and severity of coronary artery disease and of future adverse events. *J Am Heart Assoc* 2014; **3**: e001118 [PMID: [25341887](#) DOI: [10.1161/JAHA.114.001118](#)]
- 43 **Meijers B**, Poesen R, Claes K, Dietrich R, Bammens B, Sprangers B, Naesens M, Storr M, Kuypers D, Evenepoel P. Soluble urokinase receptor is a biomarker of cardiovascular disease in chronic kidney disease. *Kidney Int* 2015; **87**: 210-216 [PMID: [24897037](#) DOI: [10.1038/ki.2014.197](#)]
- 44 **Koch A**, Voigt S, Kruschinski C, Sanson E, Dücker H, Horn A, Yagmur E, Zimmermann H, Trautwein C, Tacke F. Circulating soluble urokinase plasminogen activator receptor is stably elevated during the first week of treatment in the intensive care unit and predicts mortality in critically ill patients. *Crit Care* 2011; **15**: R63 [PMID: [21324198](#) DOI: [10.1186/cc10037](#)]
- 45 **Berres ML**, Schlosser B, Berg T, Trautwein C, Wasmuth HE. Soluble urokinase plasminogen activator receptor is associated with progressive liver fibrosis in hepatitis C infection. *J Clin Gastroenterol* 2012; **46**: 334-338 [PMID: [21934527](#) DOI: [10.1097/MCG.0b013e31822da19d](#)]
- 46 **Wei C**, El Hindi S, Li J, Fornoni A, Goes N, Sageshima J, Maiguel D, Karumanchi SA, Yap HK, Saleem M, Zhang Q, Nikolic B, Chaudhuri A, Daftarian P, Salido E, Torres A, Salifu M, Sarwal MM, Schaefer F, Morath C, Schwenger V, Zeier M, Gupta V, Roth D, Rastaldi MP, Burke G, Ruiz P, Reiser J. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med* 2011; **17**: 952-960 [PMID: [21804539](#) DOI: [10.1038/nm.2411](#)]
- 47 **Black S**, Kushner I, Samols D. C-reactive Protein. *J Biol Chem* 2004; **279**: 48487-48490 [PMID: [15337754](#) DOI: [10.1074/jbc.R400025200](#)]
- 48 **Kawar B**, Ellam T, Jackson C, Kiely DG. Pulmonary hypertension in renal disease: epidemiology, potential mechanisms and implications. *Am J Nephrol* 2013; **37**: 281-290 [PMID: [23548763](#) DOI: [10.1159/000348804](#)]
- 49 **Huertas A**, Tu L, Humbert M, Guignabert C. Chronic inflammation within the vascular wall in pulmonary arterial hypertension: more than a spectator. *Cardiovasc Res* 2020; **116**: 885-893 [PMID: [31813986](#) DOI: [10.1093/cvr/cvz308](#)]
- 50 **Cheng SP**, Liu CL, Liu TP, Hsu YC, Lee JJ. Association between parathyroid hormone levels and inflammatory markers among US adults. *Mediators Inflamm* 2014; **2014**: 709024 [PMID: [24782595](#) DOI: [10.1155/2014/709024](#)]

- 51 **Morris DA**, Takeuchi M, Krisper M, Köhncke C, Bekfani T, Carstensen T, Hassfeld S, Dorenkamp M, Otani K, Takigiku K, Izumi C, Yuda S, Sakata K, Ohte N, Tanabe K, Osmanoglou E, Kühnle Y, Dungen HD, Nakatani S, Otsuji Y, Haverkamp W, Boldt LH. Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: multicentre study. *Eur Heart J Cardiovasc Imaging* 2015; **16**: 364-372 [PMID: [25368210](#) DOI: [10.1093/ehjci/jeu219](#)]
- 52 **von Roeder M**, Rommel KP, Kowallick JT, Blazek S, Besler C, Fengler K, Lotz J, Hasenfuß G, Lücke C, Gutberlet M, Schuler G, Schuster A, Lurz P. Influence of Left Atrial Function on Exercise Capacity and Left Ventricular Function in Patients With Heart Failure and Preserved Ejection Fraction. *Circ Cardiovasc Imaging* 2017; **10** [PMID: [28360259](#) DOI: [10.1161/circimaging.116.005467](#)]
- 53 **Freed BH**, Shah SJ. Stepping Out of the Left Ventricle's Shadow: Time to Focus on the Left Atrium in Heart Failure With Preserved Ejection Fraction. *Circ Cardiovasc Imaging* 2017; **10** [PMID: [28360263](#) DOI: [10.1161/CIRCIMAGING.117.006267](#)]
- 54 **Rao AK**, Djamali A, Korcarz CE, Aeschlimann SE, Wolff MR, Stein JH. Left atrial volume is associated with inflammation and atherosclerosis in patients with kidney disease. *Echocardiography* 2008; **25**: 264-269 [PMID: [18307439](#) DOI: [10.1111/j.1540-8175.2007.00589.x](#)]
- 55 **Walther CP**, Nambi V, Hanania NA, Navaneethan SD. Diagnosis and Management of Pulmonary Hypertension in Patients With CKD. *Am J Kidney Dis* 2020; **75**: 935-945 [PMID: [32199709](#) DOI: [10.1053/j.ajkd.2019.12.005](#)]
- 56 **Tang M**, Batty JA, Lin C, Fan X, Chan KE, Kalim S. Pulmonary Hypertension, Mortality, and Cardiovascular Disease in CKD and ESRD Patients: A Systematic Review and Meta-analysis. *Am J Kidney Dis* 2018; **72**: 75-83 [PMID: [29429751](#) DOI: [10.1053/j.ajkd.2017.11.018](#)]
- 57 **Bolignano D**, Rastelli S, Agarwal R, Fliser D, Massy Z, Ortiz A, Wiecek A, Martinez-Castelao A, Covic A, Goldsmith D, Suleymanlar G, Lindholm B, Parati G, Sicari R, Gargani L, Mallamaci F, London G, Zoccali C. Pulmonary hypertension in CKD. *Am J Kidney Dis* 2013; **61**: 612-622 [PMID: [23164943](#) DOI: [10.1053/j.ajkd.2012.07.029](#)]
- 58 **Webster AC**, Nagler EV, Morton RL, Masson P. Chronic Kidney Disease. *Lancet* 2017; **389**: 1238-1252 [PMID: [27887750](#) DOI: [10.1016/S0140-6736\(16\)32064-5](#)]
- 59 **Eriksen BO**, Ingebrechtsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006; **69**: 375-382 [PMID: [16408129](#) DOI: [10.1038/sj.ki.5000058](#)]
- 60 **Patel AD**, Ibrahim M, Swaminathan RV, Minhas IU, Kim LK, Venkatesh P, Feldman DN, Minutello RM, Bergman GW, Wong SC, Singh HS. Five-year mortality outcomes in patients with chronic kidney disease undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2017; **89**: E124-E132 [PMID: [27519355](#) DOI: [10.1002/ccd.26664](#)]
- 61 **Kalantar-Zadeh K**, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 2001; **38**: 1251-1263 [PMID: [11728958](#) DOI: [10.1053/ajkd.2001.29222](#)]
- 62 **Obokata M**, Reddy YNV, Borlaug BA. Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction: Understanding Mechanisms by Using Noninvasive Methods. *JACC Cardiovasc Imaging* 2020; **13**: 245-257 [PMID: [31202759](#) DOI: [10.1016/j.jcmg.2018.12.034](#)]
- 63 **Tennøe AH**, Murbræck K, Andreassen JC, Fretheim H, Garen T, Gude E, Andreassen A, Aakhus S, Molberg Ø, Hoffmann-Vold AM. Left Ventricular Diastolic Dysfunction Predicts Mortality in Patients With Systemic Sclerosis. *J Am Coll Cardiol* 2018; **72**: 1804-1813 [PMID: [30286924](#) DOI: [10.1016/j.jacc.2018.07.068](#)]
- 64 **Jentzer JC**, Anavekar NS, Mankad SV, Khasawneh M, White RD, Barsness GW, Rabinstein AA, Kashani KB, Pislaru SV. Echocardiographic left ventricular diastolic dysfunction predicts hospital mortality after out-of-hospital cardiac arrest. *J Crit Care* 2018; **47**: 114-120 [PMID: [29945067](#) DOI: [10.1016/j.jcrc.2018.06.016](#)]
- 65 **Lassen MCH**, Sengeløv M, Qasim A, Jørgensen PG, Bruun NE, Olsen FJ, Fritz-Hansen T, Gislason G, Biering-Sørensen T. Ratio of Transmitral Early Filling Velocity to Early Diastolic Strain Rate Predicts All-Cause Mortality in Heart Failure with Reduced Ejection Fraction. *J Card Fail* 2019; **25**: 877-885 [PMID: [31336135](#) DOI: [10.1016/j.cardfail.2019.07.007](#)]
- 66 **Dubin RF**, Deo R, Bansal N, Anderson AH, Yang P, Go AS, Keane M, Townsend R, Porter A, Budoff M, Malik S, He J, Rahman M, Wright J, Cappola T, Kallem R, Roy J, Sha D, Shlipak MG; CRIC Study Investigators. Associations of Conventional Echocardiographic Measures with Incident Heart Failure and Mortality: The Chronic Renal Insufficiency Cohort. *Clin J Am Soc Nephrol* 2017; **12**: 60-68 [PMID: [28062676](#) DOI: [10.2215/CJN.02700316](#)]
- 67 **Mancia G**, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; **31**: 1281-1357 [PMID: [23817082](#) DOI: [10.1097/01.hjh.0000431740.32696.cc](#)]
- 68 **Park M**, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, Dries D, Xie D, Chen J, He J, Anderson A, Go AS, Shlipak MG; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol* 2012; **23**: 1725-1734 [PMID: [22935481](#) DOI: [10.1681/ASN.2012020145](#)]

- 69 **Tripepi G**, D'Arrigo G, Mallamaci F, London G, Tangri N, Hsu JY, Feldman HI, Zoccali C. Prognostic values of left ventricular mass index in chronic kidney disease patients. *Nephrol Dial Transplant* 2021; **36**: 665-672 [PMID: [31860093](#) DOI: [10.1093/ndt/gfz254](#)]
- 70 **Pérez de Isla L**, Rodrigo JL, Almería C, Pérez Ferro M, Serra V, Zamorano JL. Myocardial contrast echocardiography in coronary artery disease. *Eur J Echocardiogr* 2004; **5** Suppl 2: S11-S16 [PMID: [15698555](#) DOI: [10.1016/s1525-2167\(04\)80003-9](#)]
- 71 **McClellan WM**, Anson C, Birkeli K, Tuttle E. Functional status and quality of life: predictors of early mortality among patients entering treatment for end stage renal disease. *J Clin Epidemiol* 1991; **44**: 83-89 [PMID: [1986062](#) DOI: [10.1016/0895-4356\(91\)90204-m](#)]
- 72 **Knaus WA**, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; **100**: 1619-1636 [PMID: [1959406](#) DOI: [10.1378/chest.100.6.1619](#)]
- 73 **Havekes B**, van Manen JG, Krediet RT, Boeschoten EW, Vandenbroucke JP, Dekker FW; NECOSAD Study Group. Serum troponin T concentration as a predictor of mortality in hemodialysis and peritoneal dialysis patients. *Am J Kidney Dis* 2006; **47**: 823-829 [PMID: [16632021](#) DOI: [10.1053/j.ajkd.2006.01.019](#)]
- 74 **Ouellet G**, Malhotra R, Penne EL, Usuya L, Levin NW, Kotanko P. Neutrophil-lymphocyte ratio as a novel predictor of survival in chronic hemodialysis patients. *Clin Nephrol* 2016; **85**: 191-198 [PMID: [26951970](#) DOI: [10.5414/CN108745](#)]
- 75 **Uslu AU**, Küçük A, Şahin A, Ugan Y, Yılmaz R, Güngör T, Bağcı S, Küçükşen S. Two new inflammatory markers associated with Disease Activity Score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. *Int J Rheum Dis* 2015; **18**: 731-735 [PMID: [25900081](#) DOI: [10.1111/1756-185X.12582](#)]
- 76 **Turkmen K**, Ozcicek F, Ozcicek A, Akbas EM, Erdur FM, Tonbul HZ. The relationship between neutrophil-to-lymphocyte ratio and vascular calcification in end-stage renal disease patients. *Hemodial Int* 2014; **18**: 47-53 [PMID: [23819627](#) DOI: [10.1111/hdi.12065](#)]
- 77 **Agarwal R**, Light RP. Patterns and prognostic value of total and differential leukocyte count in chronic kidney disease. *Clin J Am Soc Nephrol* 2011; **6**: 1393-1399 [PMID: [21551023](#) DOI: [10.2215/CJN.10521110](#)]
- 78 **Meerwaldt R**, Graaff R, Oomen PHN, Links TP, Jager JJ, Alderson NL, Thorpe SR, Baynes JW, Gans ROB, Smit AJ. Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia* 2004; **47**: 1324-1330 [PMID: [15243705](#) DOI: [10.1007/s00125-004-1451-2](#)]
- 79 **Meerwaldt R**, Hartog JW, Graaff R, Huisman RJ, Links TP, den Hollander NC, Thorpe SR, Baynes JW, Navis G, Gans RO, Smit AJ. Skin autofluorescence, a measure of cumulative metabolic stress and advanced glycation end products, predicts mortality in hemodialysis patients. *J Am Soc Nephrol* 2005; **16**: 3687-3693 [PMID: [16280473](#) DOI: [10.1681/ASN.2005020144](#)]
- 80 **den Hollander NC**, Mulder DJ, Graaff R, Thorpe SR, Baynes JW, Smit GP, Smit AJ. Advanced glycation end products and the absence of premature atherosclerosis in glycogen storage disease Ia. *J Inher Metab Dis* 2007; **30**: 916-923 [PMID: [17570077](#) DOI: [10.1007/s10545-007-0507-0](#)]
- 81 **Lutgers HL**, Graaff R, Links TP, Ubink-Veltmaat LJ, Bilo HJ, Gans RO, Smit AJ. Skin autofluorescence as a noninvasive marker of vascular damage in patients with type 2 diabetes. *Diabetes Care* 2006; **29**: 2654-2659 [PMID: [17130200](#) DOI: [10.2337/dc05-2173](#)]
- 82 **McIntyre NJ**, Fluck RJ, McIntyre CW, Taal MW. Skin autofluorescence and the association with renal and cardiovascular risk factors in chronic kidney disease stage 3. *Clin J Am Soc Nephrol* 2011; **6**: 2356-2363 [PMID: [21885790](#) DOI: [10.2215/CJN.02420311](#)]
- 83 **Jiang J**, Chen P, Chen J, Yu X, Xie D, Mei C, Xiong F, Shi W, Zhou W, Liu X, Sun S, Zhang P, Yang X, Zhang Y, Liang X, Zhang Z, Lin Q, Yu Y, Miyata T, Tian J, Liang M, Luo W, Xu X, Hou F. Accumulation of tissue advanced glycation end products correlated with glucose exposure dose and associated with cardiovascular morbidity in patients on peritoneal dialysis. *Atherosclerosis* 2012; **224**: 187-194 [PMID: [22857897](#) DOI: [10.1016/j.atherosclerosis.2012.06.022](#)]
- 84 **Meerwaldt R**, Lutgers HL, Links TP, Graaff R, Baynes JW, Gans RO, Smit AJ. Skin autofluorescence is a strong predictor of cardiac mortality in diabetes. *Diabetes Care* 2007; **30**: 107-112 [PMID: [17192342](#) DOI: [10.2337/dc06-1391](#)]
- 85 **Aronson D**. Cross-linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of aging and diabetes. *J Hypertens* 2003; **21**: 3-12 [PMID: [12544424](#) DOI: [10.1097/00004872-200301000-00002](#)]
- 86 **Pischetsrieder M**. Chemistry of glucose and biochemical pathways of biological interest. *Perit Dial Int* 2000; **20** Suppl 2: S26-S30 [PMID: [10911639](#)]
- 87 **Sims TJ**, Rasmussen LM, Oxlund H, Bailey AJ. The role of glycation cross-links in diabetic vascular stiffening. *Diabetologia* 1996; **39**: 946-951 [PMID: [8858217](#) DOI: [10.1007/BF00403914](#)]
- 88 **Vidal-Petiot E**, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, Tendera M, Tavazzi L, Bhatt DL, Steg PG; CLARIFY Investigators. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. *Lancet* 2016; **388**: 2142-2152 [PMID: [27590221](#) DOI: [10.1016/S0140-6736\(16\)31326-5](#)]
- 89 **Oikawa K**, Ishihara R, Maeda T, Yamaguchi K, Koike A, Kawaguchi H, Tabata Y, Murotani N, Itoh H. Prognostic value of heart rate variability in patients with renal failure on hemodialysis. *Int J*

- Cardiol* 2009; **131**: 370-377 [PMID: [18199499](#) DOI: [10.1016/j.ijcard.2007.10.033](#)]
- 90 **Mylonopoulou M**, Tentolouris N, Antonopoulos S, Mikros S, Katsaros K, Melidonis A, Sevastos N, Katsilambros N. Heart rate variability in advanced chronic kidney disease with or without diabetes: midterm effects of the initiation of chronic haemodialysis therapy. *Nephrol Dial Transplant* 2010; **25**: 3749-3754 [PMID: [20466659](#) DOI: [10.1093/ndt/gfq226](#)]
 - 91 **Seely AJ**, Macklem PT. Complex systems and the technology of variability analysis. *Crit Care* 2004; **8**: R367-R384 [PMID: [15566580](#) DOI: [10.1186/cc2948](#)]
 - 92 **Peng CK**, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos* 1995; **5**: 82-87 [PMID: [11538314](#) DOI: [10.1063/1.166141](#)]
 - 93 **Hu K**, Ivanov PC, Chen Z, Carpena P, Stanley HE. Effect of trends on detrended fluctuation analysis. *Phys Rev E Stat Nonlin Soft Matter Phys* 2001; **64**: 011114 [PMID: [11461232](#) DOI: [10.1103/PhysRevE.64.011114](#)]
 - 94 **Ho KK**, Moody GB, Peng CK, Mietus JE, Larson MG, Levy D, Goldberger AL. Predicting survival in heart failure case and control subjects by use of fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. *Circulation* 1997; **96**: 842-848 [PMID: [9264491](#) DOI: [10.1161/01.cir.96.3.842](#)]
 - 95 **Huikuri HV**, Mäkikallio TH, Peng CK, Goldberger AL, Hintze U, Møller M. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation* 2000; **101**: 47-53 [PMID: [10618303](#) DOI: [10.1161/01.cir.101.1.47](#)]
 - 96 **Mäkikallio TH**, Huikuri HV, Mäkikallio A, Sourander LB, Mitrani RD, Castellanos A, Myerburg RJ. Prediction of sudden cardiac death by fractal analysis of heart rate variability in elderly subjects. *J Am Coll Cardiol* 2001; **37**: 1395-1402 [PMID: [11300452](#) DOI: [10.1016/s0735-1097\(01\)01171-8](#)]
 - 97 **Vonend O**, Rump LC, Ritz E. Sympathetic overactivity--the Cinderella of cardiovascular risk factors in dialysis patients. *Semin Dial* 2008; **21**: 326-330 [PMID: [18627567](#) DOI: [10.1111/j.1525-139X.2008.00456.x](#)]
 - 98 **Converse RL Jr**, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, Victor RG. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**: 1912-1918 [PMID: [1454086](#) DOI: [10.1056/NEJM199212313272704](#)]
 - 99 **Tulppo MP**, Kiviniemi AM, Hautala AJ, Kallio M, Seppänen T, Mäkikallio TH, Huikuri HV. Physiological background of the loss of fractal heart rate dynamics. *Circulation* 2005; **112**: 314-319 [PMID: [16009791](#) DOI: [10.1161/CIRCULATIONAHA.104.523712](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>



World Journal of *Nephrology*

World J Nephrol 2021 September 25; 10(5): 76-108



MINIREVIEWS

- 76 Serum phosphate and chronic kidney and cardiovascular disease: Phosphorus potential implications in general population

Raikou VD

- 88 Trends in pediatric nephrotic syndrome

Tamura H

CASE REPORT

- 101 Lemierre's syndrome caused by *Klebsiella pneumoniae*: A case report

Hwang SY, Shin SJ, Yoon HE

ABOUT COVER

Editorial Board Member of *World Journal of Nephrology*, Marcelo R. Choi, MD, PhD, MSc, Professor, Department of Anatomy and Histology, Faculty of Pharmacy and Biochemistry, University of Buenos Aires, Junin 956, Buenos Aires 1113, Argentina. mchoi@ffyb.uba.ar

AIMS AND SCOPE

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

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc.*

INDEXING/ABSTRACTING

The WJN is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Rui-Rui Wu, Production Department Director: Yu-Jie Ma, Editorial Office Director: Yan-Xia Xing.

NAME OF JOURNAL

World Journal of Nephrology

ISSN

ISSN 2220-6124 (online)

LAUNCH DATE

February 6, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Li Zuo, Ying-Yong Zhao

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2220-6124/editorialboard.htm>

PUBLICATION DATE

September 25, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Serum phosphate and chronic kidney and cardiovascular disease: Phosphorus potential implications in general population

Vaia D Raikou

ORCID number: Vaia D Raikou
0000-0002-4290-8426.

Author contributions: Raikou VD wrote this manuscript.

Conflict-of-interest statement: The author declares no conflict of interests.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Urology and nephrology

Country/Territory of origin: Greece

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0

Vaia D Raikou, Department of Nephrology, Doctors' Hospital, Athens 11257, Greece

Corresponding author: Vaia D Raikou, PhD, Chief Doctor, Department of Nephrology, Doctors' Hospital, 26 Kefallinias, Athens 11257, Greece. vraikou@med.uoa.gr

Abstract

It has already been established that in end-stage renal disease, hyperphosphatemia causes soft tissue calcification including vascular calcifications. It has also been supported that there is a connection between increased serum phosphate and morbidity in subjects, who suffer from renal disease. However, studies in these populations conferred mixed results. Several warnings are included in the role of serum phosphorus on cardiovascular disease in normal populations. Homeostasis of serum phosphate is obtained by the cooperation between regulatory hormones, cellular receptors and bone metabolic factors. There is the probability that one or more phosphate regulatory factors, rather than phosphate directly, may be responsible for observed associations with calcification and cardiovascular events in normal populations. Experimental studies have shown that the restriction of dietary phosphate prevents the progression of kidney dysfunction, although high dietary phosphate aggravates the renal function. In the current review, we discuss the role of serum phosphorus on progression of renal dysfunction and cardiovascular outcomes in chronic kidney disease patients and its involvement in important health risks in the general population.

Key Words: Phosphorus; Renal insufficiency; Chronic; Dialysis; Cardiovascular diseases

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Disordered phosphorus homeostasis in chronic kidney diseases is associated with bad outcomes including cardiovascular morbidity/mortality and progression of renal dysfunction in end-stage of renal disease. Potential health consequences in cardiovascular and kidney disease could be developed in subjects with a high intake of dietary phosphorus despite the apparently normal renal function, due mainly to abnormalities in metabolism and in regulatory factors, rather than to serum phosphorus itself. The maintenance of serum phosphorus in normal range should be obtained.

Grade C (Good): C, C
 Grade D (Fair): 0
 Grade E (Poor): 0

Received: February 27, 2021

Peer-review started: February 27, 2021

First decision: May 6, 2021

Revised: May 20, 2021

Accepted: July 23, 2021

Article in press: July 23, 2021

Published online: September 25, 2021

P-Reviewer: Prasad G, Saracyn M

S-Editor: Ma YJ

L-Editor: Filipodia

P-Editor: Wu RR



Citation: Raikou VD. Serum phosphate and chronic kidney and cardiovascular disease: Phosphorus potential implications in general population. *World J Nephrol* 2021; 10(5): 76-87
URL: <https://www.wjgnet.com/2220-6124/full/v10/i5/76.htm>
DOI: <https://dx.doi.org/10.5527/wjn.v10.i5.76>

INTRODUCTION

High serum phosphate concentrations have been connected to adverse health outcomes in chronic kidney disease (CKD) including cardiovascular disease, progression of kidney disease and all-cause mortality[1-3]. Hyperphosphatemia in CKD has been also associated with the development of secondary hyperparathyroidism, which is responsible for bone disease implicating the stimulation of regulatory hormones such as fibroblast growth factor-23 (FGF23) and parathyroid hormone (PTH), which in turn may promote left ventricular hypertrophy[4,5]. The kidneys are unable to regulate the serum phosphorus concentrations despite the wide fluctuations in dietary phosphorus intake[6]. In a normal kidney function the phosphorus urinary excretion is increased independently of dietary intake and phosphorus absorption from the gastrointestinal tract and fasting serum phosphate is maintained within a tight range. Therefore, elevation of serum phosphate due to reduced urinary excretion is a main manifestation of advanced renal failure. Previously, we considered the importance of serum phosphate in elderly patients with type 2 diabetes mellitus (T2DM) and we observed the high serum phosphate to be associated with both low estimated glomerular filtration rate (eGFR) and albuminuria, despite the fact that high serum phosphorus levels were found to be non-significant risk factor for the occurrence of T2DM[7]. A positive phosphate balance occurs in the early stage of renal dysfunction, serum phosphate levels mainly increase in advanced stages of CKD and remain elevated in patients in the end-stage renal disease (ESRD) without dialysis treatment (Figure 1).

In the meantime, phosphate is needed in mineralization and bone growth and phosphorus intake is obtained by a rich diet in meat, grains, and dairy products. However, it has been shown that the elevation of serum 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] concentrations due to low dietary calcium intake is inhibited by high phosphorus intake. Moreover, phosphorus intake may be a major source of acid load in the body[8-10]. Therefore, there remains the question whether high phosphorus intake adversely affects bone mass rather than improves bone function. Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines recommended the maintenance of serum phosphate concentrations within the normal laboratory range in dialysis patients using dietary phosphate restriction or intestinal phosphate binders in order to achieve a such as goal[11]. Several studies have also considered the effectiveness of these approaches in patients with CKD stages 3-5 before the initiation of dialysis[12-17]. It should initiate interventions in early stages of CKD including the control of phosphorus and the use of vitamin D analogs, thus the development of parathyroid hyperplasia and the skeletal complications of CKD to be prevented[18]. Vitamin D analogs are used to suppress hyperparathyroidism having lesser toxicity on calcium and phosphorus than calcitriol. However, it is important that PTH is not over-suppressed, because the decrease of bone turnover to abnormally low levels includes the risk for adynamic renal bone disease, which is combined by exacerbation of extra-skeletal deposition of calcium in blood vessels and other tissues.

In the current review, we discuss the role of serum phosphorus on progression of renal dysfunction and cardiovascular outcomes in CKD patients and its involvement in potential health risks in the general population. We also report evidence for the relationship between dietary phosphate intake and adverse outcomes in these populations.

RELATIONSHIP BETWEEN SERUM PHOSPHORUS AND PROGRESSION OF KIDNEY DYSFUNCTION

Many years ago, experimental studies showed that the restriction of dietary phosphate prevents the progression of kidney dysfunction, although high dietary phosphate aggravates the renal function[19,20].

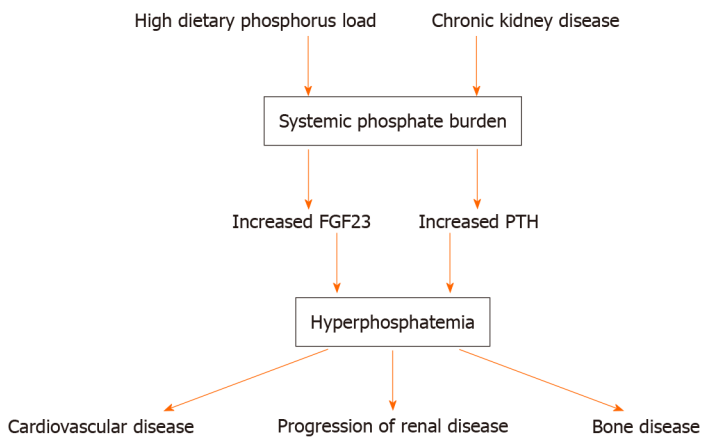


Figure 1 Influence of hyperphosphatemia on different organs/tissues.

However, few clinical studies were conducted to the effect of serum phosphorus concentrations on the rate of CKD progression. It has been shown that in CKD patients serum phosphorus concentrations > 4 mg/dL were associated with an increased risk of ESRD development in both National Health and Nutrition Examination Survey (NHANES) participants and in a United States veterans with CKD study[21,22]. In the Ramipril Efficacy In Nephropathy (REIN) Study, an independent risk of elevated serum phosphorus for exacerbation of renal function in patients with proteinuric CKD was found, although a restriction of the risk was shown caused by the renoprotective action of ramipril[23]. Elevated baseline serum phosphate concentrations were found to be independently related to progression of renal disease in a post hoc analysis of the African American Study of Hypertension and Kidney Disease (AASK) Study[24]. Large study including almost 100000 patients showed that increased serum phosphate concentrations were combined with high incidence of ESRD[25]. Controversially, the Kidney Early Evaluation Program (KEEP) Study did not show an independent association between serum phosphorus concentrations and exacerbation of renal function in ESRD adjusting for demographic and clinical characteristics in multivariable analysis, despite there being a higher prevalence rate of cardiovascular disease (CVD) among patients with higher serum phosphorus[26]. The above studies were different regarding follow-up time and, particularly in the KEEP study, the measurements of serum phosphorus became the baseline and an averaged over time value was not used.

The positive association between serum phosphorus and progression of kidney disease may be attributed to the extension of endothelial dysfunction to the glomerular endothelium, due to acute phosphorus loading, in addition to phosphorus-induced calcification. Another proposed potential mechanism includes the injury of podocytes and overexpression of pituitary-specific positive transcription factor 1 (Pit-1) transporter in rats caused by the elevation of serum phosphorus[27].

Fibroblast growth factor 23 (FGF23) is a hormonal factor, which is significantly involved in maintenance of serum phosphate balance. FGF23 concentrations increase progressively starting in the early CKD as a physiologic adaptation to serum phosphate homeostasis. Eventually, the elevated FGF23 concentrations play an important role on bone disease of these patients[28]. ESRD incidence has also been associated with increased concentrations of FGF23. Studies including participants with mild CKD showed that the risk of all-cause mortality and progression to ESRD was higher in combination with increased FGF23[29,30]. However, a more complicated relationship between FGF23, phosphorus and CKD progression was suggested, due to the association remained stable despite adjustment for phosphorus concentrations.

Accounting for the daily fluctuation of phosphorus, it seems that vascular calcification, endothelial dysfunction, injury of podocytes and high FGF23 result in progression of renal disease, due to high serum phosphorus.

In **Figure 2**, mechanisms which are connected to the relationship between serum phosphorus and the progression of renal dysfunction are shown.

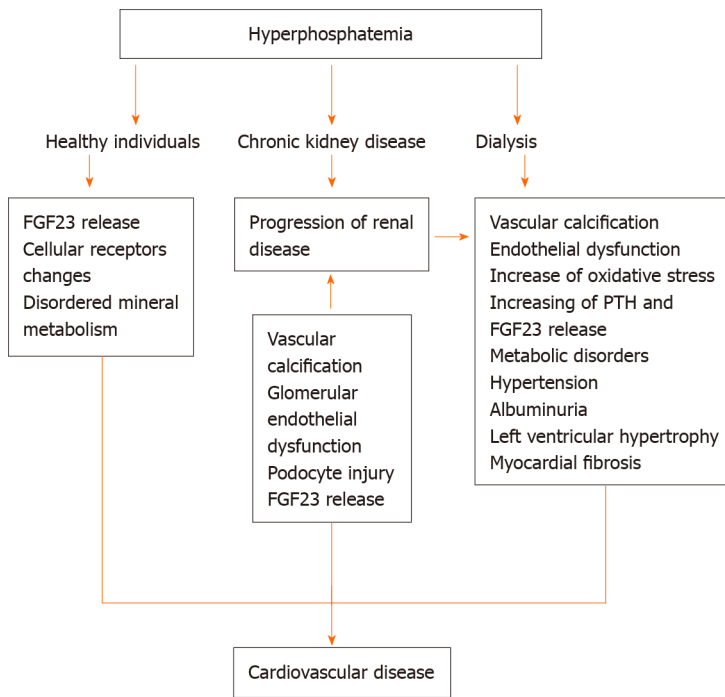


Figure 2 Actions and pathophysiological implications of hyperphosphatemia in different populations.

SERUM PHOSPHATE AND CARDIOVASCULAR DISEASE IN ADVANCED CHRONIC KIDNEY DISEASE

The patients in advanced CKD present increased calcifications, even those at a young age[31]. It has already been established that in ESRD patients, hyperphosphatemia is the reason of soft tissue calcification including vascular calcifications. Loss of the smooth muscle phenotype, expression of bone-specific markers and mineralization of the extracellular matrix was caused by the addition of exogenous phosphate to cultured vascular smooth muscle cells[32,33]. These processes collectively have as an effect calcification of the medial blood vessel wall (Mönckeberg's arteriosclerosis) resulting in the loss of normal vessel compliance. It has been shown that inferior epigastric arteries removed from ESRD patients undergoing renal transplantation presented medial arterial calcification in a 44% prevalence rate[34,35].

High evidence connecting phosphate overload with medial arterial calcification in renal failure was provided by animal models.

Moreover, it has been highly supported that extended vascular calcification, especially coronary artery calcification may play a potential role in the disproportionately increased prevalence rate of CVD in this population of patients[36]. Many years ago, an independent association between serum phosphate ≥ 5.5 mg/dL and all-cause and cardiovascular mortality in hemodialysis patients was shown[37]. Another large study including > 40000 hemodialysis patients showed that serum phosphorus concentrations ≥ 5 mg/dL were associated with a high risk of death[38]. However, such an association is not restricted to hemodialysis patients in different countries. A serum phosphate concentration > 3.5 mg/dL was independently associated with mortality and this risk was linearly elevated with an increase in concentration equal to each 0.5 mg/dL in a large retrospective study including 6730 CKD patients from Veterans Affairs Medical Centers[3]. An Italian study including > 1700 CKD patients showed a significant relationship between serum phosphorus and the likelihood of death[39]. Furthermore, the evidence for significant relationship between higher serum phosphorus and mortality in CKD patients was confirmed by a meta-analysis including 47 studies and 327644 CKD participants[40].

Currently, a multinational, randomized controlled large simple trial including a total of 3600 adult ESKD patients receiving dialysis is ongoing with primary endpoints the cardiovascular death, non-fatal major cardiovascular or peripheral arterial events (ClinicalTrials.gov Identifier: NCT03573089). The participants were randomized either to intensive (≤ 1.50 mmol/L) or liberalized (2.0-2.5 mmol/L) serum phosphate target. The choice and dose of phosphate binders is at the treating physician's discretion and local practice to achieve and maintain serum phosphate concentration within the

required target range according to randomization.

Furthermore, HiLo is currently running as another multicenter, cluster-randomized clinical trial of approximately 4400 patients with ESRD undergoing hemodialysis with a primary hypothesis the targeting serum phosphate levels of < 5.5 mg/dL to be compared to less stringent control of serum phosphate to target levels of > 6.5 mg/dL having as a goal the reduction of all-cause mortality and all-cause hospitalization among these patients (ClinicalTrials.gov Identifier: NCT04095039). Secondly, this trial will test if less stringent control of serum phosphate results in increased serum albumin and protein catabolic rate (PCR), as markers of diet and nutrition.

The main mechanism for the relationship between hyperphosphatemia and adverse cardiovascular outcomes has been attributed to vascular calcification caused by phosphorus, but there may be additional potential explanations including acute endothelial dysfunction particularly in cases of an acute elevation of serum phosphorus. It has been used a diet containing either low (400 mg) or high (1200 mg) phosphorus and serum phosphate concentrations were measured before and 2 h after the meals in combination with flow-mediated dilation of the brachial artery measurement. It was found that the high dietary phosphorus load increased serum phosphorus at 2 h (by an average of 0.8 mg/dL) and significantly decreased flow-mediated dilation (by an average of 4.5%)[41]. Such a finding supports that a significant elevation of serum phosphorus, due to oral phosphorus loading, may be important in the pathogenesis of CVD. We recently considered the importance of serum phosphate in elderly patients with T2DM, strongly related to endothelial dysfunction, *vs* non-diabetes mellitus in relation to renal function[7]. We enclosed 110 subjects and 29 of the participants had T2DM (a ratio equal to 26.4%). We found high serum phosphate to be associated with hypertension, albuminuria, smoking, low estimated glomerular filtration rate (eGFR) and metabolic disorders including higher body mass index (BMI), higher serum glucose and higher uric acid levels, possibly due to phosphorus contribution to diabetes mellitus-induced endothelial dysfunction and/or vascular calcification.

In vitro experiments also showed that high phosphorus loading inhibited nitric oxide (NO) production due to increased reactive oxygen species release and endothelial NO synthase inactivation *via* conventional protein kinase C (PKC), resulting in impaired vasodilation[41].

Furthermore, there are reports that phosphorus might result in direct actions on the myocardium, causing fibrosis[42]. Although one such as conception was supported by *in vitro* studies, direct clinical evidence has been provided by studies, which have connected hyperphosphatemia with left ventricular hypertrophy in CKD[43] and ESRD patients[44]. A relationship between high serum phosphorus and arterial compliance, which may indirectly result in left ventricular hypertrophy, has also been reported[45].

High FGF23 concentrations have been already found to be a significant risk factor for adverse outcomes including death in patients with CKD[29,46,47]. Higher risk of heart failure, stroke, and death among individuals with preserved renal function were also associated with increased FGF23 concentrations[48].

According to the above, calcification of the medial blood vessel wall (Mönckeberg's arteriosclerosis), endothelial dysfunction and inhibition of nitric oxide (NO) production caused by increased reactive oxygen species release, mainly in cases of acute overload of phosphorus, are involved in the pathophysiological mechanisms of CVD in advanced CKD due to phosphorus. Regulatory factors of serum phosphorus including FGF23 are also implicated in bad outcomes in these patients and high phosphorus may have an additional direct action on myocardium inducing fibrosis (Figure 2).

SERUM PHOSPHATE AND CARDIOVASCULAR DISEASE IN EARLY RENAL DYSFUNCTION AND IN GENERAL POPULATION

A connection between increased serum phosphate and adverse outcomes in patients who suffer from mild to moderate renal dysfunction or even in subjects who have apparently a normal kidney function has been supported. However, studies in these populations conferred mixed results. Among 3490 male United States veterans with stage III-IV CKD it was demonstrated that there is a significant relationship between higher serum phosphate concentrations and mortality and incident myocardial infarction[3]. Controversially, another previous study did not find any adjusted association of serum phosphate concentrations with all-cause mortality or progression of

renal dysfunction among 10672 individuals who had early CKD in the community-based Kidney Early Evaluation Program (KEEP)[26]. Different demographic characteristics, causes of CKD, comorbidities and the timing of serum phosphate measurements, which vary throughout the day as 1.0 mg/dL, may have contributed to heterogeneous associations[49]. Data from the CARE (Cholesterol And Recurrent Events) study showed an independent association between increased phosphorus and risk of mortality in subjects who had undergone a myocardial infarction[50]. It is worth mentioning that most of the enrolled patients in this study had baseline serum phosphate in normal range and the baseline eGFR was more than 60 mL/min per 1.73 m². Supportively, a number of large epidemiological studies have suggested that mild elevations of serum phosphorus even within the normal range are associated with the risk of CVD including cardiovascular events, vascular calcification and cardiac valve calcification in general population[51-54]. Interestingly, a previous study found that the risk of mortality increases by 1.09 (HR: 1.09; 95%CI: 1.06, 1.84) per every 1.0 mg/dL increase in serum phosphorus considering the relationship between elevated serum phosphorus concentrations over time and mortality in participants with eGFR > 60 mL/min per 1.73 m²[25]. Another study found that young men and women with relatively high serum phosphate concentrations (> 3.9 mg/dL) had a greater prevalence rate of coronary artery calcification 15 years later[55].

Many warnings are included in the role of serum phosphorus on CVD in normal populations. Phosphate homeostasis is obtained by regulatory hormones, cellular receptors and bone metabolic factors[56-58]. Common genetic variants located within or near multiple genes of mineral metabolism have been identified, which were associated with serum phosphate concentrations among 16264 individuals without apparently kidney dysfunction[59]. It is probable that one or more regulatory factors of phosphorus, rather than phosphate directly, may be responsible for observed associations with calcification and cardiovascular events in normal populations.

On the other hand, in early CKD and general populations the range of serum phosphate concentrations is typically found within or just above the normal laboratory range. In experimental models higher concentrations of phosphorus were used to induce calcification, ruling out the manifestation of calcification to be a plausible mechanism for the observed associations between serum phosphorus and cardiovascular events in normal populations. Coronary artery calcium represents calcified atherosclerosis rather than medial arterial calcification in normal populations in contrast to advanced renal disease population of patients[60].

Findings related to the risk due to high phosphorus were shown to be controversial in early stages of CKD, because of different demographic characteristics, causes of CKD, comorbidities and the timing of serum phosphate measurements, which vary throughout the day. One or more phosphate regulatory factors including FGF23 and/or cellular receptors, due to genetic variants linked to multiple genes of mineral metabolism, rather than serum phosphate itself directly, are responsible for observed associations between high serum phosphate and both calcification and cardiovascular events in normal populations.

In Figure 3, potential mechanisms which are involved to the relationship between serum phosphorus and cardiovascular disease in different stages of renal dysfunction are shown.

IMPORTANCE OF DIETARY PHOSPHORUS INTAKE

Previous studies have supported that the elevated dietary phosphorus intake is connected to endothelial dysfunction[41] and increased FGF23 concentrations[61]. Particularly in subjects with a normal kidney function it has been shown a significant relationship between high FGF23 Levels and acute oral phosphorus loads[62]. In disagreement, in the Chronic Renal Insufficiency Cohort (CRIC) Study an association between dietary phosphorus intake and FGF23 concentrations was not found[63]. It seems that the interrelation between FGF23 and phosphorus intake is influenced by the kidney function and a preserved kidney function rather than CKD is required thus the association between them to be significant. Moreover, the usage of foods containing inorganic phosphorus additives confuses the results, because inorganic phosphorus is not captured completely by dietary surveys resulting in invalid findings regarding the association between FGF23 and dietary phosphorus intake. On the other hand, a strong, independent association between dietary phosphorus intake and left ventricular mass assessed by magnetic resonance was shown in MESA (Multi-Ethnic Study of Atherosclerosis) Study[64]. Increased oral phosphorus load was also found to

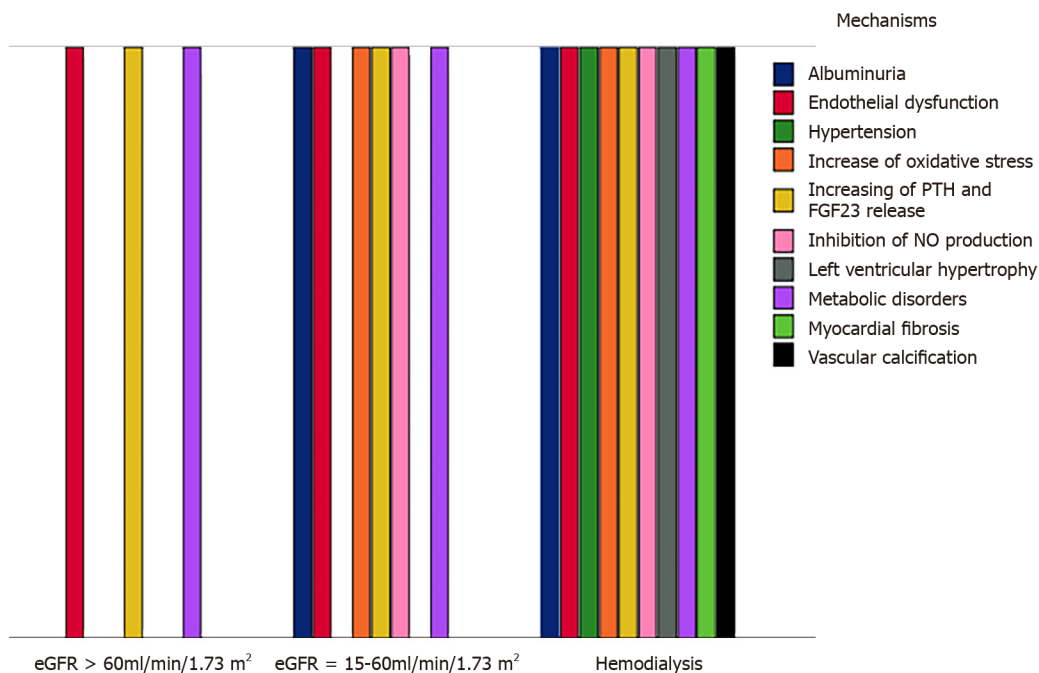


Figure 3 Mechanisms, which are involved to the relationship between serum phosphorus and cardiovascular disease in different stages of renal dysfunction.

promote the generation of tumors and a significant association between phosphorus and cancer may occur[65].

According to above discussed, the elevated intake of dietary phosphorus seriously disrupts phosphate homeostasis in healthy individuals. A disordered phosphorus homeostasis has potential health consequences in bones, cardiovascular, and kidney disease, even in the presence of reserved kidney function. Furthermore, the increased serum phosphorus, even without elevated oral phosphorus intake, as in advanced CKD patients, may be linked to worse outcomes.

The dietary phosphorus intake is reflected by the serum phosphate concentrations in dialysis patients. It has been established that a significant fall in serum phosphorus is clearly obtained by the restriction of dietary phosphorus or the use of oral phosphate binders[66]. Therefore, serum phosphate levels could be used as a marker of dietary intake in this population. However, a such as relation has not been completely established in CKD patients without dialysis or in normal population, despite a cross-sectional study in NHANES III which showed a mildly significant association between dietary and fasting serum phosphorus concentrations[67]. Since kidney function maintains the balance of serum phosphorus independently on phosphorus intake, fasting serum phosphorus is a very poor indicator of dietary phosphorus intake in normal population or in patients without dialysis. In these subjects repeated measurements of serum phosphorus throughout the day could reflect the wide fluctuation in phosphorus intake.

Moreover, it has been shown a circadian variation of serum phosphorus in healthy subjects and in patients with early renal failure[49,68]. The phosphorus concentrations might vary to 2 mg/dL during a 24-h time. It has been proved that the lowest serum phosphate concentration is in morning specimens and the least difference in serum phosphate concentrations on high- compared with low-phosphate diets also to be at this time of day, without an increase of urine phosphate excretion, PTH or FGF23 to be combined[49]. The mechanisms for phosphorus circadian variation phenomenon are still unclear. Nevertheless, the high variation of serum phosphorus during daytime, due to high oral phosphate load, could result in adverse outcomes, even in normal kidney function[41]. Other factors which influences the relation between dietary phosphorus intake and serum phosphate levels may be the use of foods with additives containing inorganic phosphate and the different bioavailability of phosphorus from various food sources. Phosphorus in meat can be absorbed more than the same amount of phosphorus in cereals. The ratio between calcium and phosphorus dietary intake is also other confounder in the relation between intake and serum phosphorus concentrations.

Table 1 Dietary phosphorus recommendations

Dietary phosphorus recommendations
Restricting dietary phosphorus intake in dialysis patients, thus serum phosphate levels to be maintained within normal range with the use of intestinal phosphate binders or intensive hemodialysis
Restricting dietary phosphorus intake in adults CKD stages 3-5, thus serum phosphate levels in repeated measurements to be maintained within normal range with the use of intestinal phosphate binders
Consideration of bioavailability of phosphorus sources (animals, vegetables, additives) in patients with CKD stages 1-5
Control of serum phosphorus to be in normal range in healthy individuals
Prescribing a high phosphorus intake (diet or supplements) in adult kidney transplant recipients with hypophosphatemia, because a severe drop in serum phosphorus 1.5 mg/dL or below can cause neuromuscular disturbances, due to impaired cellular metabolism

CKD: Chronic kidney disease.

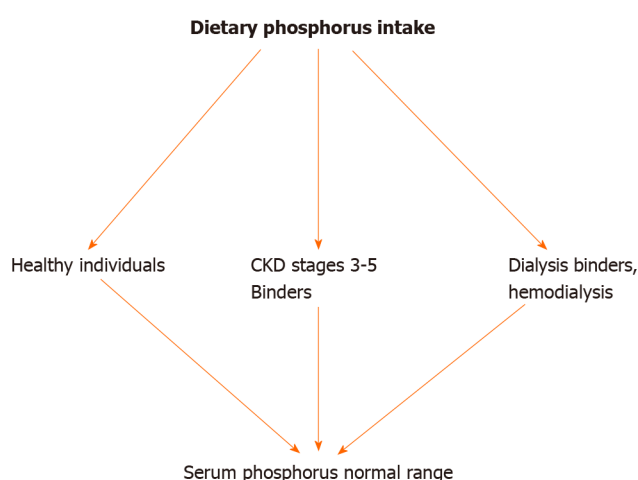


Figure 4 Phosphate control is schematically depicted in different populations.

Although many observational studies have been conducted on the relation between serum phosphorus concentrations/dietary intake and outcomes, it still remains undetermined whether phosphorus is a real toxin or is a simple marker for adverse events. The cause for this would be the lack of a reasonable approach. However, clinical studies including The Modification of Diet in Renal Disease (MDRD) study observed a significant reduction in the risk of ESRD or death with reduced dietary protein intake and, by extension, reduced intake of dietary phosphorus, as the main intervention[69,70]. Even though the comparisons of randomized groups in previous studies do not prove a beneficial cause effect of either protein restriction or phosphorus restriction on morbidity/mortality, such a restriction should be recommended, thus serum phosphorus could be retained within normal range for the reduction of risk for cardiovascular events and the protection of renal function.

In Table 1, recommendations of dietary phosphorus are listed and in Figure 4, phosphate control in different populations of patients are included.

CONCLUSION

Disordered phosphorus homeostasis in CKD is associated with bad outcomes including cardiovascular morbidity/mortality and progression of renal dysfunction in ESRD. Elevated intake of dietary phosphorus seems to disrupt phosphate homeostasis even in healthy individuals, due mainly to abnormalities in regulatory factors including FGF23 connected to genetic variants of mineral metabolism multiple genes, eventually resulting in potential health consequences in bones, cardiovascular, and kidney disease. Therefore, the maintenance of serum phosphorus in normal range should be obtained. However, further studies are still required to clarify the underlying pathophysiologic mechanisms and, particularly, to define interventions,

which would attenuate the adverse outcomes due to phosphorus.

REFERENCES

- 1 **Scialla JJ**, Astor BC, Isakova T, Xie H, Appel LJ, Wolf M. Mineral metabolites and CKD progression in African Americans. *J Am Soc Nephrol* 2013; **24**: 125-135 [PMID: [23243213](#) DOI: [10.1681/ASN.2012070713](#)]
- 2 **Adeney KL**, Siscovick DS, Ix JH, Seliger SL, Shlipak MG, Jenny NS, Kestenbaum BR. Association of serum phosphate with vascular and valvular calcification in moderate CKD. *J Am Soc Nephrol* 2009; **20**: 381-387 [PMID: [19073826](#) DOI: [10.1681/ASN.2008040349](#)]
- 3 **Kestenbaum B**, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 2005; **16**: 520-528 [PMID: [15615819](#) DOI: [10.1681/ASN.2004070602](#)]
- 4 **Antonucci DM**, Yamashita T, Portale AA. Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. *J Clin Endocrinol Metab* 2006; **91**: 3144-3149 [PMID: [16735491](#) DOI: [10.1210/jc.2006-0021](#)]
- 5 **Faul C**, Amaral AP, Oskoue B, Hu MC, Sloan A, Isakova T, Gutiérrez OM, Aguillon-Prada R, Lincoln J, Hare JM, Mundel P, Morales A, Scialla J, Fischer M, Soliman EZ, Chen J, Go AS, Rosas SE, Nessel L, Townsend RR, Feldman HI, St John Sutton M, Ojo A, Gadegbeku C, Di Marco GS, Reuter S, Kentrup D, Tiemann K, Brand M, Hill JA, Moe OW, Kuro-O M, Kusek JW, Keane MG, Wolf M. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; **121**: 4393-4408 [PMID: [21985788](#) DOI: [10.1172/JCI46122](#)]
- 6 **Calvo MS**, Uribarri J. Public health impact of dietary phosphorus excess on bone and cardiovascular health in the general population. *Am J Clin Nutr* 2013; **98**: 6-15 [PMID: [23719553](#) DOI: [10.3945/ajcn.112.053934](#)]
- 7 **Raikou VD**, Kyriaki D, Gavril S. Importance of serum phosphate in elderly patients with diabetes mellitus. *World J Diabetes* 2020; **11**: 416-424 [PMID: [33133389](#) DOI: [10.4239/wjdv11.i10.416](#)]
- 8 **Kemi VE**, Kärkkäinen MU, Karp HJ, Laitinen KA, Lamberg-Allardt CJ. Increased calcium intake does not completely counteract the effects of increased phosphorus intake on bone: an acute dose-response study in healthy females. *Br J Nutr* 2008; **99**: 832-839 [PMID: [17903344](#) DOI: [10.1017/S0007114507831783](#)]
- 9 **Takeda E**, Sakamoto K, Yokota K, Shinohara M, Taketani Y, Morita K, Yamamoto H, Miyamoto K, Shibayama M. Phosphorus supply per capita from food in Japan between 1960 and 1995. *J Nutr Sci Vitaminol (Tokyo)* 2002; **48**: 102-108 [PMID: [12171429](#) DOI: [10.3177/jnsv.48.102](#)]
- 10 **Remer T**, Dimitriou T, Manz F. Dietary potential renal acid load and renal net acid excretion in healthy, free-living children and adolescents. *Am J Clin Nutr* 2003; **77**: 1255-1260 [PMID: [12716680](#) DOI: [10.1093/ajcn/77.5.1255](#)]
- 11 **Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group**. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009; **113**: S1-130
- 12 **Block GA**, Wheeler DC, Persky MS, Kestenbaum B, Ketteler M, Spiegel DM, Allison MA, Asplin J, Smits G, Hoofnagle AN, Kooienga L, Thadhani R, Mannstadt M, Wolf M, Chertow GM. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol* 2012; **23**: 1407-1415 [PMID: [22822075](#) DOI: [10.1681/ASN.2012030223](#)]
- 13 **Chue CD**, Townsend JN, Moody WE, Zehnder D, Wall NA, Harper L, Edwards NC, Steeds RP, Ferro CJ. Cardiovascular effects of sevelamer in stage 3 CKD. *J Am Soc Nephrol* 2013; **24**: 842-852 [PMID: [23599381](#) DOI: [10.1681/ASN.2012070719](#)]
- 14 **Isakova T**, Gutiérrez OM, Smith K, Epstein M, Keating LK, Juppner H, Wolf M. Pilot study of dietary phosphorus restriction and phosphorus binders to target fibroblast growth factor 23 in patients with chronic kidney disease. *Nephrol Dial Transplant* 2011; **26**: 584-591 [PMID: [20631407](#) DOI: [10.1093/ndt/gfq419](#)]
- 15 **Oliveira RB**, Cancela AL, Gracioli FG, Dos Reis LM, Draibe SA, Cuppari L, Carvalho AB, Jorgetti V, Canziani ME, Moysés RM. Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? *Clin J Am Soc Nephrol* 2010; **5**: 286-291 [PMID: [19965540](#) DOI: [10.2215/CJN.05420709](#)]
- 16 **Gonzalez-Parra E**, Gonzalez-Casas ML, Galán A, Martinez-Calero A, Navas V, Rodriguez M, Ortiz A. Lanthanum carbonate reduces FGF23 in chronic kidney disease Stage 3 patients. *Nephrol Dial Transplant* 2011; **26**: 2567-2571 [PMID: [21436379](#) DOI: [10.1093/ndt/gfr144](#)]
- 17 **Seifert ME**, de las Fuentes L, Rothstein M, Dietzen DJ, Bierhals AJ, Cheng SC, Ross W, Windus D, Dávila-Román VG, Hruska KA. Effects of phosphate binder therapy on vascular stiffness in early-stage chronic kidney disease. *Am J Nephrol* 2013; **38**: 158-167 [PMID: [23941761](#) DOI: [10.1159/000353569](#)]
- 18 **Gallieni M**, De Luca N, Santoro D, Meneghel G, Formica M, Grandaliano G, Pizzarelli F, Cossu M, Segoloni G, Quintaliani G, Di Giulio S, Pisani A, Malaguti M, Marseglia C, Oldrizzi L, Pacilio M, Conte G, Dal Canton A, Minutolo R. Management of CKD-MBD in non-dialysis patients under regular nephrology care: a prospective multicenter study. *J Nephrol* 2016; **29**: 71-78 [PMID: [25986389](#) DOI: [10.1007/s40620-015-0202-4](#)]

- 19 **Cozzolino M**, Staniforth ME, Liapis H, Finch J, Burke SK, Dusso AS, Slatopolsky E. Sevelamer hydrochloride attenuates kidney and cardiovascular calcifications in long-term experimental uremia. *Kidney Int* 2003; **64**: 1653-1661 [PMID: [14531797](#) DOI: [10.1046/j.1523-1755.2003.00284.x](#)]
- 20 **Kobayashi S**, Abe K, Isobe A, Nakayama A, Akimoto T, Hatakeyama T, Saito Y, Yanagisawa R, Koike E, Suzuki N, Kawaguchi M, Ohta R. Novel toxicity of tris(1,3-dichloro-2-propyl) phosphate in adult male rats. *J Appl Toxicol* 2021; **41**: 987-992 [PMID: [32996631](#) DOI: [10.1002/jat.4075](#)]
- 21 **O'Seaghdha CM**, Hwang SJ, Muntner P, Melamed ML, Fox CS. Serum phosphorus predicts incident chronic kidney disease and end-stage renal disease. *Nephrol Dial Transplant* 2011; **26**: 2885-2890 [PMID: [21292817](#) DOI: [10.1093/ndt/gfq808](#)]
- 22 **Schwarz S**, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. *Clin J Am Soc Nephrol* 2006; **1**: 825-831 [PMID: [17699293](#) DOI: [10.2215/CJN.02101205](#)]
- 23 **Zoccali C**, Ruggenenti P, Perna A, Leonardis D, Tripepi R, Tripepi G, Mallamaci F, Remuzzi G; REIN Study Group. Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. *J Am Soc Nephrol* 2011; **22**: 1923-1930 [PMID: [21852581](#) DOI: [10.1681/ASN.2011020175](#)]
- 24 **Norris KC**, Greene T, Kopple J, Lea J, Lewis J, Lipkowitz M, Miller P, Richardson A, Rostand S, Wang X, Appel LJ. Baseline predictors of renal disease progression in the African American Study of Hypertension and Kidney Disease. *J Am Soc Nephrol* 2006; **17**: 2928-2936 [PMID: [16959828](#) DOI: [10.1681/ASN.2005101101](#)]
- 25 **Sim JJ**, Bhandari SK, Smith N, Chung J, Liu IL, Jacobsen SJ, Kalantar-Zadeh K. Phosphorus and risk of renal failure in subjects with normal renal function. *Am J Med* 2013; **126**: 311-318 [PMID: [23375678](#) DOI: [10.1016/j.amjmed.2012.08.018](#)]
- 26 **Mehrotra R**, Peralta CA, Chen SC, Li S, Sachs M, Shah A, Norris K, Saab G, Whaley-Connell A, Kestenbaum B, McCullough PA; Kidney Early Evaluation Program (KEEP) Investigators. No independent association of serum phosphorus with risk for death or progression to end-stage renal disease in a large screen for chronic kidney disease. *Kidney Int* 2013; **84**: 989-997 [PMID: [23615501](#) DOI: [10.1038/ki.2013.145](#)]
- 27 **Sekiguchi S**, Suzuki A, Asano S, Nishiwaki-Yasuda K, Shibata M, Nagao S, Yamamoto N, Matsuyama M, Sato Y, Yan K, Yaoita E, Itoh M. Phosphate overload induces podocyte injury via type III Na-dependent phosphate transporter. *Am J Physiol Renal Physiol* 2011; **300**: F848-F856 [PMID: [21307129](#) DOI: [10.1152/ajprenal.00334.2010](#)]
- 28 **Musgrove J**, Wolf M. Regulation and Effects of FGF23 in Chronic Kidney Disease. *Annu Rev Physiol* 2020; **82**: 365-390 [PMID: [31743079](#) DOI: [10.1146/annurev-physiol-021119-034650](#)]
- 29 **Marthi A**, Donovan K, Haynes R, Wheeler DC, Baigent C, Rooney CM, Landray MJ, Moe SM, Yang J, Holland L, di Giuseppe R, Bouma-de Krijger A, Mihaylova B, Herrington WG. Fibroblast Growth Factor-23 and Risks of Cardiovascular and Noncardiovascular Diseases: A Meta-Analysis. *J Am Soc Nephrol* 2018; **29**: 2015-2027 [PMID: [29764921](#) DOI: [10.1681/ASN.2017121334](#)]
- 30 **Fliser D**, Kollerits B, Neyer U, Ankerst DP, Lhotta K, Lingenhel A, Ritz E, Kronenberg F; MMKD Study Group, Kuen E, König P, Kraatz G, Mann JF, Müller GA, Köhler H, Riegler P. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: the Mild to Moderate Kidney Disease (MMKD) Study. *J Am Soc Nephrol* 2007; **18**: 2600-2608 [PMID: [17656479](#) DOI: [10.1681/ASN.2006080936](#)]
- 31 **Goodman WG**, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000; **342**: 1478-1483 [PMID: [10816185](#) DOI: [10.1056/NEJM200005183422003](#)]
- 32 **Reynolds JL**, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, Jahnke-Dechent W, Weissberg PL, Shanahan CM. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. *J Am Soc Nephrol* 2004; **15**: 2857-2867 [PMID: [15504939](#) DOI: [10.1097/01.ASN.0000141960.01035.28](#)]
- 33 **Shroff RC**, McNair R, Skepper JN, Figg N, Schurgers LJ, Deanfield J, Rees L, Shanahan CM. Chronic mineral dysregulation promotes vascular smooth muscle cell adaptation and extracellular matrix calcification. *J Am Soc Nephrol* 2010; **21**: 103-112 [PMID: [19959717](#) DOI: [10.1681/ASN.2009060640](#)]
- 34 **Moe SM**, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, Fineberg N, Kopecky K. Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. *Kidney Int* 2002; **61**: 638-647 [PMID: [11849407](#) DOI: [10.1046/j.1523-1755.2002.00170.x](#)]
- 35 **London GM**, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003; **18**: 1731-1740 [PMID: [12937218](#) DOI: [10.1093/ndt/gfg414](#)]
- 36 **Sigrist MK**, Taal MW, Bungay P, McIntyre CW. Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. *Clin J Am Soc Nephrol* 2007; **2**: 1241-1248 [PMID: [17928470](#) DOI: [10.2215/CJN.02190507](#)]
- 37 **Fukagawa M**, Kido R, Komaba H, Onishi Y, Yamaguchi T, Hasegawa T, Kurita N, Fukuma S, Akizawa T, Fukuhara S. Abnormal mineral metabolism and mortality in hemodialysis patients with secondary hyperparathyroidism: evidence from marginal structural models used to adjust for time-

- dependent confounding. *Am J Kidney Dis* 2014; **63**: 979-987 [PMID: [24119541](#) DOI: [10.1053/j.ajkd.2013.08.011](#)]
- 38 **Block GA**, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004; **15**: 2208-2218 [PMID: [15284307](#) DOI: [10.1097/01.ASN.0000133041.27682.A2](#)]
 - 39 **Bellasi A**, Mandreoli M, Baldrati L, Corradini M, Di Nicolò P, Malmusi G, Santoro A. Chronic kidney disease progression and outcome according to serum phosphorus in mild-to-moderate kidney dysfunction. *Clin J Am Soc Nephrol* 2011; **6**: 883-891 [PMID: [21393493](#) DOI: [10.2215/CJN.07810910](#)]
 - 40 **Palmer SC**, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, Strippoli GF. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA* 2011; **305**: 1119-1127 [PMID: [21406649](#) DOI: [10.1001/jama.2011.308](#)]
 - 41 **Shuto E**, Taketani Y, Tanaka R, Harada N, Isshiki M, Sato M, Nashiki K, Amo K, Yamamoto H, Higashi Y, Nakaya Y, Takeda E. Dietary phosphorus acutely impairs endothelial function. *J Am Soc Nephrol* 2009; **20**: 1504-1512 [PMID: [19406976](#) DOI: [10.1681/ASN.2008101106](#)]
 - 42 **Amann K**, Törnig J, Kugel B, Gross ML, Tyralla K, El-Shakmak A, Szabo A, Ritz E. Hyperphosphatemia aggravates cardiac fibrosis and microvascular disease in experimental uremia. *Kidney Int* 2003; **63**: 1296-1301 [PMID: [12631346](#) DOI: [10.1046/j.1523-1755.2003.00864.x](#)]
 - 43 **Chue CD**, Edwards NC, Moody WE, Steeds RP, Townend JN, Ferro CJ. Serum phosphate is associated with left ventricular mass in patients with chronic kidney disease: a cardiac magnetic resonance study. *Heart* 2012; **98**: 219-224 [PMID: [22021416](#) DOI: [10.1136/heartjnl-2011-300570](#)]
 - 44 **Stróżecki P**, Adamowicz A, Nartowicz E, Odrowaz-Sypniewska G, Włodarczyk Z, Manitius J. Parathormon, calcium, phosphorus, and left ventricular structure and function in normotensive hemodialysis patients. *Ren Fail* 2001; **23**: 115-126 [PMID: [11256521](#) DOI: [10.1081/jdi-100001291](#)]
 - 45 **Toussaint ND**, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic kidney disease. *Nephrol Dial Transplant* 2008; **23**: 586-593 [PMID: [17933842](#) DOI: [10.1093/ndt/gfm660](#)]
 - 46 **Gutiérrez OM**, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Jüppner H, Wolf M. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; **359**: 584-592 [PMID: [18687639](#) DOI: [10.1056/NEJMoa0706130](#)]
 - 47 **Seiler S**, Reichart B, Roth D, Seibert E, Fliser D, Heine GH. FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. *Nephrol Dial Transplant* 2010; **25**: 3983-3989 [PMID: [20525642](#) DOI: [10.1093/ndt/gfq309](#)]
 - 48 **Parker BD**, Schurgers LJ, Brandenburg VM, Christenson RH, Vermeer C, Ketteler M, Shlipak MG, Whooley MA, Ix JH. The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: the Heart and Soul Study. *Ann Intern Med* 2010; **152**: 640-648 [PMID: [20479029](#) DOI: [10.7326/0003-4819-152-10-201005180-00004](#)]
 - 49 **Perwad F**, Portale AA. Vitamin D metabolism in the kidney: regulation by phosphorus and fibroblast growth factor 23. *Mol Cell Endocrinol* 2011; **347**: 17-24 [PMID: [21914460](#) DOI: [10.1016/j.mce.2011.08.030](#)]
 - 50 **Tonelli M**, Sacks F, Pfeffer M, Gao Z, Curhan G; Cholesterol And Recurrent Events Trial Investigators. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation* 2005; **112**: 2627-2633 [PMID: [16246962](#) DOI: [10.1161/CIRCULATIONAHA.105.553198](#)]
 - 51 **Dhingra R**, Sullivan LM, Fox CS, Wang TJ, D'Agostino RB Sr, Gaziano JM, Vasan RS. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch Intern Med* 2007; **167**: 879-885 [PMID: [17502528](#) DOI: [10.1001/archinte.167.9.879](#)]
 - 52 **Tuttle KR**, Short RA. Longitudinal relationships among coronary artery calcification, serum phosphorus, and kidney function. *Clin J Am Soc Nephrol* 2009; **4**: 1968-1973 [PMID: [19965546](#) DOI: [10.2215/CJN.01250209](#)]
 - 53 **Linefsky JP**, O'Brien KD, Sachs M, Katz R, Eng J, Michos ED, Budoff MJ, de Boer I, Kestenbaum B. Serum phosphate is associated with aortic valve calcification in the Multi-ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2014; **233**: 331-337 [PMID: [24530958](#) DOI: [10.1016/j.atherosclerosis.2013.12.051](#)]
 - 54 **Uribarri J**, Calvo MS. Dietary phosphorus excess: a risk factor in chronic bone, kidney, and cardiovascular disease? *Adv Nutr* 2013; **4**: 542-544 [PMID: [24038251](#) DOI: [10.3945/an.113.004234](#)]
 - 55 **Foley RN**, Collins AJ, Herzog CA, Ishani A, Kalra PA. Serum phosphorus levels associate with coronary atherosclerosis in young adults. *J Am Soc Nephrol* 2009; **20**: 397-404 [PMID: [18987306](#) DOI: [10.1681/ASN.2008020141](#)]
 - 56 **Bowe AE**, Finnegan R, Jan de Beur SM, Cho J, Levine MA, Kumar R, Schiavi SC. FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. *Biochem Biophys Res Commun* 2001; **284**: 977-981 [PMID: [11409890](#) DOI: [10.1006/bbrc.2001.5084](#)]
 - 57 **Yoshida T**, Yoshida N, Monkawa T, Hayashi M, Saruta T. Dietary phosphorus deprivation induces 25-hydroxyvitamin D(3) 1 α -hydroxylase gene expression. *Endocrinology* 2001; **142**: 1720-1726 [PMID: [11316734](#) DOI: [10.1210/endo.142.5.8119](#)]
 - 58 **Gutiérrez O**, Isakova T, Rhee E, Shah A, Holmes J, Collierone G, Jüppner H, Wolf M. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney

- disease. *J Am Soc Nephrol* 2005; **16**: 2205-2215 [PMID: [15917335](#) DOI: [10.1681/ASN.2005010052](#)]
- 59 **Kestenbaum B**, Glazer NL, Köttgen A, Felix JF, Hwang SJ, Liu Y, Lohman K, Kritchevsky SB, Hausman DB, Petersen AK, Gieger C, Ried JS, Meitinger T, Strom TM, Wichmann HE, Campbell H, Hayward C, Rudan I, de Boer IH, Psaty BM, Rice KM, Chen YD, Li M, Arking DE, Boerwinkle E, Coresh J, Yang Q, Levy D, van Rooij FJ, Dehghan A, Rivadeneira F, Uitterlinden AG, Hofman A, van Duijn CM, Shlipak MG, Kao WH, Witteman JC, Siscovick DS, Fox CS. Common genetic variants associate with serum phosphorus concentration. *J Am Soc Nephrol* 2010; **21**: 1223-1232 [PMID: [20558539](#) DOI: [10.1681/ASN.2009111104](#)]
 - 60 **Nakano T**, Ninomiya T, Sumiyoshi S, Fujii H, Doi Y, Hirakata H, Tsuruya K, Iida M, Kiyohara Y, Sueishi K. Association of kidney function with coronary atherosclerosis and calcification in autopsy samples from Japanese elders: the Hisayama study. *Am J Kidney Dis* 2010; **55**: 21-30 [PMID: [19765871](#) DOI: [10.1053/j.ajkd.2009.06.034](#)]
 - 61 **Vervloet MG**, van Ittersum FJ, Büttler RM, Heijboer AC, Blankenstein MA, ter Wee PM. Effects of dietary phosphate and calcium intake on fibroblast growth factor-23. *Clin J Am Soc Nephrol* 2011; **6**: 383-389 [PMID: [21030580](#) DOI: [10.2215/CJN.04730510](#)]
 - 62 **Gutiérrez OM**, Wolf M, Taylor EN. Fibroblast growth factor 23, cardiovascular disease risk factors, and phosphorus intake in the health professionals follow-up study. *Clin J Am Soc Nephrol* 2011; **6**: 2871-2878 [PMID: [22034506](#) DOI: [10.2215/CJN.02740311](#)]
 - 63 **Isakova T**, Wahl P, Vargas GS, Gutiérrez OM, Scialla J, Xie H, Appleby D, Nessel L, Bellovich K, Chen J, Hamm L, Gadegbeku C, Horwitz E, Townsend RR, Anderson CA, Lash JP, Hsu CY, Leonard MB, Wolf M. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011; **79**: 1370-1378 [PMID: [21389978](#) DOI: [10.1038/ki.2011.47](#)]
 - 64 **Yamamoto KT**, Robinson-Cohen C, de Oliveira MC, Kostina A, Nettleton JA, Ix JH, Nguyen H, Eng J, Lima JA, Siscovick DS, Weiss NS, Kestenbaum B. Dietary phosphorus is associated with greater left ventricular mass. *Kidney Int* 2013; **83**: 707-714 [PMID: [23283134](#) DOI: [10.1038/ki.2012.303](#)]
 - 65 **Anderson JJ**. Potential health concerns of dietary phosphorus: cancer, obesity, and hypertension. *Ann N Y Acad Sci* 2013; **1301**: 1-8 [PMID: [23848306](#) DOI: [10.1111/nyas.12208](#)]
 - 66 **Sullivan C**, Sayre SS, Leon JB, Machekano R, Love TE, Porter D, Marbury M, Sehgal AR. Effect of food additives on hyperphosphatemia among patients with end-stage renal disease: a randomized controlled trial. *JAMA* 2009; **301**: 629-635 [PMID: [19211470](#) DOI: [10.1001/jama.2009.96](#)]
 - 67 **de Boer IH**, Rue TC, Kestenbaum B. Serum phosphorus concentrations in the third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* 2009; **53**: 399-407 [PMID: [18992979](#) DOI: [10.1053/j.ajkd.2008.07.036](#)]
 - 68 **Ix JH**, Anderson CA, Smits G, Persky MS, Block GA. Effect of dietary phosphate intake on the circadian rhythm of serum phosphate concentrations in chronic kidney disease: a crossover study. *Am J Clin Nutr* 2014; **100**: 1392-1397 [PMID: [25332338](#) DOI: [10.3945/ajcn.114.085498](#)]
 - 69 **Levey AS**, Greene T, Beck GJ, Caggiula AW, Kusek JW, Hunsicker LG, Klahr S. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? *J Am Soc Nephrol* 1999; **10**: 2426-2439 [PMID: [10541304](#) DOI: [10.1681/ASN.V10112426](#)]
 - 70 **Palmer SC**, Maggo JK, Campbell KL, Craig JC, Johnson DW, Sutanto B, Ruospo M, Tong A, Strippoli GF. Dietary interventions for adults with chronic kidney disease. *Cochrane Database Syst Rev* 2017; **4**: CD011998 [PMID: [28434208](#) DOI: [10.1002/14651858.CD011998.pub2](#)]



Trends in pediatric nephrotic syndrome

Hiroshi Tamura

ORCID number: Hiroshi Tamura
0000-0001-8786-217X.

Author contributions: Tamura H wrote the paper and collected the data.

Conflict-of-interest statement: The author declare that this manuscript has no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Specialty type: Urology and nephrology

Country/Territory of origin: Japan

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C

Hiroshi Tamura, Department of Pediatrics, Kumamoto University, Kumamoto 8608556, Japan

Corresponding author: Hiroshi Tamura, MD, PhD, Assistant Professor, Department of Pediatrics, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 8608556, Japan.
bohml905ht@kuh.kumamoto-u.ac.jp

Abstract

Nephrotic syndrome (NS) is relatively common in children, with most of its histological types being minimal changed disease. Its etiology has long been attributed to lymphocyte (especially T-cell) dysfunction, while T-cell-mediated vascular hyperpermeability increases protein permeability in glomerular capillaries, leading to proteinuria and hypoproteinemia. Based on this etiology, steroids and immunosuppressive drugs that are effective against this disease have also been considered to correct T-cell dysfunction. However, in recent years, this has been questioned. The primary cause of NS has been considered damage to glomerular epithelial cells and podocyte-related proteins. Therefore, we first describe the changes in expression of molecules involved in NS etiology, and then describe the mechanism by which abnormal expression of these molecules induces proteinuria. Finally, we consider the mechanism by which infection causes the recurrence of NS.

Key Words: Nephrotic syndrome; Gene; Immunity; Viral infection; Children

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: There is no doubt that some vascular hyperpermeability factor is involved in the incidence of proteinuria in idiopathic nephrotic syndrome (INS). However, no etiological molecule has been identified in INS as a factor for increasing the permeability of renal glomerular capillaries with reproducibility and clinical consistency. In addition, since the onset is sometimes observed in the family, there is high incidence of INS in East Asian children and there is the association of steroid-sensitive NS in childhood in Japan with the *HLA-DR/DQ* region, it is highly possible that some genetic factors are involved in the onset of NS. In our opinion, INS is a multifactorial disease in which immunological stimuli, trigger the production of substances that impair podocytes, resulting in dysfunction of the slit membrane and cause proteinuria.

Grade D (Fair): 0
Grade E (Poor): 0

Received: March 21, 2021

Peer-review started: March 21, 2021

First decision: May 6, 2021

Revised: May 15, 2021

Accepted: August 10, 2021

Article in press: August 10, 2021

Published online: September 25, 2021

P-Reviewer: Ghodake DSR

S-Editor: Fan JR

L-Editor: A

P-Editor: Wu RR



Citation: Tamura H. Trends in pediatric nephrotic syndrome. *World J Nephrol* 2021; 10(5): 88-100

URL: <https://www.wjgnet.com/2220-6124/full/v10/i5/88.htm>

DOI: <https://dx.doi.org/10.5527/wjn.v10.i5.88>

INTRODUCTION

Nephrotic syndrome (NS) is a chronic kidney disease that is relatively common in children, with an annual incidence of 2 to 7 *per* 100000 in the pediatric population[1]. An epidemiological study of pediatric idiopathic NS (JP-SHINE study) was conducted in Japan, and found an incidence of 6.49 *per* 100000, which is 3 to 4 times that reported for Caucasians[2]. The male-female ratio was 1.9%, and 32.7% of patients had frequent recurrences during the 1- to 4-year observation period, which was similar to previous reports[2].

NS is classified into idiopathic (INS), secondary, and congenital depending on the cause and timing of proteinuria. INS accounts for 90% of NS in children. Furthermore, since more than 80% of INS in children is minimal change NS (MCNS), more than 70% of NS in childhood is MCNS. This epidemiology differs strongly from that in adults[1].

Focal segmental glomerulosclerosis (FSGS) is the second most common disease in pediatric INS after MCNS. However, the difference between MCNS and FSGS has been debated for many years, with no conclusions being reached[3,4]. It remains unclear whether they are distinct due to differing etiologies or stages/severity (early/mild for MCNS and advanced/severe for FSGS). The etiology of MCNS and FSGS has not yet been concluded.

TOPICS IN NS

Relationship between INS and T-cell function

Regarding INS etiology, the involvement of T-cell dysfunction proposed by Shalhoub [5] in 1974 has long been supported[5]. In this study, steroid therapy showed a rapid and significant effect in INS patients, whose lymphocytes released vascular hyperpermeability factors into the culture supernatant. Additionally, INS patients were in remission when they suffered from measles, and malignant lymphoma patients often had INS. Finally, the recurrence of INS patients was significantly higher during upper respiratory tract inflammation.

From these observations, it was concluded that lymphocytes (mainly T cells) in INS patients are dysfunctional and overproduce vascular hyperpermeability factors. These factors have been thought to increase vascular protein permeability in renal glomerular capillaries and lead to proteinuria[6,7].

In fact, when the supernatant from immortalized T cells from NS patients is administered to rats, it effaces foot processes and causes proteinuria, but the normal control T-cell supernatant does not show such changes[8].

T cells include helper T cells (CD4 antigen-positive) that are presented with antigens from monocytes and macrophages and regulate immune responses, and killer T cells (CD8 antigen-positive) that damage virus-infected cells. Furthermore, helper T cells include Th1 and Th2 cells, which differ in cytokine secretion and effector functions. Th1 cells produce interleukin (IL)-2, interferon (IFN)- γ and tumor necrosis factor (TNF)- α , and Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13. So, far, many groups have investigated the dynamics of blood cytokine levels in MCNS patients[9].

It has been reported that there is no significant difference between cytokine levels in remission in MCNS patients and controls, but IL-4 and IL-13 levels are elevated at the onset of NS, that is, Th2-dominant fluctuations are observed. On the other hand, there have been some reports denying these fluctuations, and no consensus has been reached[10,11].

Reasons for the different observations may be differences in patient backgrounds, lack of standardization of analysis methods (such as sampling and timing), and there are no suitable *in vitro* cultured cells or *in vivo* animal models. At present, there is no established evidence that Th1 or Th2 dominance causes NS. Yap *et al*[12] found the elevated mRNA expression of IL-13 in the T cells of NS patients[12]. After that, an increase IL-13 concentration in blood and T-cell were confirmed by other groups[13, 14].

IL-13 receptors are expressed in glomerular epithelial cells, and the addition of IL-13 to cultured glomerular epithelial cells reduces barrier function[15]. Furthermore, since strong expression of IL-13 in rats causes MCNS-like nephropathy[16], it is possible that an increase in IL-13 in MCNS patients has an effect on the pathology. However, there is a report that the blood concentration of IL-13 is not necessarily high in MCNS patients[17], and future examinations of cytokine concentration in the renal region are necessary.

It has been reported that the expression of a molecule called c-mip (c-maf inducing protein) is increased in MCNS T cells[18]. Subsequent analysis revealed that c-mip expression was increased not only in T cells but also in glomerular epithelial cells when NS recurred[19]. Mice in which c-mip is overexpressed in glomerular epithelial cells show proteinuria, with c-mip modifying the tyrosine kinase signal by the slit membrane. C-mip has been suggested as a mediator causing glomerular epithelial cell damage in MCNS[19].

There have also been reports of the effectiveness of TNF- α inhibitors in nephrotic patients[20] and of nuclear factor- κ B (NF- κ B) pathway activation in the blood cells of MCNS patients[21], but the number of cases was small, and then no further examinations have been reported.

The CD25- and CD4-positive regulatory T-cell population has an inhibitory effect on the immune response and specifically expresses the transcription factor Foxp3. The forkhead box P3 (*FOXP3*) gene is thought to be the master gene in regulatory T-cell development and function. Examination of recurrence of MCNS revealed that the number of suppressive T cells was the same as normal, but the regulatory T cells of ability to suppress T-cell proliferation was reduced at the time of MCNS recurrence [22]. In addition, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, multiple endocrine disorders and digestive diseases caused by mutations in the *FOXP3* gene are complicated by NS. A relationship between MCNS and regulatory T cells has been strongly suggested, while epigenomic changes in the lymphocytes of MCNS patients are also being investigated[23]. Changes in histone methylation[24] and DNA methylation[25] in MCNS have been reported, but there is currently no data on whether these are related to changes in lymphocyte function leading to MCNS. Since steroids induce epigenetic changes, this field is expected to gain interest, specifically in understanding the mechanism of steroid sensitivity in MCNS.

Relationship between INS and B cell function

Although the function of B cells in MCNS is extremely poorly understood compared to that of T cells, rituximab (a human monoclonal antibody against the B cell antigen CD20) is clinically effective against frequently relapsing NS. That is, it became clear that depletion of B cells is a treatment for MCNS[26]. However, it is unclear whether this arises from an effect of rituximab on B cells or a change in T-cell function mediated by B cells.

On the other hand, rituximab binds to acid sphingomyelinase-like phosphodiesterase 3b (SMPDL-3b), a protein expressed in glomerular epithelial cells. Serum from NS patients reduces SMPDL-3b expression levels in cultured glomerular epithelial cells, induces cytoskeletal changes, and reduces the filtration barrier function, whereas rituximab increases SMPDL-3b expression level and suppresses the changes obtained with NS patient serum[27].

This suggests that rituximab may exert a proteinuria-suppressing effect directly on glomerular epithelial cells without the intervention of immune cells. However, the extent of involvement of this mechanism in the clinical effects of rituximab is unknown at this time.

Other factors

Hemopexin: Hemopexin is a blood factor potentially associated with MCNS. It is an enzyme involved in heme metabolism, and its administration to rats induces reversible proteinuria[28]. Hemopexin activity is increased in MCNS patients[29], and since hemopexin acts on the cytoskeleton of glomerular epithelial cells *via* nephrin *in vitro* [30], it may be involved in MCNS. However, this report included a small number of cases, and it is unclear whether its observations can be generalized.

Angiopoietin-like 4: In 2011, Clement *et al*[31] found an increase in Angiopoietin-like 4 (Angptl4) levels in the blood of MCNS patients[31]. Angptl4 expression is also enhanced in epithelial cells in the glomeruli of MCNS patients, and proteinuria occurs when Angptl4 is strongly expressed specifically in glomerular epithelial cells in mice [31]. Therefore, it was suggested that an increase in Angptl4 Leads to MCNS, but this possibility has now been refuted. Subsequent analysis revealed that mice expressing

Angptl4 in the liver did not exhibit proteinuria, and that Angptl4 in the blood acted on glomerular endothelial cells and had a proteinuria-lowering effect[32]. Interestingly, Angptl4 levels are elevated by lowering blood albumin, but Angptl4 suppresses lipoprotein lipase activity, which suppresses the conversion of triglycerides to free fatty acids and causes hyperlipidemia[32]. Therefore, Angptl4 may play a role in NS hyperlipidemia.

CD80: CD80 (B7-1) is a membrane protein that is expressed on activated B cells and antigen-presenting cells. It binds to CD28 on CD4 + T cells in response to T-cell receptor activation and promotes T-cell proliferation. Thus, interaction co-stimulation signaling between CD80 and CD28 mediates the interaction between T cells and B cells or antigen-presenting cells and regulates the adaptive immune response. On the other hand, cytotoxic lymphocytes-associated antigen-4 (CTLA-4), which is a negative co-stimulatory receptor, also binds to CD80 as a ligand, but its affinity is ten times higher than that of CD28 and CD80, and therefore strongly inhibits the binding of CD28 and CD80.

Animal experiments have shown that when glomerular epithelial cells are stimulated and injured, they express CD80[33]. Urinary CD80 levels increase during recurrence of MCNS, which is not seen in FSGS patients or those in remission, suggesting that changes in CD80 expression may be specific to MCNS[34]. The addition of serum from MCNS patients to cultured podocytes has been shown to increase CD80 expression *in vitro*[35], suggesting that there is a close relationship between MCNS and CD80 expression. It is believed that these are not only involved in the onset and recurrence of MCNS, but are also potential biomarkers for differentiating MCNS from FSGS.

A two-hit hypothesis has been proposed, whereby the induction of CD80 expression by a serum stimulus is the first hit, and the subsequent decrease in CTLA4 expression that suppresses the CD80 signal is the second hit[36].

Abatacept is a chimera of CTLA4 and IgG that binds to CD80 and suppresses the CD80-CD28 signal, attenuating the immune response. Therefore, several groups have recently investigated whether suppressing CD80 on glomerular epithelial cells by abatacept leads to an attenuation of proteinuria. Yu *et al*[37] reported the administration of abatacept to 5 FSGS patients [4 rituximab-resistant and 1 steroid-resistant NS (SRNS)] and the improvement of nephrotic-level proteinuria in all of them[37].

On the other hand, Garin *et al*[38] reported that abatacept had a temporary inhibitory effect on proteinuria in MCNS patients, whereas there was no change in proteinuria in FSGS patients despite a decrease in urinary CD80 antigen[38]. Another group has reported that abatacept has a poor effect on proteinuria in FSGS patients[39]. Future cases need to be collected to analyze the involvement of CD80 and abatacept on NS.

Genetic factors

More than 50 genes mutated in hereditary podocytopathies have been identified (Table 1). The causative gene of congenital and SRNS is being elucidated. Depending on the gene mutated, NS can be roughly classified into three types for convenience: congenital NS developing symptoms early in life (*NPHS1*, *NPHS2*, *NPHS3*, *CD2AP*, *MYO1E*, *PTPRO* *etc.*), NS with an adult onset in the form of autosomal dominant inheritance (*TRPC6*, *ACTN4*, *INF2* *etc.*), and NS with symptoms in other organs (*WT1*, *LAMB2*, *LMX1B*, *MYH9* *etc.*). Many of these genes encode proteins that are strongly expressed in glomerular epithelial cells, so these genetic diseases are considered podocyte diseases. In Western studies, two-thirds of infant NS cases developing within the first year of life are explained by four gene mutations (*NPHS1*, 24%; *NPHS2*, 38%; *LAMB2*, 5%; and *WT1*, 3%). It has also been reported that in steroid-resistant congenital NS that develops under 2 years of age, mutations in 24 of the currently known genes are found in nearly 90% of cases[40]. The analysis of more than 2000 cases of SRNS found that 30% of cases were explained by 27 known genes[41].

It is important to understand to what extent genetic background is involved in the onset of steroid-sensitive NS (SSNS) and MCNS. Familial onset of SSNS is rare, in fact, it was reported that the onset of SSNS in the sibs is 3%[42]. Certainly, the frequency of known genetic abnormalities in SSNS is extremely lower than that in SRNS. For example, the analysis of 38 SSNS patients did not find any genetic abnormalities[43]. Minor nephrin abnormalities have been reported in siblings with proteinuria[44]. In addition, a mutation in *LMX1B*, the causative gene of Nail-Patella syndrome, has been found in patients with proteinuria without extrarenal symptoms[45]. Furthermore, a gene mutation in *EMP2* was found by analysis of familial SSNS that developed in early

Table 1 Genetic forms of podocytopathies

Gene	Inheritance	OMIM ID	Pathology	Function	Features
<i>NPHS1</i>	AR	602716	FSGS/MCD	Slit membrane	Congenital. Finish type
<i>NPHS2</i>	AR	604766	FSGS/MCD	Slit membrane	Develop ESRD in the first or second decades
<i>CD2AP</i>	AR	607832	FSGS	Slit membrane	Severe early-onset SRNS
<i>CRB2</i>	AR	609720	FSGS	Slit membrane	Child onset SRNS
<i>FAT1</i>	AR	600976	FSGS	Slit membrane	First or second decade onset SRNS. Tubular ectasia, haematuria and facultative neurological involvement
<i>TRPC6</i>	AD	603652	FSGS	Slit membrane	Both child and adult onset SRNS
<i>MYO1E</i>	AR	601479	FSGS	Actin binding	Child onset SRNS
<i>PLCE1</i>	AR	608414	FSGS/MCD	Actin binding	Infantile to child onset SRNS
<i>INF2</i>	AD	613237	FSGS	Actin binding	Complicated by Charcot-Marie-Tooth disease
<i>ACTN4</i>	AD	604638	FSGS	Actin binding	Adult onset SRNS
<i>MYH9</i>	AD	160775	FSGS/MCD	Actin binding	Complicated by Epstein syndrome
<i>ANLN</i>	AD	616027	FSGS	Actin binding	Both child and adult onset SRNS
<i>KANK1</i>	AR	607704	MCD	Actin regulation	
<i>KANK2</i>	AR	614610	MCD	Actin regulation	Early-onset SSNS
<i>KANK4</i>	AR	614612	FSGS	Actin regulation	Early-onset SRNS
<i>ARHGDI1</i>	AR	601925	FSGS/DMS	Actin regulation	Onset age is younger than 3 yr
<i>ITSN1</i>	AR	602442	FSGS/MCD	Actin regulation	SSNS
<i>ITSN2</i>	AR	604464	FSGS	Actin regulation	SSNS
<i>MAGI2</i>	AR	606382	MCD	Actin regulation	SSNS
<i>TNS2</i>	AR	607717	FSGS/MCD	Actin regulation	SSNS
<i>DLC1</i>	AR	604258	FSGS	Actin regulation	SSNS
<i>ARHGAP24</i>	AD	610586	FSGS	Actin regulation	
<i>LAMB2</i>	AR	609049	DMS/FSGS	Integrin and laminin	Pierson syndrome
<i>ITGA3</i>	AR	605025	FSGS	Integrin and laminin	Infantile onset SRNS. Congenital interstitial lung disease and mild epidermolysis bullosa
<i>ITGB4</i>	AR	147557	FSGS	Integrin and laminin	Congenital or infantile onset SRNS. Epidermolysis bullosa and pyloric atresia
<i>WT1</i>	AD	256370	DMS/FSGS	Nucleus	Denys-Drash syndrome. Frasier syndrome. Wilms tumor
<i>LMX1B</i>	AD	161200	FSGS/MCD	Nucleus	Nail-patella syndrome
<i>SMARCA1</i>	AR	606622	FSGS	Nucleus	Schimke immunoosseous dysplasia
<i>NUP93</i>	AR	614351	FSGS	Nucleoporins	Child onset SRNS
<i>NUP107</i>	AR	607617	FSGS	Nucleoporins	Child onset SRNS
<i>NUP205</i>	AR	614352	FSGS	Nucleoporins	Early onset SRNS
<i>XPO5</i>	AR	607845	FSGS	Nucleoporins	Speech development delay
<i>COQ2</i>	AR	609825	FSGS/CG	CoQ10 biosynthesis	Early-onset NS
<i>COQ6</i>	AR	624647	FSGS	CoQ10 biosynthesis	Early-onset NS. Hearing loss
<i>PDSS2</i>	AR	610564	FSGS	CoQ10 biosynthesis	Leigh syndrome
<i>MTTL1</i>	AR	590050	FSGS	CoQ10 biosynthesis	

SGPL1	AR	603729	FSGS	S1P metabolism	Hyperpigmentation, increased ACTH, hypoglycemia, and hypocalcemia with seizures, ichthyosis, primary hypothyroidism and developmental delay
SCARB2	AR	602257	FSGS	Lysosome	Progressive myoclonic epilepsy

FSGS: Focal segmental glomerulosclerosis; MCD: Minimal change disease; ESRD: End-stage renal disease; ACTH: Adrenocorticotrophic hormone; SRNS: Steroid-resistant nephrotic syndrome; DMS: Diffuse mesangial sclerosis; CG: Collapsing glomerulopathy.

childhood[46]. *EMP2* is expressed in glomerular epithelial and endothelial cells, regulates the expression of the membrane protein caveolin, and its mutation is thought to cause morphological changes to epithelial cells. Additionally, mutations of the kidney ankyrin repeat-containing proteins 1, 2 and 4 known as the cause of SRNS have also been found in SSNS patients[47].

Ashraf *et al*[48] focused on a family with SSNS and performed a whole exome analysis of its members. A novel causative gene, called *ITSN2*, was identified in this family. By combining this result with those from the genomic analysis of NS families with a blood relative, six novel causative genes were identified. The 17 families with mutations in this gene had an NS which was partially sensitive to steroid treatment. Interestingly, all identified genes were involved in the same pathway (Rho signaling) and were found to interact with each other. This pathway also includes genes involved in SRNS, which is indicative of a common mechanism in SSNS and SRNS. In addition, this study suggested that steroids also act on this signaling pathway[48].

These facts suggest that gene mutations affect glomerular epithelial cell function.

Large-scale studies have begun on not only causative genes whose mutations determine the onset of disease, but also polymorphisms in susceptibility genes that increase the risk of onset. In the case of diseases affected by multiple susceptibility genes, the magnitude of the risk of developing the disease is expressed by the “odds ratio.” Specifically, it is expressed as a numerical value indicating how many times the risk of developing the disease is higher in a person who has a susceptibility gene than that of a person who does not have the susceptibility gene.

Genome-wide association studies (GWAS) are comprehensive analyses of the single nucleotide polymorphisms (SNPs) an individual has in their genome. A GWAS was performed in less than 200 cases of acquired NS in Japan, and an SNP in the intron of *GPC5*, which encodes Glypican-5, was found to correlate with NS onset. Glypican-5 is expressed in glomerular epithelial cells and its specific knockdown in these cells turns mice resistant to the development of experimental proteinuria. It is believed that the expression levels of this gene define susceptibility to glomerular epithelial cell damage [49].

In a GWAS of about 200 childhood-onset SSNS cases, the proportion of *HLA-DQA1* polymorphisms on chromosome 6 was significantly increased in SSNS (odds ratio 2.1) [50]. Jia *et al*[51] performed a GWAS using an SNP array optimized for Japanese patients, including 224 pediatric SSNS patient and 419 healthy subject control specimens. As a result, SNPs showed a significant genome-wide association in the *HLA-DR, DQ* region of the short arm of chromosome 6. This result was also confirmed in another cohort consisting of 213 pediatric SSNS patients and 710 healthy controls[51].

A GWAS using an SNP array optimized for Japanese patients was performed on 987 pediatric SSNS patients and 3206 healthy controls. As a result, in addition to the *HLA-DR, DQ* region, variants (polymorphisms) showing a significant genome-wide association with the *NPHS1-KIRREL2* region of chromosome 19 19q13.12 were identified. Furthermore, the relationship between multiple *NPHS1* variants and glomerular *NPHS1* mRNA expression was investigated. The expression of *NPHS1* mRNA from chromosomes having haplotypes with these risk variants was reduced. It has been clarified that *NPHS1* is involved in expression regulation[52].

Although polymorphisms in the multiple susceptibility genes do not cause the disease, they can have a significant impact on the risk of developing NS. These macroscopic genome analyses, which are expected to gain popularity in the future, are effective not only for clarifying the dynamics of susceptibility genes but also for establishing the genetic differences found in populations such as specific ethnic groups and races.

Mechanism of glomerular epithelial cell damage in NS

As mentioned above, various genetic abnormalities can cause NS. It has also been suggested that changes in circulatory factors and local tissues may be involved in the onset of non-genetic NS. Despite these various causes, changes in glomerular epithelial

cells are common throughout NS. In particular, fusion of the foot process is observed in most cases, and basement membrane detachment, vacuolar degeneration, and inclusion body formation are strongly associated with barrier rupture.

Glomerular epithelial cells receive chemical or mechanical stimuli from the glomerular blood vessels and Bowman's cavity to transmit intracellular signals[53]. These signals control the development, morphogenesis, and maintenance of morphology of glomerular epithelial cells, and are closely related to proteinuria[54].

Slit membrane complexes such as Neph1, Neph2, and Podocin play a major role in controlling the cytoskeletal structure of glomerular epithelial cells, and various adapter proteins are used in the intracellular region of slit membrane proteins, due to stimulation-dependent phosphorylation[55,56]. The slit membrane functions as a conversion point for receiving extracellular signals such as humoral factors[19,57]. This signaling system is extremely important for executing reversible morphological changes in epithelial cells and as the point of action of NS drugs.

Significance of viral infection in the onset and recurrence of INS in children

There are many reports on the immunological background of INS patients and abnormalities in renal glomeruli. In recent years, there have been an increasing number of research papers on relationship between upper respiratory tract infection (URI) and the onset and recurrence of INS.

In children, it has been known for over 30 years that the onset and recurrence of INS are observed in URI. Specifically, about 70% of INS recurrences are triggered by URI [58]. Despite interesting findings reported in recent years, the molecular mechanism that links URI to the onset and recurrence of INS has not been elucidated.

Involvement of Toll-like receptors in INS pathology

Innate immunity plays an important role in the initial recognition of pathogens (e.g., bacteria, viruses, and parasites), phagocytosis or digestion, and the subsequent induction of an inflammatory response and the induction of acquired immunity. Macrophages, neutrophils, and phagocytes such as dendritic cells play a central role in this process. These cells express pattern recognition receptors (PRRs) that recognize pathogen-associated molecular patterns (PAMPs) and transmit activation signals through PRRs. The Toll-like receptor (TLR) family of PRRs, consist of 13 types reported in humans, each of which recognizes different PAMPs such as proteins lipids, and nucleic acids of bacteria, viruses, and parasites. TLRs have specific signaling pathways depending on the adapter molecule which lead to the induction of differential gene expression patterns. The main signal transduction pathways are the MyD88-dependent and TRIF-dependent pathways. The former is involved in the induction of the inflammatory response through NF- κ B activation, and the latter activates the IFN regulatory factor (a transcription factor) which finally induces type I IFN and is involved in the antiviral response.

There are some reports that the expression of TLR-3 and TLR-4 in peripheral blood mononuclear cells (PBMC) is enhanced at the time of INS onset or recurrence[59,60]. Mishra *et al*[60] compared the mRNA expression levels of TLR-3, TLR-4, and CD80 using PBMC of 40 SSNS cases (25 of whom were initial or recurrent and 15 were in remission; histological type was mainly MCNS), 30 cases of SRNS (tissue type was mainly FSGS) and 23 control children. The mRNA expression levels of these molecules were increased in patients with initial and recurrent SSNS. On the other hand, patients with SRNS displayed a decreased expression compared to those of normal controls [60].

TLR-3 is localized in the cell and recognizes viral double-stranded RNA, while TLR-4 is present on the cell surface and recognizes sugars, lipids, and proteins derived from the virus[61]. Therefore, the fact that the expression of these TLRs is enhanced is consistent with the fact that many INS recurrences are triggered by URI.

Involvement of alveolar surfactant protein in recurrence of INS

When MCNS patients relapse with URI, their levels of pulmonary surfactant proteins surfactant protein A (SP-A) and surfactant protein D (SP-D) in the serum increase. As a result of activating signal-regulatory protein- α (SIRP α), structural changes (such as disappearance of podocyte foot protrusions) occur, resulting in the appearance of proteinuria[62].

This inference is based on the elevation of SP-A and SP-D levels in the serum collected at the time of recurrence of MCNS patients. SIRP α is stimulated by adding the MCNS patient's serum at the time of recurrence to cultured podocytes, and protein phosphatase non-receptor type 1 is released, which dephosphorylates nephrin, activates podocyte NF- κ B, promotes CD80 and pro-inflammatory cytokine production,

and causes structural podocyte changes. SIRP α is a transmembrane protein that contains a tyrosine phosphorylation site in the cytoplasmic region and is expressed in dendritic cells, macrophages, nerve cells, and microglia. SIRP α is also expressed in podocytes, and it was clarified that it is involved in the regulation of podocyte structure and function as one of the major tyrosine phosphorylated proteins in renal glomeruli[63-65].

In addition, SP-A and SP-D, which are mainly produced by alveolar type II epithelial and Clara cells, are known as useful biomarkers of interstitial pneumonia, but they are also SIRP α agonists[66]. Therefore, a hypothesis that SP-A and SP-D serum levels increase during URI causing abnormalities SIRP α in podocytes and leads to recurrence of INS can be formulated.

Certain viruses that are prone to the onset and recurrence of INS in children

Approximately 85% of microorganisms that cause URI, the so-called cold syndrome, are viruses. The main causative viruses are rhinovirus and coronavirus, followed by RS virus, parainfluenza virus, and adenovirus. It is well known that pediatric INS patients are prone to recurrence when suffering from cold syndrome. There were various studies examining the link between recurrence and the causative virus such as RS virus, influenza virus A and B, parainfluenza virus, varicella herpes zoster virus, and adenovirus, but it was unclear whether a specific pathogen was involved in recurrence. In 2017, two facilities reported that infection with a specific virus was involved in recurrence. Lin *et al*[67] proposed the hypothesis that rhinovirus (HRV) infection leads to increased expression of CD80 in the renal podocytes of patients and causes recurrence[67]. Lin *et al*[67] examined 32 MCNS patients who relapsed during URI due to HRV, using PBMC and renal biopsy tissue, and compared the patients with CD80-positive T cells of PBMC to control children with PBMC. The ratios of CD80-positive T cells to CTLA-4 positive T cells and the ratios of Th17 to Treg increased at the time of recurrence in MCNS when compared to those in control children, but they normalized during the remission period. Furthermore, in an immunostaining study using renal tissue of MCNS patients who underwent renal biopsy at the time of recurrence, CD80 was strongly expressed renal glomeruli, but CTLA-4 was weakly expressed. It is speculated that HRV infection increases the CD80 CTLA-4 ratio of PBMC in MCNS patients, resulting in an increase in the Th17 Treg ratio. As a result, the expression of CD80 in podocytes is enhanced and structural podocyte changes occur, leading to recurrence[67].

The Epstein-Barr (EB) virus is a double-stranded DNA herpesvirus found in cultured cells of Burkitt lymphoma that frequently occurs in children in equatorial Africa. It is also called human herpesvirus type 4. A characteristic of herpesviruses, including EB virus, is that they cause latent infections centered on B lymphocytes[68]. Dossier *et al*[69,70] have proposed the etiologic significance of the EB virus in INS because of findings of infection and reactivation of the EB virus in pediatric patients with initial INS[69,70]. According to them, about half of children with INS have amplification of EB virus DNA. This amplification occurs in a locus with a previously reported monobasic polymorphism in children with SSNS (6p21.32), associated with the ability to produce EB virus nuclear antigen 1. Additionally, depletion of B cells with rituximab relieves INS, but the cells that are persistently infected with EB virus are B cells. These facts were cited as the basis for the EB virus etiology[70].

On the other hand, it is a well-known fact that pediatric INS resolved due to viral infections, such as influenza and measles[71,72].

It has been reported that CD25, CD4, Foxp3, and regulatory T cells (Tregs) levels increase in the blood during measles, and that changes in the T-cell-producing cytokine balance during measles are involved in NS remission[73]. An increase in the number of Tregs was observed in response to intercurrent influenza B virus infection and prednisolone administration, along with a parallel decrease in the amount of proteinuria[74]. Moreover, both influenza virus infection and glucocorticoid (GC) administration, which is the key treatment for INS, increase the number of Tregs[75, 76]. Therefore, it may be hypothesized that Tregs play an important role in INS pathogenesis in patients with INS complicated by influenza B and measles infections.

New insights in the drugs of MCNS

(1) GC: Approximately 80% of pediatric MCNS patients are in remission with GC, but how GC improves MCNS remains unclear. GC may act directly on podocyte receptors to suppress the appearance of proteinuria. In fact, dexamethasone has a significant effect on the structure and function of human podocytes[77], and has been shown to suppress the intracellular signaling of podocyte NF κ B[78]; (2) Cyclosporine (CsA): The suppression of intracellular signal transduction of activated T cells was thought to be a

possible mechanism of CsA in MCNS. CsA acts on the calcineurin-dependent dephosphorylation of synaptopodin in podocytes to stabilize the actin cytoskeleton and reduce proteinuria[79]; and (3) Rituximab (RTX): RTX, a monoclonal antibody that acts against the B cell surface antigen CD20, is also highly effective in MCNS. However, its mechanism of action is not well known.

It speculated that the depletion of B cells may reduce self-reactive T cells through cell-cell interactions[80]. Fornoni *et al*[27] indicated that RTX not only recognizes CD20 on the surface of B cells, but also binds to and protects podocyte SMPDL-3b preventing the destruction of the actin cytoskeleton and suppressing proteinuria[27].

Why don't we still understand the cause of MCNS?

Among the genetic abnormalities identified for congenital NS and SRNS, many have been found to be explained by glomerular epithelial cell abnormalities, however, many aspects of MCNS pathogenesis remain unknown. There are various possible reasons for this. (1) Factors other than the currently analyzed blood factors; (2) Involvement of not one but multiple factors (Genetic, immunological or circulatory factors *etc.*); and (3) Caused by a combination of such factors (*e.g.*, glomerular epithelial cell factor + immunological factor, T cell factor + B cell factor, 1st hit + 2nd hit, *etc.*)

Considering these problems, carrying out comprehensive analysis, such as analysis of genome, epigenome, proteome, and transcriptome using a large cohort will be essential for future studies. Additionally, clarifying the genetic background of patients with a familial history may provide an opportunity to approach the more common cause of idiopathic INS.

CONCLUSION

There is no doubt that some vascular hyperpermeability factor is involved in the incidence of proteinuria in INS. However, no etiological molecule has been identified in INS as a factor for increasing the permeability of renal glomerular capillaries with reproducibility and clinical consistency.

In addition, since the onset is sometimes observed in the family, there is high incidence of INS in East Asian children[2] and there is the association of SSNS in childhood in Japan with the *HLA-DR DQ* region[51], it is highly possible that some genetic factors are involved in the onset of NS.

In our opinion, INS is a multifactorial disease in which immunological stimuli, trigger the production of substances that impair podocytes, resulting in the dysfunction of the slit membrane and causing proteinuria.

REFERENCES

- 1 Kaneko K, Tsuji S, Kimata T, Kitao T, Yamanouchi S, Kato S. Pathogenesis of childhood idiopathic nephrotic syndrome: a paradigm shift from T-cells to podocytes. *World J Pediatr* 2015; **11**: 21-28 [PMID: 25822700 DOI: 10.1007/s12519-015-0003-9]
- 2 Kikunaga K, Ishikura K, Terano C, Sato M, Komaki F, Hamasaki Y, Sasaki S, Iijima K, Yoshikawa N, Nakanishi K, Nakazato H, Matsuyama T, Ando T, Ito S, Honda M; Japanese Pediatric Survey Holding Information of NEphrotic syndrome (JP-SHINE) study of the Japanese Study Group of Renal Disease in Children. High incidence of idiopathic nephrotic syndrome in East Asian children: a nationwide survey in Japan (JP-SHINE study). *Clin Exp Nephrol* 2017; **21**: 651-657 [PMID: 27590892 DOI: 10.1007/s10157-016-1319-z]
- 3 Neuhaus TJ, Fay J, Dillon MJ, Trompeter RS, Barratt TM. Alternative treatment to corticosteroids in steroid sensitive idiopathic nephrotic syndrome. *Arch Dis Child* 1994; **71**: 522-526 [PMID: 7726612 DOI: 10.1136/adc.71.6.522]
- 4 Maas RJ, Deegens JK, Smeets B, Moeller MJ, Wetzels JF. Minimal change disease and idiopathic FSGS: manifestations of the same disease. *Nat Rev Nephrol* 2016; **12**: 768-776 [PMID: 27748392 DOI: 10.1038/nrneph.2016.147]
- 5 Shalhoub RJ. Pathogenesis of lipoid nephrosis: a disorder of T-cell function. *Lancet* 1974; **2**: 556-560 [PMID: 4140273 DOI: 10.1016/s0140-6736(74)91880-7]
- 6 Garin EH. Circulating mediators of proteinuria in idiopathic minimal lesion nephrotic syndrome. *Pediatr Nephrol* 2000; **14**: 872-878 [PMID: 10955948 DOI: 10.1007/s004679900269]
- 7 Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet* 2003; **362**: 629-639 [PMID: 12944064 DOI: 10.1016/S0140-6736(03)14184-0]
- 8 Koyama A, Fujisaki M, Kobayashi M, Igarashi M, Narita M. A glomerular permeability factor produced by human T cell hybridomas. *Kidney Int* 1991; **40**: 453-460 [PMID: 1787645 DOI: 10.1038/ki.1991.232]

- 9 **Pereira Wde F**, Brito-Melo GE, Guimarães FT, Carvalho TG, Mateo EC, Simões e Silva AC. The role of the immune system in idiopathic nephrotic syndrome: a review of clinical and experimental studies. *Inflamm Res* 2014; **63**: 1-12 [PMID: [24121975](#) DOI: [10.1007/s00011-013-0672-6](#)]
- 10 **Araya CE**, Wasserfall CH, Brusko TM, Mu W, Segal MS, Johnson RJ, Garin EH. A case of unfulfilled expectations. Cytokines in idiopathic minimal lesion nephrotic syndrome. *Pediatr Nephrol* 2006; **21**: 603-610 [PMID: [16525836](#) DOI: [10.1007/s00467-006-0026-5](#)]
- 11 **Kanai T**, Shiraishi H, Yamagata T, Ito T, Odaka J, Saito T, Aoyagi J, Momoi MY. Th2 cells predominate in idiopathic steroid-sensitive nephrotic syndrome. *Clin Exp Nephrol* 2010; **14**: 578-583 [PMID: [20686809](#) DOI: [10.1007/s10157-010-0330-z](#)]
- 12 **Yap HK**, Cheung W, Murugasu B, Sim SK, Seah CC, Jordan SC. Th1 and Th2 cytokine mRNA profiles in childhood nephrotic syndrome: evidence for increased IL-13 mRNA expression in relapse. *J Am Soc Nephrol* 1999; **10**: 529-537 [PMID: [10073603](#) DOI: [10.1681/ASN.V103529](#)]
- 13 **Mishra OP**, Teli AS, Singh U, Abhinay A, Prasad R. Serum immunoglobulin E and interleukin-13 levels in children with idiopathic nephrotic syndrome. *J Trop Pediatr* 2014; **60**: 467-471 [PMID: [25124794](#) DOI: [10.1093/tropej/fmu040](#)]
- 14 **Komatsuda A**, Wakui H, Iwamoto K, Togashi M, Masai R, Maki N, Sawada K. GATA-3 is upregulated in peripheral blood mononuclear cells from patients with minimal change nephrotic syndrome. *Clin Nephrol* 2009; **71**: 608-616 [PMID: [19473628](#) DOI: [10.5414/cnp71608](#)]
- 15 **VAN DEN Berg JG**, Aten J, Chand MA, Claessen N, Dijkink L, Wijdenes J, Lakkis FG, Weening JJ. Interleukin-4 and interleukin-13 act on glomerular visceral epithelial cells. *J Am Soc Nephrol* 2000; **11**: 413-422 [PMID: [10703665](#) DOI: [10.1681/ASN.V113413](#)]
- 16 **Lai KW**, Wei CL, Tan LK, Tan PH, Chiang GS, Lee CG, Jordan SC, Yap HK. Overexpression of interleukin-13 induces minimal-change-like nephropathy in rats. *J Am Soc Nephrol* 2007; **18**: 1476-1485 [PMID: [17429054](#) DOI: [10.1681/ASN.2006070710](#)]
- 17 **Nahid M**, Hasan O, Rozita H, Fereshteh M. Serum Interleukin 13 Level in Steroid Sensitive Nephrotic Syndrome. *J Compr Ped* 2017; **8**: e12765 [DOI: [10.5812/compreped.12765](#)]
- 18 **Grimbert P**, Valanciute A, Audard V, Pawlak A, Le gouvelo S, Lang P, Niaudet P, Bensman A, Guellaën G, Sahali D. Truncation of C-mip (Tc-mip), a new proximal signaling protein, induces c-maf Th2 transcription factor and cytoskeleton reorganization. *J Exp Med* 2003; **198**: 797-807 [PMID: [12939343](#) DOI: [10.1084/jem.20030566](#)]
- 19 **Zhang SY**, Kamal M, Dahan K, Pawlak A, Ory V, Desvaux D, Audard V, Candelier M, BenMohamed F, Matignon M, Christov C, Decrouy X, Bernard V, Mangiapan G, Lang P, Guellaën G, Ronco P, Sahali D. c-mip impairs podocyte proximal signaling and induces heavy proteinuria. *Sci Signal* 2010; **3**: ra39 [PMID: [20484117](#) DOI: [10.1126/scisignal.2000678](#)]
- 20 **Bitzan M**, Babayeva S, Vasudevan A, Goodyer P, Torban E. TNF α pathway blockade ameliorates toxic effects of FSGS plasma on podocyte cytoskeleton and β 3 integrin activation. *Pediatr Nephrol* 2012; **27**: 2217-2226 [PMID: [22538781](#) DOI: [10.1007/s00467-012-2163-3](#)]
- 21 **Sahali D**, Pawlak A, Gouvello SL, Lang P, Valanciute A, Remy P, Loirat C, Niaudet P, Bensman A, Guellaën G. Transcriptional and post-transcriptional alterations of IkappaBalpha in active minimal-change nephrotic syndrome. *J Am Soc Nephrol* 2001; **12**: 1648-1658 [PMID: [11461937](#) DOI: [10.1681/ASN.V1281648](#)]
- 22 **Araya C**, Diaz L, Wasserfall C, Atkinson M, Mu W, Johnson R, Garin E. T regulatory cell function in idiopathic minimal lesion nephrotic syndrome. *Pediatr Nephrol* 2009; **24**: 1691-1698 [PMID: [19495805](#) DOI: [10.1007/s00467-009-1214-x](#)]
- 23 **Hashimura Y**, Nozu K, Kanegane H, Miyawaki T, Hayakawa A, Yoshikawa N, Nakanishi K, Takemoto M, Iijima K, Matsuo M. Minimal change nephrotic syndrome associated with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome. *Pediatr Nephrol* 2009; **24**: 1181-1186 [PMID: [19189134](#) DOI: [10.1007/s00467-009-1119-8](#)]
- 24 **Zhang L**, Dai Y, Peng W, Lu J, Zhang Y, Wang L. Genome-wide analysis of histone H3 lysine 4 trimethylation in peripheral blood mononuclear cells of minimal change nephrotic syndrome patients. *Am J Nephrol* 2009; **30**: 505-513 [PMID: [19797895](#) DOI: [10.1159/000243811](#)]
- 25 **Kobayashi Y**, Aizawa A, Takizawa T, Yoshizawa C, Horiguchi H, Ikeuchi Y, Kakegawa S, Watanabe T, Maruyama K, Morikawa A, Hatada I, Arakawa H. DNA methylation changes between relapse and remission of minimal change nephrotic syndrome. *Pediatr Nephrol* 2012; **27**: 2233-2241 [PMID: [22855301](#) DOI: [10.1007/s00467-012-2248-z](#)]
- 26 **Iijima K**, Sako M, Nozu K, Mori R, Tuchida N, Kamei K, Miura K, Aya K, Nakanishi K, Ohtomo Y, Takahashi S, Tanaka R, Kaito H, Nakamura H, Ishikura K, Ito S, Ohashi Y; Rituximab for Childhood-onset Refractory Nephrotic Syndrome (RCRNS) Study Group. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2014; **384**: 1273-1281 [PMID: [24965823](#) DOI: [10.1016/S0140-6736\(14\)60541-9](#)]
- 27 **Fornoni A**, Sageshima J, Wei C, Merscher-Gomez S, Aguillon-Prada R, Jauregui AN, Li J, Mattiazzi A, Ciancio G, Chen L, Zilleruelo G, Abitbol C, Chandar J, Seeherunvong W, Ricordi C, Ikehata M, Rastaldi MP, Reiser J, Burke GW 3rd. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. *Sci Transl Med* 2011; **3**: 85ra46 [PMID: [21632984](#) DOI: [10.1126/scitranslmed.3002231](#)]
- 28 **Cheung PK**, Klok PA, Baller JF, Bakker WW. Induction of experimental proteinuria in vivo following infusion of human plasma hemopexin. *Kidney Int* 2000; **57**: 1512-1520 [PMID: [10760087](#) DOI: [10.1046/j.1523-1755.2000.00996.x](#)]

- 29 **Bakker WW**, van Dael CM, Pierik LJ, van Wijk JA, Nauta J, Borghuis T, Kapoos JJ. Altered activity of plasma hemopexin in patients with minimal change disease in relapse. *Pediatr Nephrol* 2005; **20**: 1410-1415 [PMID: 16079987 DOI: 10.1007/s00467-005-1936-3]
- 30 **Lennon R**, Singh A, Welsh GI, Coward RJ, Satchell S, Ni L, Mathieson PW, Bakker WW, Saleem MA. Hemopexin induces nephrin-dependent reorganization of the actin cytoskeleton in podocytes. *J Am Soc Nephrol* 2008; **19**: 2140-2149 [PMID: 18753258 DOI: 10.1681/ASN.2007080940]
- 31 **Clement LC**, Avila-Casado C, Macé C, Soria E, Bakker WW, Kersten S, Chugh SS. Podocyte-secreted angiopoietin-like-4 mediates proteinuria in glucocorticoid-sensitive nephrotic syndrome. *Nat Med* 2011; **17**: 117-122 [PMID: 21151138 DOI: 10.1038/nm.2261]
- 32 **Clement LC**, Macé C, Avila-Casado C, Joles JA, Kersten S, Chugh SS. Circulating angiopoietin-like 4 links proteinuria with hypertriglyceridemia in nephrotic syndrome. *Nat Med* 2014; **20**: 37-46 [PMID: 24317117 DOI: 10.1038/nm.3396]
- 33 **Reiser J**, von Gersdorff G, Loos M, Oh J, Asanuma K, Giardino L, Rastaldi MP, Calvaresi N, Watanabe H, Schwarz K, Faul C, Kretzler M, Davidson A, Sugimoto H, Kalluri R, Sharpe AH, Kreidberg JA, Mundel P. Induction of B7-1 in podocytes is associated with nephrotic syndrome. *J Clin Invest* 2004; **113**: 1390-1397 [PMID: 15146236 DOI: 10.1172/JCI20402]
- 34 **Garin EH**, Mu W, Arthur JM, Rivard CJ, Araya CE, Shimada M, Johnson RJ. Urinary CD80 is elevated in minimal change disease but not in focal segmental glomerulosclerosis. *Kidney Int* 2010; **78**: 296-302 [PMID: 20485332 DOI: 10.1038/ki.2010.143]
- 35 **Ishimoto T**, Cara-Fuentes G, Wang H, Shimada M, Wasserfall CH, Winter WE, Rivard CJ, Araya CE, Saleem MA, Mathieson PW, Johnson RJ, Garin EH. Serum from minimal change patients in relapse increases CD80 expression in cultured podocytes. *Pediatr Nephrol* 2013; **28**: 1803-1812 [PMID: 23689904 DOI: 10.1007/s00467-013-2498-4]
- 36 **Ishimoto T**, Shimada M, Araya CE, Huskey J, Garin EH, Johnson RJ. Minimal change disease: a CD80 podocytopathy? *Semin Nephrol* 2011; **31**: 320-325 [PMID: 21839364 DOI: 10.1016/j.semnephrol.2011.06.002]
- 37 **Yu CC**, Fornoni A, Weins A, Hakrout S, Maiguel D, Sageshima J, Chen L, Ciancio G, Faridi MH, Behr D, Campbell KN, Chang JM, Chen HC, Oh J, Faul C, Arnaout MA, Fiorina P, Gupta V, Greka A, Burke GW 3rd, Mundel P. Abatacept in B7-1-positive proteinuric kidney disease. *N Engl J Med* 2013; **369**: 2416-2423 [PMID: 24206430 DOI: 10.1056/NEJMoa1304572]
- 38 **Garin EH**, Reiser J, Cara-Fuentes G, Wei C, Matar D, Wang H, Alachkar N, Johnson RJ. Case series: CTLA4-IgG1 therapy in minimal change disease and focal segmental glomerulosclerosis. *Pediatr Nephrol* 2015; **30**: 469-477 [PMID: 25239302 DOI: 10.1007/s00467-014-2957-6]
- 39 **Alkandari O**, Nampoory N, Nair P, Atta A, Zakaria Z, Mossad A, Yagan J, Al-Otaibi T. Recurrent Focal Segmental Glomerulosclerosis and Abatacept: Case Report. *Exp Clin Transplant* 2016; **14**: 456-459 [PMID: 25432003 DOI: 10.6002/ect.2014.0154]
- 40 **Rood IM**, Deegens JK, Wetzels JF. Genetic causes of focal segmental glomerulosclerosis: implications for clinical practice. *Nephrol Dial Transplant* 2012; **27**: 882-890 [PMID: 22334613 DOI: 10.1093/ndt/gfr771]
- 41 **Sadowski CE**, Lovric S, Ashraf S, Pabst WL, Gee HY, Kohl S, Engelmann S, Vega-Warner V, Fang H, Halbritter J, Somers MJ, Tan W, Shril S, Fessi I, Lifton RP, Bockenhauer D, El-Desoky S, Kari JA, Zenker M, Kemper MJ, Mueller D, Fathy HM, Soliman NA; SRNS Study Group, Hildebrandt F. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. *J Am Soc Nephrol* 2015; **26**: 1279-1289 [PMID: 25349199 DOI: 10.1681/ASN.2014050489]
- 42 **Xia Y**, Mao J, Jin X, Wang W, Du L, Liu A. Familial steroid-sensitive idiopathic nephrotic syndrome: seven cases from three families in China. *Clinics (Sao Paulo)* 2013; **68**: 628-631 [PMID: 23778422 DOI: 10.6061/clinics/2013(05)08]
- 43 **Giglio S**, Provenzano A, Mazzinghi B, Becherucci F, Giunti L, Sansavini G, Ravaglia F, Roperto RM, Farsetti S, Benetti E, Rotondi M, Murer L, Lazzeri E, Lasagni L, Materassi M, Romagnani P. Heterogeneous genetic alterations in sporadic nephrotic syndrome associate with resistance to immunosuppression. *J Am Soc Nephrol* 2015; **26**: 230-236 [PMID: 25060053 DOI: 10.1681/ASN.2013111155]
- 44 **Kitamura A**, Tsukaguchi H, Hiramoto R, Shono A, Doi T, Kagami S, Iijima K. A familial childhood-onset relapsing nephrotic syndrome. *Kidney Int* 2007; **71**: 946-951 [PMID: 17290294 DOI: 10.1038/sj.ki.5002110]
- 45 **Isojima T**, Harita Y, Furuyama M, Sugawara N, Ishizuka K, Horita S, Kajiho Y, Miura K, Igarashi T, Hattori M, Kitanaka S. LMX1B mutation with residual transcriptional activity as a cause of isolated glomerulopathy. *Nephrol Dial Transplant* 2014; **29**: 81-88 [PMID: 24042019 DOI: 10.1093/ndt/gft359]
- 46 **Gee HY**, Ashraf S, Wan X, Vega-Warner V, Esteve-Rudd J, Lovric S, Fang H, Hurd TW, Sadowski CE, Allen SJ, Otto EA, Korkmaz E, Washburn J, Levy S, Williams DS, Bakkaloglu SA, Zolotnitskaya A, Ozaltin F, Zhou W, Hildebrandt F. Mutations in EMP2 cause childhood-onset nephrotic syndrome. *Am J Hum Genet* 2014; **94**: 884-890 [PMID: 24814193 DOI: 10.1016/j.ajhg.2014.04.010]
- 47 **Gee HY**, Zhang F, Ashraf S, Kohl S, Sadowski CE, Vega-Warner V, Zhou W, Lovric S, Fang H, Nettleton M, Zhu JY, Hoefele J, Weber LT, Podracka L, Boor A, Fehrenbach H, Innis JW, Washburn J, Levy S, Lifton RP, Otto EA, Han Z, Hildebrandt F. KANK deficiency leads to podocyte dysfunction and nephrotic syndrome. *J Clin Invest* 2015; **125**: 2375-2384 [PMID: 25961457 DOI: 10.1172/JCI79504]

- 48 **Ashraf S**, Kudo H, Rao J, Kikuchi A, Widmeier E, Lawson JA, Tan W, Hermle T, Warejko JK, Shril S, Airik M, Jobst-Schwan T, Lovric S, Braun DA, Gee HY, Schapiro D, Majmundar AJ, Sadowski CE, Pabst WL, Daga A, van der Ven AT, Schmidt JM, Low BC, Gupta AB, Tripathi BK, Wong J, Campbell K, Metcalfe K, Schanze D, Niihori T, Kaito H, Nozu K, Tsukaguchi H, Tanaka R, Hamahira K, Kobayashi Y, Takizawa T, Funayama R, Nakayama K, Aoki Y, Kumagai N, Iijima K, Fehrenbach H, Kari JA, El Desoky S, Jalalah S, Bogdanovic R, Stajić N, Zappel H, Rakhmetova A, Wassmer SR, Jungrathmayr T, Strehlau J, Kumar AS, Bagga A, Soliman NA, Mane SM, Kaufman L, Lowy DR, Jairajpuri MA, Lifton RP, Pei Y, Zenker M, Kure S, Hildebrandt F. Mutations in six nephrosis genes delineate a pathogenic pathway amenable to treatment. *Nat Commun* 2018; **9**: 1960 [PMID: 29773874 DOI: 10.1038/s41467-018-04193-w]
- 49 **Okamoto K**, Tokunaga K, Doi K, Fujita T, Suzuki H, Katoh T, Watanabe T, Nishida N, Mabuchi A, Takahashi A, Kubo M, Maeda S, Nakamura Y, Noiri E. Common variation in GPC5 is associated with acquired nephrotic syndrome. *Nat Genet* 2011; **43**: 459-463 [PMID: 21441931 DOI: 10.1038/ng.792]
- 50 **Gbadegesin RA**, Adeyemo A, Webb NJ, Greenbaum LA, Abeyagunawardena A, Thalagahagoda S, Kale A, Gipson D, Srivastava T, Lin JJ, Chand D, Hunley TE, Brophy PD, Bagga A, Sinha A, Rheault MN, Ghali J, Nicholls K, Abraham E, Janjua HS, Omolaja A, Barletta GM, Cai Y, Milford DD, O'Brien C, Awan A, Belostotsky V, Smoyer WE, Homstad A, Hall G, Wu G, Nagaraj S, Wigfall D, Foreman J, Winn MP; Mid-West Pediatric Nephrology Consortium. HLA-DQA1 and PLCG2 Are Candidate Risk Loci for Childhood-Onset Steroid-Sensitive Nephrotic Syndrome. *J Am Soc Nephrol* 2015; **26**: 1701-1710 [PMID: 25349203 DOI: 10.1681/ASN.2014030247]
- 51 **Jia X**, Horinouchi T, Hitomi Y, Shono A, Khor SS, Omai Y, Kojima K, Kawai Y, Nagasaki M, Kaku Y, Okamoto T, Ohwada Y, Ohta K, Okuda Y, Fujimaru R, Hatae K, Kumagai N, Sawanobori E, Nakazato H, Ohtsuka Y, Nakanishi K, Shima Y, Tanaka R, Ashida A, Kamei K, Ishikura K, Nozu K, Tokunaga K, Iijima K; Research Consortium on Genetics of Childhood Idiopathic Nephrotic Syndrome in Japan. Strong Association of the *HLA-DR/DQ* Locus with Childhood Steroid-Sensitive Nephrotic Syndrome in the Japanese Population. *J Am Soc Nephrol* 2018; **29**: 2189-2199 [PMID: 30012571 DOI: 10.1681/ASN.2017080859]
- 52 **Jia X**, Yamamura T, Gbadegesin R, McNulty MT, Song K, Nagano C, Hitomi Y, Lee D, Aiba Y, Khor SS, Ueno K, Kawai Y, Nagasaki M, Noiri E, Horinouchi T, Kaito H, Hamada R, Okamoto T, Kamei K, Kaku Y, Fujimaru R, Tanaka R, Shima Y; Research Consortium on Genetics of Childhood Idiopathic Nephrotic Syndrome in Japan, Baek J, Kang HG, Ha IS, Han KH, Yang EM; Korean Consortium of Hereditary Renal Diseases in Children, Abeyagunawardena A, Lane B, Chryst-Stangl M, Esezobor C, Solarin A; Midwest Pediatric Nephrology Consortium (Genetics of Nephrotic Syndrome Study Group), Dossier C, Deschênes G; NEPHROVIR, Vivarelli M, Debiec H, Ishikura K, Matsuo M, Nozu K, Ronco P, Cheong HI, Sampson MG, Tokunaga K, Iijima K. Common risk variants in NPHS1 and TNFSF15 are associated with childhood steroid-sensitive nephrotic syndrome. *Kidney Int* 2020; **98**: 1308-1322 [PMID: 32554042 DOI: 10.1016/j.kint.2020.05.029]
- 53 **Greka A**, Mundel P. Cell biology and pathology of podocytes. *Annu Rev Physiol* 2012; **74**: 299-323 [PMID: 22054238 DOI: 10.1146/annurev-physiol-020911-153238]
- 54 **Garg P**, Holzman LB. Podocytes: gaining a foothold. *Exp Cell Res* 2012; **318**: 955-963 [PMID: 22421512 DOI: 10.1016/j.yexcr.2012.02.030]
- 55 **Harita Y**, Kurihara H, Kosako H, Tezuka T, Sekine T, Igarashi T, Ohsawa I, Ohta S, Hattori S. Phosphorylation of Nephron Triggers Ca²⁺ Signaling by Recruitment and Activation of Phospholipase C- γ 1. *J Biol Chem* 2009; **284**: 8951-8962 [PMID: 19179337 DOI: 10.1074/jbc.M806851200]
- 56 **Jones N**, Blasutig IM, Eremina V, Ruston JM, Bladt F, Li H, Huang H, Larose L, Li SS, Takano T, Quaggin SE, Pawson T. Nck adaptor proteins link nephrin to the actin cytoskeleton of kidney podocytes. *Nature* 2006; **440**: 818-823 [PMID: 16525419 DOI: 10.1038/nature04662]
- 57 **Hattori S**, Kanda S, Harita Y. Tyrosine kinase signaling in kidney glomerular podocytes. *J Signal Transduct* 2011; **2011**: 317852 [PMID: 21776384 DOI: 10.1155/2011/317852]
- 58 **MacDonald NE**, Wolfish N, McLaine P, Phipps P, Rossier E. Role of respiratory viruses in exacerbations of primary nephrotic syndrome. *J Pediatr* 1986; **108**: 378-382 [PMID: 3005537 DOI: 10.1016/s0022-3476(86)80876-9]
- 59 **Jamin A**, Dehoux L, Dossier C, Fila M, Heming N, Monteiro RC, Deschênes G. Toll-like receptor 3 expression and function in childhood idiopathic nephrotic syndrome. *Clin Exp Immunol* 2015; **182**: 332-345 [PMID: 26123900 DOI: 10.1111/cei.12659]
- 60 **Mishra OP**, Kumar R, Narayan G, Srivastava P, Abhinav A, Prasad R, Singh A, Batra VV. Toll-like receptor 3 (TLR-3), TLR-4 and CD80 expression in peripheral blood mononuclear cells and urinary CD80 levels in children with idiopathic nephrotic syndrome. *Pediatr Nephrol* 2017; **32**: 1355-1361 [PMID: 28210837 DOI: 10.1007/s00467-017-3613-8]
- 61 **Misako M**, Tsukasa S. Function of Toll-like receptor. *J Jap Bio Soci* 2009; **81**: 156-164 [DOI: 10.1042/bj20131492]
- 62 **Lanaspa M**, Andres-herando A, Cicerchi C, Johnson RJ. (TH-PO074) Novel role for podocyte SIRP α and pulmonary surfactants in minimal change disease. *J Am Soc Nephrol* 2017; **28**: 122 [DOI: 10.1038/ncomms14181]
- 63 **Kurihara H**, Harita Y, Ichimura K, Hattori S, Sakai T. SIRP- α -CD47 system functions as an intercellular signal in the renal glomerulus. *Am J Physiol Renal Physiol* 2010; **299**: F517-F527 [PMID: 20554646 DOI: 10.1152/ajprenal.00571.2009]
- 64 **Kajiho Y**, Harita Y, Kurihara H, Horita S, Matsunaga A, Tsurumi H, Kanda S, Sugawara N, Miura K,

- Sekine T, Hattori S, Hattori M, Igarashi T. SIRP α interacts with nephrin at the podocyte slit diaphragm. *FEBS J* 2012; **279**: 3010-3021 [PMID: [22747997](#) DOI: [10.1111/j.1742-4658.2012.08682.x](#)]
- 65 **Takahashi S**, Tomioka M, Hiromura K, Sakairi T, Hamatani H, Watanabe M, Ikeuchi H, Kaneko Y, Maeshima A, Aoki T, Ohnishi H, Matozaki T, Nojima Y. SIRP α signaling regulates podocyte structure and function. *Am J Physiol Renal Physiol* 2013; **305**: F861-F870 [PMID: [23842779](#) DOI: [10.1152/ajprenal.00597.2012](#)]
- 66 **Fournier B**, Andargachew R, Robin AZ, Laur O, Voelker DR, Lee WY, Weber D, Parkos CA. Surfactant protein D (Sp-D) binds to membrane-proximal domain (D3) of signal regulatory protein α (SIRP α), a site distant from binding domain of CD47, while also binding to analogous region on signal regulatory protein β (SIRP β). *J Biol Chem* 2012; **287**: 19386-19398 [PMID: [22511785](#) DOI: [10.1074/jbc.M111.324533](#)]
- 67 **Lin CY**. (FR-OR022) Rhinovirus-induced defect of CTLA-4 expression plays a critical role in relapse of childhood idiopathic nephrotic syndrome. *J Am Soc Nephrol* 2017; **28**: 42
- 68 **Hiroyuki K**. Basics of EB virus and infectious pathology. *Shinshu Med J* 2016; **64**: 173-181 [DOI: [10.1136/jcp.25.suppl_6.58](#)]
- 69 **Dossier C**, Sellier-Leclerc AL, Rousseau A, Michel Y, Gautheret-Dejean A, Englender M, Madhi F, Charbit M, Ulinski T, Simon T, Jacqz-Aigrain E, Deschênes G. Prevalence of herpesviruses at onset of idiopathic nephrotic syndrome. *Pediatr Nephrol* 2014; **29**: 2325-2331 [PMID: [24899237](#) DOI: [10.1007/s00467-014-2860-1](#)]
- 70 **Dossier C**, Jamin A, Deschênes G. Idiopathic nephrotic syndrome: the EBV hypothesis. *Pediatr Res* 2017; **81**: 233-239 [PMID: [27682967](#) DOI: [10.1038/pr.2016.200](#)]
- 71 **Lin CY**, Hsu HC. Histopathological and immunological studies in spontaneous remission of nephrotic syndrome after intercurrent measles infection. *Nephron* 1986; **42**: 110-115 [PMID: [3484807](#) DOI: [10.1159/000183647](#)]
- 72 **Tamura H**, Kuraoka S, Hidaka Y, Nagata H, Furuie K, Nakazato H. A Case of Nephrotic Syndrome that Resolved with Influenza B Infection. *Case Rep Nephrol Dial* 2021; **11**: 103-109 [PMID: [34055920](#) DOI: [10.1159/000515062](#)]
- 73 **Sellin CI**, Jégou JF, Renneson J, Druelle J, Wild TF, Marie JC, Horvat B. Interplay between virus-specific effector response and Foxp3 regulatory T cells in measles virus immunopathogenesis. *PLoS One* 2009; **4**: e4948 [PMID: [19319188](#) DOI: [10.1371/journal.pone.0004948](#)]
- 74 **Kimata T**, Tsuji S, Kino J, Kitao T, Yamanouchi S, Kaneko K. Close association between proteinuria and regulatory T cells in patients with idiopathic nephrotic syndrome. *Pediatr Nephrol* 2013; **28**: 667-669 [PMID: [23263711](#) DOI: [10.1007/s00467-012-2387-2](#)]
- 75 **Betts RJ**, Prabhu N, Ho AW, Lew FC, Hutchinson PE, Rotzschke O, Macary PA, Kemeny DM. Influenza A virus infection results in a robust, antigen-responsive, and widely disseminated Foxp3+ regulatory T cell response. *J Virol* 2012; **86**: 2817-2825 [PMID: [22205730](#) DOI: [10.1128/JVI.05685-11](#)]
- 76 **Karagiannidis C**, Akdis M, Holopainen P, Woolley NJ, Hense G, Rückert B, Mantel PY, Menz G, Akdis CA, Blaser K, Schmidt-Weber CB. Glucocorticoids upregulate FOXP3 expression and regulatory T cells in asthma. *J Allergy Clin Immunol* 2004; **114**: 1425-1433 [PMID: [15577848](#) DOI: [10.1016/j.jaci.2004.07.014](#)]
- 77 **Xing CY**, Saleem MA, Coward RJ, Ni L, Witherden IR, Mathieson PW. Direct effects of dexamethasone on human podocytes. *Kidney Int* 2006; **70**: 1038-1045 [PMID: [16837924](#) DOI: [10.1038/sj.ki.5001655](#)]
- 78 **Hussain S**, Romio L, Saleem M, Mathieson P, Serrano M, Moscat J, Diaz-Meco M, Scambler P, Koziell A. Nephrin deficiency activates NF-kappaB and promotes glomerular injury. *J Am Soc Nephrol* 2009; **20**: 1733-1743 [PMID: [19497968](#) DOI: [10.1681/ASN.2008111219](#)]
- 79 **Faul C**, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, Chang JM, Choi HY, Campbell KN, Kim K, Reiser J, Mundel P. The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 2008; **14**: 931-938 [PMID: [18724379](#) DOI: [10.1038/nm.1857](#)]
- 80 **Datta SK**. Anti-CD20 antibody is an efficient therapeutic tool for the selective removal of autoreactive T cells. *Nat Clin Pract Rheumatol* 2009; **5**: 80-82 [PMID: [19092831](#) DOI: [10.1038/ncprheum0983](#)]



Lemierre's syndrome caused by *Klebsiella pneumoniae*: A case report

So Yeon Hwang, Seok Joon Shin, Hye Eun Yoon

ORCID number: So Yeon Hwang 0000-0001-9233-470X; Seok Joon Shin 0000-0001-7642-2849; Hye Eun Yoon 0000-0002-6347-7282.

Author contributions: Hwang SY reviewed the literature and contributed to manuscript drafting; Shin SJ and Yoon HE were responsible for the revision of the manuscript for important intellectual content; all authors approved the final version of the manuscript to be submitted.

Informed consent statement:

Informed consent was obtained from the patients and their caregivers. The images were published in agreement with the patient.

Conflict-of-interest statement:

None of the authors have any financial or other conflicts of interest to declare with regard to this manuscript.

CARE Checklist (2016) statement:

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in

So Yeon Hwang, Seok Joon Shin, Hye Eun Yoon, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon 21431, South Korea

Corresponding author: Seok Joon Shin, MD, PhD, Full Professor, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 56 Dongsuro, Bupyeong-Gu, Incheon 21431, South Korea. imkidney@catholic.ac.kr

Abstract

BACKGROUND

Lemierre's syndrome is a disease that causes anaerobic sepsis, internal jugular vein thrombosis, and septic embolism in the lungs and other organs after acute oropharyngeal infection. It was named after André-Alfred Lemierre in 1936.

CASE SUMMARY

Here, we have reported a case of Lemierre's syndrome in a 56-year-old female patient who presented with a sore throat. The patient had septic shock, had not voided, and had severe hyperglycemia at the time of her visit. Imaging tests revealed bilateral pneumonia, pleural effusion, pulmonary embolism, and renal vein thrombosis. The patient was admitted to the intensive care unit and placed on mechanical ventilation due to acute respiratory distress syndrome. Continuous renal replacement therapy was administered to treat renal failure with anuria. *Klebsiella pneumoniae* was cultured from blood and sputum samples. After reviewing various results, the patient was ultimately diagnosed with Lemierre's syndrome. The patient was treated with appropriate antibiotics and thrombolytic agents. She was discharged from the hospital after recovery.

CONCLUSION

Lemierre's syndrome is associated with a high mortality rate. Therefore, clinicians should be familiar with the signs and symptoms of this disease as well as the preemptive examinations, procedures, and treatments.

Key Words: Lemierre's syndrome; *Klebsiella pneumoniae*; Diabetes Mellitus; Pulmonary embolism; Septic pneumonia; Case report

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Specialty type: Medicine, general and internal

Country/Territory of origin: South Korea

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 24, 2021

Peer-review started: April 24, 2021

First decision: June 6, 2021

Revised: June 19, 2021

Accepted: July 30, 2021

Article in press: July 30, 2021

Published online: September 25, 2021

P-Reviewer: Dumic I, Shelat VG

S-Editor: Gong ZM

L-Editor: A

P-Editor: Ma YJ



Core Tip: Lemierre's syndrome is mostly caused by *Fusobacterium*. However, we present a rare case of Lemierre's syndrome caused by *Klebsiella pneumoniae* in a patient with poor glycemic control. Uncommon in Lemierre's syndrome, renal vein thrombosis and acute kidney injury occurred, continuous renal replacement therapy was performed, and mechanical ventilation was performed for serious pulmonary complications. The incidence of Lemierre's syndrome decreased after antibiotics were developed. However, when Lemierre's syndrome occurs, the mortality rate from its complications is high, so we want to emphasize that patients with systemic symptoms accompanied by fever and sore throat should be suspicious of Lemierre's syndrome.

Citation: Hwang SY, Shin SJ, Yoon HE. Lemierre's syndrome caused by *Klebsiella pneumoniae*: A case report. *World J Nephrol* 2021; 10(5): 101-108

URL: <https://www.wjgnet.com/2220-6124/full/v10/i5/101.htm>

DOI: <https://dx.doi.org/10.5527/wjn.v10.i5.101>

INTRODUCTION

Lemierre's syndrome, also known as postanginal sepsis, was first named in 1936 after the French microbiologist André-Alfred Lemierre. This syndrome is characterized by anaerobic sepsis and blood clots in the internal jugular vein (IJV) after acute oropharyngeal infection. It also causes septic embolism in the lungs and other organs [1].

Lemierre's syndrome is typically caused by *Fusobacterium necrophorum*, which is a part of the normal flora of the oropharynx. However, the recent development of various antibiotics and advancements in medical care have led to diversified and antibiotic-resistant strains.

Therefore, after referring to the current literature, we have reported a single case of Lemierre's syndrome caused by *Klebsiella pneumoniae* (*K. pneumoniae*). In accordance with the course of this disease, pulmonary embolism, occurring after oropharyngeal infection, developed into acute respiratory distress syndrome.

CASE PRESENTATION

Chief complaints

A 56-year-old female patient presented to the emergency department of our institution with sore throat, dyspnea, abdominal pain, and diarrhea.

History of present illness

The patient was unable to eat due to a sore throat and had been unable to take her diabetes medication for 5 d prior to the visit.

Subsequently, the patient visited the hospital with abdominal pain, diarrhea, and shortness of breath.

History of past illness

The patient had been prescribed medication for diabetes and hypertension 2 years previously. She also had a history of a canceled surgery for chronic right-sided otitis media.

Personal and family history

The patient had diabetes, hypertension, and chronic otitis media.

Physical examination

At the time of admission, the patient's blood pressure, pulse rate, respiratory rate, body temperature, and oxygen saturation level were 11.3/7.8 kPa, 104, 22, 36 °C, and 90%, respectively. The patient was conscious. Swelling and redness were observed in the left neck and both tonsils. Rales were auscultated throughout the chest. Auscultation of the abdomen revealed a normoactive bowel sound with no tenderness.

No urine was produced after catheter insertion.

Laboratory examinations

Blood tests revealed an evaluated white blood cell count ($16.47 \times 10^3/\mu\text{L}$), anemia (hemoglobin level, 7.2 g/dL; hematocrit level, 24.4%), renal failure (blood urea nitrogen, 78.8 mg/dL; creatinine level, 4.22 mg/dL). The patient was hyperglycemic, with a glucose level of 32.6 mmol/L. The patient had uncontrolled diabetes, with a glycated hemoglobin level of 11%. The C-reactive protein level was also elevated at 207.58 mg/dL. An arterial blood gas test revealed acidosis of pH 7.27. Additionally, a pCO_2 level of 25 mmHg, a pO_2 level of 83 mmHg, and a bicarbonate level of 11.5 mEq/L indicated metabolic acidosis.

The anion gap was 21.5 mEq/L, and the serum lactate level was 1.8 mmol/L. Therefore, a provisional diagnosis of lactic acidosis was established. Urine ketone was present in trace amounts. Spot urine microalbumin/creatinine ratio was 123.6 mg/gCr.

Imaging examinations

Chest radiography showed multiple patchy infiltrations in both lungs (Figure 1).

Chest computed tomography (CT) revealed peribronchial consolidation and ground-glass opacity with cavitary nodules in both lungs. Pulmonary thromboembolism (PTE) in the segmental and subsegmental pulmonary arteries of the right lower lobe was suspected (Figure 2).

Abdominal computed tomography showed extensive thrombosis in the left renal vein, extending to partial thrombosis in the suprarenal inferior vena cava (IVC).

A neck angio CT was performed on the third day to assess left neck swelling. A 13 mm $\times$ 10 mm nodular lesion was observed on the left parotid gland (Figure 3).

Further diagnostic work-up

For further evaluation, blood, sputum, and urine cultures, hypercoagulability test were performed.

The hypercoagulability test showed decreased protein S activity and less free protein S antigen but normal total protein S antigen, protein C activity, and protein C antigen. The von Willebrand factor and factor V Leiden were normal, and lupus anticoagulant level was elevated. However, anticardiolipin and anti- β_2 glycoprotein-1 antibodies were absent.

Additionally, the following findings were noted: prothrombin time, 14.5 s; antithrombin III, 72.1; D-dimer, 2.01; and fibrinogen, 926.1. These results did not meet the diagnostic criteria for disseminated intravascular coagulation.

On the fourth day of hospitalization, as pneumonia was worsening, sputum analysis was performed using bronchoalveolar lavage.

A fine-needle aspiration biopsy of the nodule on the left parotid gland was performed on day 14. The nodule was found on neck angio CT. Biopsy results indicated that the nodule consisted of inflammatory cells. Although there was a possibility of cervical lymphadenopathy, the mass was not removed and was closely observed.

The patient had a history of discontinued treatment for chronic right-sided otitis media. Therefore, she underwent otoscopy after being transferred to a general hospital unit. Chronic otitis media with cholesteatoma was suspected. An additional temporal bone was identified on CT. The focal bone defect was suspected to be the right tegmen mastoideum. Therefore, surgical therapy was considered after the acute inflammation was controlled.

Follow-up chest CT was performed as there was no further clinical improvement in pneumonia. Progression of invasive aspergillosis was observed.

Microbiological identification of the causative agent

K. pneumoniae was identified on culture of blood samples taken immediately after admission and on culture of sputum samples extracted *via* bronchoscopy. Except for piperacillin and ampicillin, the bacteria were susceptible to other antibiotics.

Aspergillus niger (*A. niger*) was identified on a follow-up sputum culture. The (1-3)- β -D-glucan assay confirmed the presence of invasive *Aspergillus*.



Figure 1 Chest radiography showed multiple patchy infiltrations at both lungs.



Figure 2 Computed tomography scan of the chest showed suspicious pulmonary thromboembolism in segmental and subsegmental pulmonary arteries of right lower lobe (orange arrow).

FINAL DIAGNOSIS

The final diagnosis was Lemierre's syndrome due to *K. pneumoniae*.

TREATMENT

After admission, the patient was transferred to the intensive care unit to undergo treatment for anuria and metabolic acidosis. After continuous renal replacement therapy and administration of a large amount of fluid, the patient started to urinate on the first day of hospitalization. Acute renal failure improved on the second day. However, oxygen demand gradually increased, and pneumonia was aggravated in both lungs on chest radiographs. Therefore, mechanical ventilation was initiated.

Piperacillin-tazobactam and levofloxacin were used as empirical antibiotics. They were used to simultaneously manage *Streptococcus pneumoniae* and *Pseudomonas spp.*,

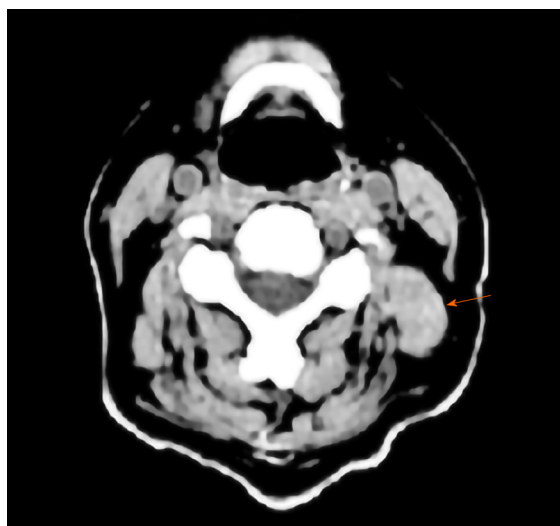


Figure 3 Computed tomography scan of the neck showed the 13 mm × 10 mm size nodular lesion (orange arrow) in left parotid gland.

the causative agents of severe community-acquired pneumonia. These antibiotics were selected based on previous reports of fluoroquinolone combination therapy leading to a better prognosis than β -lactam alone in severe cases[2].

Enoxaparin, a low-molecular-weight heparin, was initiated on the second day to treat the pulmonary thromboembolism.

However, the patient's clinical condition further deteriorated due to pneumonia. Therefore, on the fourth day, the initial antibiotics were replaced with vancomycin and meropenem.

As there was no improvement in pneumonia after the antibiotics were changed, mechanical ventilation was continued. On the ninth day, vancomycin was discontinued due to a lack of evidence of a gram-positive bacterial infection. Amikacin was added to meropenem. On day 13, improvement was seen in pneumonia. The patient's oxygen demand decreased, and therefore, she was weaned from mechanical respiratory support. She was subsequently transferred to a general hospital unit.

Moreover, *A. niger* was isolated in a follow-up sputum culture. Therefore, we started administering amphotericin following consultation with the infectious disease medical staff.

Subsequently, the patient recovered gradually, amphotericin was switched to itraconazole and low-molecular-weight heparin was switched to apixaban. She was ultimately discharged from the hospital.

OUTCOME AND FOLLOW-UP

Leukocytosis occurred on the 12th day after discharge; therefore, the patient was re-hospitalized. There was suspicion of an abscess in the right lung field. An air-fluid level was identified (Figure 4).

A. niger was not identified in the follow-up culture performed after hospitalization. *K. pneumoniae* susceptible to third-generation cephalosporins was identified, consistent with the initial culture result. Therefore, during hospitalization, piperacillin-tazobactam was administered. The patient was discharged with a prescription of ceftidoren and itraconazole.

Itraconazole was discontinued after 3 mo. The lung lesion with bilateral ground-glass opacity on radiography did not improve. Therefore, the patient continued taking ceftidoren and received continuous respiratory rehabilitation treatment. To reduce the risk of PTE recurrence, apixaban was administered for ≥ 6 mo.

DISCUSSION

In 1989, Sinave *et al*[3] summarized the key symptoms of Lemierre's syndrome and suggested the following diagnostic criteria: (1) Primary infection of the oropharynx; (2)



Figure 4 Chest radiography showed large cavitary consolidation with internal air-fluid level in right upper and middle lobes.

Sepsis with at least one bacteria identified on a blood culture; (3) Clinical or imaging findings of IJV thrombosis; and (4) At least one metastasis.

Lemierre's syndrome was a common disease until the development of antibiotics. However, recently it has become a rare disease and has been called the "forgotten disease"[1].

This disease occurs mainly in adolescents and young adults. However, its cause has not been clearly established.

In young adults, pharyngitis symptoms are observed during the initial stages of the disease. In contrast, elderly individuals manifest early metastatic complications, such as pneumonia and brain abscesses. This suggests that infection of the IJV causes complications in other organs through blood circulation. In recent studies, 7% cases of Lemierre's syndrome progressed to septic shock[4]. Pulmonary impairment was the most common metastatic complication, leading to pneumonia, pulmonary embolism, pleural effusion, pneumothorax, and thoracic empyema. A total of 10% cases required mechanical respiratory assistance for acute respiratory distress syndrome. This was the case in our study.

Less than 5% patients receive renal replacement therapy for acute renal failure[4]. However, for 2 d, our patient underwent continuous renal replacement therapy for acute kidney injury caused by septic shock and renal vein thrombosis.

Lemierre's syndrome is primarily caused by *Fusobacterium*, which are a part of the normal flora in the oropharynx, genitourinary tract, and gastrointestinal tract. Among the 13 species of *Fusobacterium*, *F. necrophorum* is the most common pathogen[5]. In other case reports, *Bacteroides* spp., *Streptococcus* spp., *Enterococcus* spp., *Peptostreptococci*, and *Proteus mirabilis* have been identified as pathogens.

In the present case, *K. pneumoniae* was the causative pathogen. However, *K. pneumoniae* has rarely been reported as a cause of Lemierre's syndrome in previous case reports. Based on some retrospective studies, only 2.5% cases have been reported to be caused by *K. pneumoniae*[6].

In a study published in 2015, eight of nine patients with Lemierre's syndrome associated with *K. pneumoniae* had poorly controlled diabetes[7].

Similarly, our patient had poor blood glucose control with a glycated hemoglobin level of 11% and a serum glucose level of 32.6 mmol/L at the time of admission.

Patients with type 2 diabetes mellitus are vulnerable to infection because of the decreased activity of neutrophils[8]. The underlying mechanism of the increased susceptibility of patients with type 2 diabetes mellitus to *K. pneumoniae* is as follows. The hypermucoviscosity phenotype of *K. pneumoniae*, especially K1/K2 isolates, is resistant to phagocytosis[9]. Poor glycemic control significantly reduces phagocytosis of virulent K1/K2 *K. pneumoniae*. Additionally, Lin *et al*[10] showed that older patients

with poor glycemic control had decreased phagocytosis activity.

Beta-lactamase-resistant beta-lactam antibiotics are recommended for typical Lemierre's syndrome. Beta-lactamase produced by *F. necrophorum* may lead to therapy failure[7].

Therefore, treatment should be changed from empirical antibiotics to targeted antibiotics based on the results of the blood culture and antibiotic susceptibility analysis.

If *K. pneumoniae* is the likely cause of Lemierre's syndrome, drugs that can also treat gram-negative aerobic rods should be used until the causative pathogen is identified. Additionally, the appropriate drug must be selected based on the susceptibility data of *K. pneumoniae* in the region and the risk of an Extended-spectrum beta-lactamases-producing strain[11,12].

In our patient, IJV thrombosis was not observed. Instead, pulmonary thromboembolism, partial thrombosis of the suprarenal IVC, and extensive thrombosis of the left renal vein were observed.

The hypercoagulability test results led to the suspicion of protein S deficiency. However, protein S deficiency is difficult to diagnose solely based on the results obtained once in the acute phase[13].

We have scheduled another test for the protein S deficiency diagnosis 3 mo later. Since prolonged prothrombin time and decreased antithrombin III levels are common in sepsis, the result was considered to be non-specific.

We compared the hypercoagulability properties of *F. necrophorum* and *K. pneumoniae* because they are related to the pathogenesis of Lemierre's syndrome.

F. necrophorum produces a component of the cell surface called hemagglutinin, which forms thrombi[4]. Russo *et al*[14] have suggested that this is because *K. pneumoniae* causes more frequent metastatic spread in the K1/K2 group. Another possibility is increased capsule production in the hypervirulent type.

Although the hypothesis has not been tested, it appears that the mucoviscosity of the strain's thick capsules persists in the bloodstream and causes greater aggregation of bacterial cells to form thrombi[14].

The role of anticoagulation for IJV thrombosis is controversial. As Lemierre's syndrome has a low incidence rate, there is a lack of controlled investigations for anticoagulation treatment.

Also, anticoagulation medication was introduced to prevent respiratory failure and propagation of the septic thrombus to the intracranial sinuses.

There is no clear evidence to outline the appropriate duration of anticoagulation treatment. Previously reported findings suggest a duration of 4 wk to 6 mo[15]. Schubert *et al*[16] analyzed 23 patients diagnosed with septic thrombosis of the IJV from 1998 to 2010. The primary infection site in 11 patients was the middle ear[16]. Otitis is a common disease. However, it can progress to systematic infection by forming septic thromboses in the IJV. Therefore, source control is fundamental even if it is a local infection.

In addition, the incidence rate of Lemierre's syndrome is increasing again in recent years. The development of various antibiotics and advancements in medical care have led to the emergence of various new pathogenic strains and multidrug-resistant strains. The syndrome may be fatal as it is accompanied by numerous systemic complications. Therefore, Lemierre's syndrome must be suspected in cases of fever or throat pain associated with infections of the oropharynx and middle ear. Preemptive examinations, consultation with other specialists, appropriate procedures, and targeted treatments are essential.

CONCLUSION

The primary site of infection in Lemierre's syndrome is the oropharynx. Oropharyngeal infections cause IJV thrombosis and anaerobic sepsis. The disease typically manifests as sore throat, a symptom of oropharyngeal infection. This can lead to metastatic complications and death. Lemierre's syndrome is a rare disease[17]. Therefore, it is difficult for doctors with no experience with this syndrome to suspect it [5]. In addition, symptoms of oropharyngeal infection are often resolved when the patient visits the hospital. This disease should be considered in the differential diagnosis when systemic complications caused by upper respiratory tract infection are suspected.

Atypical Lemierre's syndrome should be suspected in cases in which a typical causative strain is not identified or cases of thromboembolism at a site other than the

IJV thrombosis. After diagnosis, it is essential to assess whether surgery or intervention is necessary through active consultation with other specialists. Appropriate antibiotic treatment according to the causative strain must be initiated.

REFERENCES

- 1 **Johannesen KM**, Bodtger U. Lemierre's syndrome: current perspectives on diagnosis and management. *Infect Drug Resist* 2016; **9**: 221-227 [PMID: [27695351](#) DOI: [10.2147/IDR.S95050](#)]
- 2 **Martínez JA**, Horcajada JP, Almela M, Marco F, Soriano A, García E, Marco MA, Torres A, Mensa J. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. *Clin Infect Dis* 2003; **36**: 389-395 [PMID: [12567294](#) DOI: [10.1086/367541](#)]
- 3 **Sinave CP**, Hardy GJ, Fardy PW. The Lemierre syndrome: suppurative thrombophlebitis of the internal jugular vein secondary to oropharyngeal infection. *Medicine* **68**: 85-94 [PMID: [2646510](#)]
- 4 **Riordan T**. Human infection with *Fusobacterium necrophorum* (Necrobacillosis), with a focus on Lemierre's syndrome. *Clin Microbiol Rev* 2007; **20**: 622-659 [PMID: [17934077](#) DOI: [10.1128/CMR.00011-07](#)]
- 5 **Kuppalli K**, Livorsi D, Talati NJ, Osborn M. Lemierre's syndrome due to *Fusobacterium necrophorum*. *Lancet Infect Dis* 2012; **12**: 808-815 [PMID: [22633566](#) DOI: [10.1016/S1473-3099\(12\)70089-0](#)]
- 6 **Garbati MA**, Ahsan AM, Hakawi AM. Lemierre's syndrome due to *Klebsiella pneumoniae* in a 63-year-old man with diabetes: a case report. *J Med Case Rep* 2012; **6**: 97 [PMID: [22472458](#) DOI: [10.1186/1752-1947-6-97](#)]
- 7 **Chuncharunee A**, Khawcharoenporn T. Lemierre's Syndrome Caused by *Klebsiella pneumoniae* in a Diabetic Patient: A Case Report and Review of the Literature. *Hawaii J Med Public Health* 2015; **74**: 260-266 [PMID: [26279962](#)]
- 8 **Delamaire M**, Maugeudre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. *Diabet Med* 1997; **14**: 29-34 [PMID: [9017350](#) DOI: [10.1002/\(SICI\)1096-9136\(199701\)14:1<29::AID-DIA300>3.0.CO;2-V](#)]
- 9 **Lin JC**, Chang FY, Fung CP, Xu JZ, Cheng HP, Wang JJ, Huang LY, Siu LK. High prevalence of phagocytic-resistant capsular serotypes of *Klebsiella pneumoniae* in liver abscess. *Microbes Infect* 2004; **6**: 1191-1198 [PMID: [15488738](#) DOI: [10.1016/j.micinf.2004.06.003](#)]
- 10 **Lin JC**, Siu LK, Fung CP, Tsou HH, Wang JJ, Chen CT, Wang SC, Chang FY. Impaired phagocytosis of capsular serotypes K1 or K2 *Klebsiella pneumoniae* in type 2 diabetes mellitus patients with poor glycemic control. *J Clin Endocrinol Metab* 2006; **91**: 3084-3087 [PMID: [16720670](#) DOI: [10.1210/jc.2005-2749](#)]
- 11 **Paterson DL**, Ko WC, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, Mulazimoglu L, Trenholme G, Klugman KP, Bonomo RA, Rice LB, Wagener MM, McCormack JG, Yu VL. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum beta-lactamases. *Clin Infect Dis* 2004; **39**: 31-37 [PMID: [15206050](#) DOI: [10.1086/420816](#)]
- 12 **Sabaka P**, Kachlíková M, Bendžala M, Káčerová H. Lemierre syndrome caused by *Klebsiella pneumoniae* complicated by epidural abscess - Case report. *IDCases* 2020; **19**: e00664 [PMID: [32226757](#) DOI: [10.1016/j.idcr.2019.e00664](#)]
- 13 **Campello E**, Spiezia L, Simion C, Tormene D, Camporese G, Dalla Valle F, Poretto A, Bulato C, Gavasso S, Radu CM, Simioni P. Direct Oral Anticoagulants in Patients With Inherited Thrombophilia and Venous Thromboembolism: A Prospective Cohort Study. *J Am Heart Assoc* 2020; **9**: e018917 [PMID: [33222589](#) DOI: [10.1161/JAHA.120.018917](#)]
- 14 **Russo TA**, Marr CM. Hypervirulent *Klebsiella pneumoniae*. *Clin Microbiol Rev* 2019; **32** [PMID: [31092506](#) DOI: [10.1128/CMR.00001-19](#)]
- 15 **Phua CK**, Chadachan VM, Acharya R. Lemierre syndrome-should we anticoagulate? *Int J Angiol* 2013; **22**: 137-142 [PMID: [24436600](#) DOI: [10.1055/s-0033-1336828](#)]
- 16 **Schubert AD**, Hotz MA, Caversaccio MD, Arnold A. Septic thrombosis of the internal jugular vein: Lemierre's syndrome revisited. *Laryngoscope* 2015; **125**: 863-868 [PMID: [25387698](#) DOI: [10.1002/lary.24995](#)]
- 17 **Hagelskjaer Kristensen L**, Prag J. Lemierre's syndrome and other disseminated *Fusobacterium necrophorum* infections in Denmark: a prospective epidemiological and clinical survey. *Eur J Clin Microbiol Infect Dis* 2008; **27**: 779-789 [PMID: [18330604](#) DOI: [10.1007/s10096-008-0496-4](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>



World Journal of *Nephrology*

World J Nephrol 2021 November 25; 10(6): 109-121



ORIGINAL ARTICLE

Prospective Study

- 109 Efficacy and safety of recombinant human erythropoietin (Hema-Plus®) for management of anemia in Thai patients on peritoneal dialysis

Chuengsaman P, Narenpitak S, Sritippayawan S

ABOUT COVER

Editorial Board Member of *World Journal of Nephrology*, Saeed Taheri, MD, Founder & Director, the New Lahijan Scientific Foundation, Hasheminejad 3rd ave, Lahijan 44158, Iran. taherimd@gmail.com

AIMS AND SCOPE

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

WJN mainly publishes articles reporting research results obtained in the field of nephrology and covering a wide range of topics including acute kidney injury, acute or chronic interstitial nephritis, AIDS-associated nephropathy, anuria, chronic kidney disease and related complications, CKD-MBD, diabetes insipidus, diabetic nephropathies, Fanconi syndrome, glomerular diseases, inborn or acquired errors renal tubular transport, renal hypertension, kidney cortex necrosis, renal artery obstruction, renal nutcracker syndrome, renal tuberculosis, renal tubular acidosis, thrombotic microangiopathy, uremia, and Zellweger syndrome, *etc.*

INDEXING/ABSTRACTING

The WJN is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Rui-Rui Wu, Production Department Director: Yu-Jie Ma, Editorial Office Director: Yan-Xia Xing.

NAME OF JOURNAL

World Journal of Nephrology

ISSN

ISSN 2220-6124 (online)

LAUNCH DATE

February 6, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Li Zuo, Ying-Yong Zhao

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2220-6124/editorialboard.htm>

PUBLICATION DATE

November 25, 2021

COPYRIGHT

© 2021 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Prospective Study

Efficacy and safety of recombinant human erythropoietin (Hema-Plus®) for management of anemia in Thai patients on peritoneal dialysis

Piyatida Chuengsamarn, Surapong Narenpitak, Suchai Sritippayawan

ORCID number: Piyatida Chuengsamarn 0000-0002-8521-7721; Surapong Narenpitak 0000-0002-6903-5039; Suchai Sritippayawan 0000-0002-2291-1580.

Author contributions: All authors contributed in design and oversight of the study, and were involved with data collection at their sites, reviewed the results from statistical analysis and interpretation of the statistic results, read and approved the final manuscript; Chuengsamarn P mainly drafted the manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee, Institute for the Development of Human Research Protections (IHRP), No. IHRP 2365/2556; The Ethics Committee of Udon Thani Hospital, No. 8/2559; and Siriraj Institutional Review Board Faculty of Medicine Siriraj Hospital, Mahidol University, No. Si 588/2016.

Clinical trial registration statement: The study was registered on the Thai Clinical Trial Registry (TCTR), <http://www.thaiclinicaltrials.org/> (TCTR ID: 20140128002).

Informed consent statement: All

Piyatida Chuengsamarn, Banphaeo Dialysis Group, Banphaeo Hospital (Public Organization), Banphaeo 74120, Samutsakhon, Thailand

Surapong Narenpitak, Department of Medicine, Udon Thani Hospital, Udon Thani 41000, Thailand

Suchai Sritippayawan, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Corresponding author: Piyatida Chuengsamarn, MD, Doctor, Banphaeo Dialysis Group, Banphaeo Hospital (Public Organization), 198 Moo 1 Banphaeo, Banphaeo 74120, Samutsakhon, Thailand. pchuengsamarn@gmail.com

Abstract

BACKGROUND

Hema-Plus, a recombinant human erythropoietin (rHuEPO) or epoetin alfa has shown effectiveness in correction of anemia in Thai population in clinical practice. This study was aimed to demonstrate efficacy and safety under the evidence-based approach.

AIM

To evaluate the efficacy and safety of rHuEPO (Hema-Plus) for treatment of anemia over 12 wk in Thai patients with Stage V chronic kidney disease (CKD) on peritoneal dialysis (PD).

METHODS

This study was an open-label, multi-center study to enroll 30 CKD patients identified to start PD with hemoglobin (Hb) less than 9.5 g/dL, serum ferritin more than 100 ng/mL, serum transferrin saturation more than or equal to 20% and who had not previously received epoetin. Patients with conditions that could increase the risk of adverse effects from study participation or interfere with study outcomes, were using concomitant androgens or had secondary hyperparathyroidism were excluded. All eligible patients started Hema-Plus by SC injection at 4000 IU once or twice weekly (week 0) and with follow-up at weeks 2, 4, 8, and 12. Dosage adjustment could be done to achieve Hb level of 11-12 g/dL. Primary end point was mean change in Hb level from baseline to end of treatment (week

study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors declare no potential conflicting interests related to this paper. Although, Apexcela Co., Ltd. supported for the study funding and medication, the study was conducted and the study results were interpreted without the influence of the pharmaceutical company.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: We did not use CONSORT (for reporting a randomised trial).

Country/Territory of origin: Thailand

Specialty type: Urology and nephrology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 2
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Received: May 9, 2021

Peer-review started: May 9, 2021

First decision: June 6, 2021

Revised: August 19, 2021

12). Safety was assessed throughout the study. Quality of life (QoL) was assessed using KDQOL-36.

RESULTS

All 30 enrolled patients completed the study. Mean (standard deviation) Hb at baseline (week 0) to the end of 12 wk was significantly increased from 7.39 (1.29) g/dL to 11.15 (1.73) g/dL (paired *t*-test, *P* value < 0.001). Overall change of Hb means from baseline over the other 4 visits was statistically significantly increased (repeated measure ANOVA, *P* value < 0.001). Ten out of 39 adverse events (AEs) were serious. Two serious AEs were probably related to study medication by investigators' assessment. At week 12, the QoL scores in all domains were significantly increased from baseline.

CONCLUSION

Hema-Plus administered for 12 wk for treatment of anemia in patients on PD effectively increased Hb levels with acceptable safety profile.

Key Words: Recombinant human erythropoietin; Anemia; Peritoneal dialysis; Chronic kidney disease; Epoetin alfa

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: This was an open-label, single-arm, prospective, multicenter study of Hema-Plus®, a recombinant human erythropoietin (rHuEPO) for management of anemia in 30 Thai chronic kidney disease patients who started peritoneal dialysis with hemoglobin (Hb) lower than 9.5 g/dL and who had not previously received epoetin. The results showed that the rHuEPO could significantly increase Hb from baseline throughout the 12-wk treatment duration with acceptable safety profile. The quality of life (QoL) scores at week 12 assessed using KDQOL-36 were significantly increased from baseline in all domains.

Citation: Chuengsamarn P, Narenpitak S, Sritippayawan S. Efficacy and safety of recombinant human erythropoietin (Hema-Plus®) for management of anemia in Thai patients on peritoneal dialysis. *World J Nephrol* 2021; 10(6): 109-121

URL: <https://www.wjgnet.com/2220-6124/full/v10/i6/109.htm>

DOI: <https://dx.doi.org/10.5527/wjn.v10.i6.109>

INTRODUCTION

Anemia is a common condition among patients with chronic kidney disease (CKD). This anemia is an almost inevitable feature of CKD, especially end-stage renal disease because the kidneys play an important role in the production of erythropoietin which supports erythropoiesis. Renal anemia begins in early stages of CKD and worsens as it progresses[1,2]. When anemia is left untreated the consequences can be severe. The more dangerous impacts include cardiovascular disease, worsening angina symptoms, left ventricular hypertrophy (LVH) and congestive heart failure. These abnormalities reduce the quality of life (QoL), interfere with rehabilitation and decrease survival in patients with CKD[1,3-5].

The primary etiology of anemia associated with CKD is insufficient renal production of the erythropoietin. Additionally, other factors contributing to anemia in CKD include iron deficiency, hyperparathyroidism, acute and chronic inflammatory disease, and shortened red blood cell survival[4,6]. The treatment of anemia in patients with CKD provides the following known beneficial effects: A reduced requirement for blood transfusions and associated complications, improved QoL, decreased hospitalizations and reduced overall healthcare costs[4,5].

The use of erythropoiesis-stimulating agents (ESAs) for treatment of renal anemia can relieve the anemia symptoms and improve QoL[7,8]. Recombinant human erythropoietin (rHuEPO) or epoetin alfa is generally well tolerated. In patients with chronic renal failure the adverse events (AEs) reported from a clinical point of view

Accepted: September 15, 2021

Article in press: September 15, 2021

Published online: November 25, 2021

P-Reviewer: Techane T

S-Editor: Fan JR

L-Editor: A

P-Editor: Wu RR



include hypertension, increased blood pressure, seizures, thrombotic vascular events, headache, increased heart rate, nausea, vomiting, diarrhea, pyrexia, hypercalcemia, hyperkalemia, hypersensitivity reaction (rash, urticarial, anaphylactic reaction, angioedema), and increased incidence of thrombotic vascular events. A rare, but serious complication related to epoetin is antibody-mediated pure red cell aplasia (PRCA)[8, 9]. When treated with ESA, patients with anemia and CKD may encounter hyporesponsiveness. Many factors contribute to ESA hyporesponsiveness such as iron deficiency, non-adherence to iron or ESA therapy, acute/chronic blood loss, infection, inflammation, inadequate dialysis, aluminum overload, malignancy, chronic conditions, hyperparathyroidism, and PRCA[3,10]. Practice guidelines suggest evaluation for specific causes of hyporesponsiveness when the Hb level is inappropriately low for the ESA dose administered[7,11].

Hema-Plus is a rHuEPO. The product was approved for marketing in the manufacturing country in 1998. To date, the product has been registered in more than 20 countries. The product was approved for marketing in Thailand in September 2012. This study was proposed to evaluate the efficacy and safety of the product in the management of anemia in patients on peritoneal dialysis (PD) and also the QoL of those patients.

MATERIALS AND METHODS

Study design and setting

This was an open-label, single-arm, prospective, multicenter, phase IV study to evaluate efficacy and safety of Hema-Plus® in correcting anemia among CKD patients receiving PD. The study was conducted at three dialysis centers offering continuous ambulatory PD (CAPD) services in Thailand, *i.e.*, Banphaeo Hospital, Udon Thani Hospital, and Siriraj Hospital.

Patients underwent PD catheter implantation following normal practice at each study site. Following the break-in period, eligible patients commenced PD and started a 12-wk treatment of Hema-Plus® on the same day. The efficacy and safety of the study drug along with the impact on patients' QoL were assessed.

The study was conducted in accordance with International Conference on Harmonization-Good Clinical Practice Guideline and the Declaration of Helsinki. The protocol was approved by the independent ethics committee at each participating site, prior to the study initiation. All patients gave written informed consent. The study was registered on the Thai Clinical Trial Registry (TCTR), URL <http://www.thaiclinical-trials.org/> (TCTR ID: 20140128002). The study adhered to The Strengthening of the Reporting of Observational Studies in Epidemiology guidelines[12].

Patients and eligibility criteria

Eligibility was assessed during a 2-wk screening period. CKD patients aged 18–70 years who were indicated to start PD based on estimated glomerular filtration rate (eGFR) of less than 15 mL/min/1.73 m², and had hemoglobin (Hb) < 9.5 g/dL, serum ferritin > 100 ng/mL and serum transferrin saturation (TSAT) ≥ 20% were enrolled in the study. The eGFR was calculated by using the CKD epidemiology collaboration equation[13].

Patients who previously received epoetin or any investigational drugs (within 3 mo of screening) or had blood transfusion (within 7 d prior to screening) or received concurrent treatment with either androgenic agents or immunosuppressive therapy were considered ineligible. This study also excluded patients with the following conditions: Poorly controlled hypertension or ischemic heart disease; congestive heart failure; infection or inflammatory disease (within 4 wk prior to screening); secondary hyperparathyroidism; history of seizure; previous malignant tumor or residual tumor after anticancer therapy; active bleeding or history of bleeding disorders; infections with HIV or hepatitis B or C viruses; signs, symptoms and laboratory assessment associated with erythropoietin-resistant bone marrow diseases such as aplastic anemia, myelodysplastic syndrome, myelofibrosis, myelophthisis anemia and PRCA; known hypersensitivity to products derived from mammalian cells or containing human albumin; pregnant or breastfeeding; and women with childbearing potential unwilling to use an effective birth control method.

Study treatment and assessments

Participants were treated with Hema-Plus® (rHuEPO), either in the form of sterile vials or prefilled syringes, *via* self-administered subcutaneous injections at 4000 IU/dose

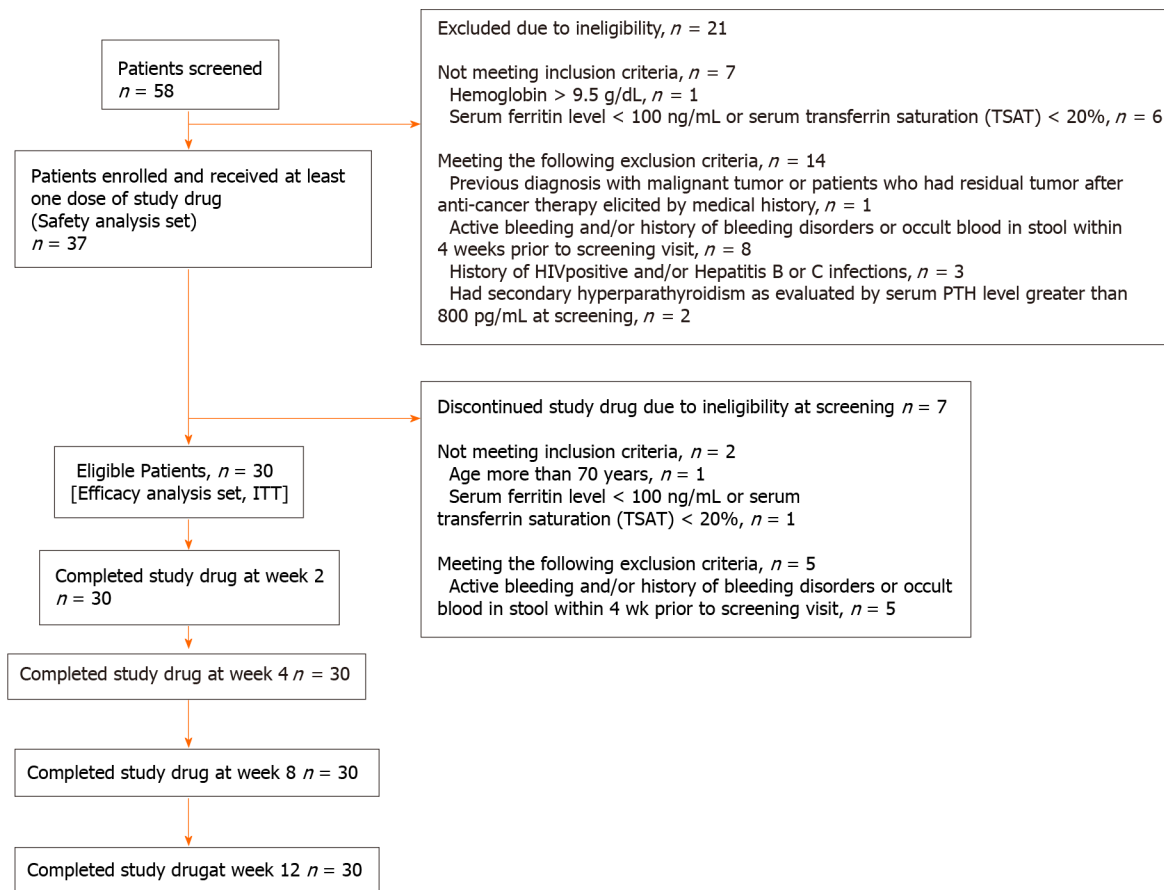


Figure 1 Study flow diagram. ITT: Intention-to-treat analysis; HIV: Human immunodeficiency virus; PTH: Parathyroid hormone.

once or twice weekly, as *per* the usual practice of each participating site. In order to achieve or maintain the Hb level within the target range of 11–12 g/dL[14], dose adjustment was permitted at the discretion of the investigator. The trial treatment period was 12 wk with the first dose was given at week 0 (baseline). It was recommended to give all patients oral supplementation of iron, vitamin B12 and/or folic acid.

A physical examination, a complete blood count and concomitant medications review was conducted at every visit (weeks 0, 2, 4, 8 and 12). AEs and serious AEs (SAEs) were assessed throughout the study and during each visit, using the following scale of severity – mild, moderate and severe. Analyses of serum ferritin, TSAT and blood chemistry were performed at weeks 4, 8 and 12. Dialysis adequacy was evaluated anytime during weeks 4 and 8. The QoL was assessed by interview at initial screening and end of the study (week 12), using the Thai language version of kidney disease QoL instrument (KDQOL-36)[15,16]. If erythropoietin-induced, antibody-mediated PRCA was suspected, an anti-erythropoietin antibodies test could be performed.

Study outcomes and follow-up

All efficacy end points were assessed at the end of study treatment (week 12), with the primary end point being mean Hb level at week 12. The secondary efficacy end points were the percentage of patients achieving target Hb level, mean percentage change from baseline of Hb level and the QoL scores. The safety end point was assessed through frequency and percentages of AEs, and SAEs throughout the treatment period.

Statistical analysis

All statistical analyses were performed in the intention-to-treat population. The sample size estimation in this study was based on changes of Hb from 8.0 ± 1.3 g/dL at baseline to 10.5 ± 1.6 g/dL at week 12 in a previous study[17] and from 7.1 ± 1.14 g/dL at baseline to 10.1 ± 1.49 g/dL at week 12 in another study[18], in which hemodialysis patients were studied, and a change of hematocrit from 23.8 ± 3.8 g/dL

at baseline to 33.7 ± 4.8 g/dL at week 12 among PD patients in a study by Nissenson *et al*[19]. With a type I error of 0.05 allowed and a power of 80% required, a sample size of 15 to 27 patients was required. With a 10% lost to follow-up, this study proposed a sample of 30 patients.

Mean Hb level and mean QoL scores at week 12 were compared with the respective data at week 0 using paired t-tests. Repeated measure ANOVA with multiple pairwise comparisons with Benferroni-Holm step down adjustment was employed to determine the changes of mean Hb level at each visit compared with their respective previous visits. All statistical analyses were performed by a qualified statistician using SPSS version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). For missing data, the last observation carried forward imputation method was employed. A two-sided *P* value for significance of less than 0.05 was applied for all statistical analyses in this study.

RESULTS

Patient characteristics

Out of 58 patients screened, 37 were enrolled and received at least one dose of the study drug. Seven patients were discontinued from the study and excluded from efficacy analysis due to ineligibility since enrollment. All patients who received at least one dose of the study drug were included in safety analysis ($n = 37$), and the thirty patients who met all inclusion criteria and did not meet any exclusion criteria were included in efficacy analysis ($n = 30$).

The 30 eligible patients completed the 12-wk treatment with Hema-Plus® (Figure 1). Of these, 18 (60%) were male. The mean age of patients was 48.8 years [standard deviation (SD) = 13.6] with the mean Hb level of 7.4 g/dL (SD = 1.3). Baseline characteristics are further described in Table 1. The average dose received by patients was 6466.7 IU/wk (SD = 1899; range: 3333.3–11666.7), equivalent to 117.6 IU/kg/week (SD = 42.2; range: 58.4–269.8).

Hb levels

At the end of the study, Hb levels of all participants increased from baseline. The mean Hb level at week 12 was significantly higher than that of week 0 [11.2 g/dL (SD = 1.7) *vs* 7.4 g/dL (SD = 1.3); $P < 0.001$], corresponding to a percentage change of 53.8% (SD = 26.7; range: 8.2–134.6). Elevation of Hb levels was observed throughout the study period (Figure 2). When the Hb levels at each visit were compared with those of the prior visit, the increases in mean Hb levels were found to be significant (Table 2).

Overall, 18 participants (60%) had achieved the Hb levels within or exceeding the targets upon completion of the study drug treatment. Of these, 8 (26.7%) had their Hb levels within the target range of 11–12 g/dL; while, the Hb levels were greater than 13 g/dL in 10 participants (33.3%). Ten out of 12 patients with below-the-target Hb levels achieved increases in Hb concentrations of equal or greater than 2 g/dL (Figure 3). This is in line with the kidney disease: Improving global outcomes (KDIGO) clinical practice guideline[20] which recommends the increase of Hb level at the rate of 1–2 g/dL *per* month. Therefore, those patients were considered as responding to the treatment.

We performed additional analysis to compare Hb levels at baseline and week 12 by the factors that could affect the ESA response, *i.e.* thalassemia, infection, hemolysis, blood loss, hyperparathyroidism, low blood folic acid, and iron deficiency. However, only infection had a certain variation, *i.e.* 36.67% of the 30 patients having infection (*i.e.* exit site infection, peritonitis, pneumonia, and cellulitis), which was adequate to test for statistical significance. Table 3 shows frequency of patients with factors potentially affecting ESA response. Repeated measure ANOVA was used to compare Hb levels between patients with and without infection. Overall, it was found that infection was significantly associated with different Hb level (P value = 0.001). Patients with infection had a significantly lower Hb level at baseline, week 2, week 4, week 8 and week 12 (P value = 0.001, 0.004, 0.034, 0.035 and 0.005, respectively) when compared to the patients without infection. Table 4 presents the comparisons of Hb at each visit by infection status and Figure 4 shows estimated marginal means of Hb levels from baseline to week 12 by infection status using repeated measure ANOVA.

QoL

Treatment with Hema-Plus® improved the patients' health-related QoL as determined by the KDQOL-36™ survey (Table 5). At week 12, there were significant increases in

Table 1 Demographic and baseline characteristics of the patients (n = 30)

Characteristics		
Sex – No. of patients (%)		
Male	18.0	(60.0)
Female	12.0	(40.0)
Age (years) ¹	48.8	(13.6)
Weight (kg) ¹	55.9	(11.1)
TSAT (%) ²	39.6	(23.0)
Ferritin (ng/mL) ²	931.2	(592.7)
Hemoglobin (g/dL) ¹	7.4	(1.3)
Hematocrit (%) ¹	22.2	(4.0)
Reticulocyte count (%) ¹	1.1	(0.9)
eGFR (ml/min/1.73 m ²)	6.2	(3.3)
BUN (mg%) ²	77.1	(34.2)
Creatinine (mg%) ²	10.0	(4.5)
Albumin (g%) ²	3.8	(0.6)
Vitamin B12 (pg/mL) ^{2,4}	922.3	(422.9)
Folic acid (ng/mL) ^{2,4}		
RBC folate (n = 19)	8192.8	(4785.0)
Serum folate (n = 10)	102.2	(217.4)
C-reactive protein (mg/L) ²	10.7	(29.5)

All data were presented as mean (standard deviation), unless otherwise stated.

¹Data from screening visit.

²Data from Week 0 prior to study drug initiation.

³Data were calculated using chronic kidney disease epidemiology collaboration formula[13].

⁴Data available in 29 patients. BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; RBC: Red blood cell; TSAT: Transferrin saturation.

Table 2 Pair-wise comparison of hemoglobin changes between 2 consecutive visits (n = 30)

Comparison	Hb change ¹	P value	Significance criteria
Week 0 vs Week 2	0.7 (0.2)	0.0003	0.0250
Week 2 vs Week 4	1.3 (0.2)	< 0.0001	0.0167
Week 4 vs Week 8	1.3 (0.2)	< 0.0001	0.0125
Week 8 vs Week 12	0.6 (0.2)	0.0060	0.0500

¹Data were presented as mean (standard error). P values and significance criteria presented were those after the pair-wise comparisons based on Bonferroni-Holm step-down adjustment. SE: Standard error; Hb: Hemoglobin.

KDQOL-36 scores from baseline in all aspects evaluated-physical and mental health as well as symptoms and burden of the kidney disease.

Safety

Overall, 39 AEs were reported from 18 patients (out of 37 patients included in the safety population) during the study period (Table 6). Most of those (37/39) were deemed very unlikely to be related to the study drug. All reported AEs were mild (30/39) to moderate (7/39), except one case of volume overload which was classified as a severe event, but very unlikely to be related to the study drug. A total of 10 SAEs occurred in 7 patients. Of these, two occurrences of hypertensive urgency were deemed to be probably related to the study drug. The most frequently reported AEs,

Table 3 Frequency of patients with factors potentially affecting erythropoiesis-stimulating agent response (*n* = 30)

Factors potentially affecting ESA response	<i>n</i> (%)
Thalassemia	1 (3.33)
Infection	11 (36.67)
Hemolysis	0
Blood loss	0
Hyperparathyroidism	1 (3.33)
Low blood folic acid	0
Iron deficiency	3 (10.00)

ESA: Erythropoiesis-stimulating agent.

Table 4 Comparisons of hemoglobin at each visit by infection status (*n* = 30)

Visit	Hemoglobin levels (g/dL), mean (SD)		<i>P</i> value	
	Infection (<i>n</i> = 11)	Non-infection (<i>n</i> = 19)		
Visit 2 (week 0; baseline)	6.41 (1.48)	7.95 (0.75)	0.001 ^a	0.001 ^b
Visit 3 (week 2)	7.00 (1.51)	8.68 (1.33)	0.004 ^a	
Visit 4 (week 4)	8.56 (1.53)	9.75 (1.33)	0.034 ^a	
Visit 5 (week 8)	9.85 (1.40)	11.00 (1.36)	0.035 ^a	
Visit 6 (week 12)	10.04 (1.73)	11.80 (1.39)	0.005 ^a	

Data were presented as mean (standard deviation).

^aRepeated measure ANOVA comparing hemoglobin (Hb) level between patients with and without infection within each visit.

^bRepeated measure ANOVA testing the effect of infection on overall Hb level.

Table 5 Comparisons of kidney disease quality of life instrument–36 scores at baseline and week 12 (*n* = 30)

Parameter	Week 0		Week 12		Δ		<i>P</i> value ¹
SF-12 scores							
Physical health composite	36.8	(8.2)	41.5	(9.8)	4.8	(8.5)	0.004
Mental health composite	41.5	(9.6)	48.4	(8.4)	6.9	(10.7)	0.001
Burden of kidney disease	34.4	(28.4)	46.0	(31.3)	11.7	(25.0)	0.016
Symptoms/problems of kidney disease	65.6	(19.6)	79.4	(13.6)	13.8	(20.4)	0.001
Effects of kidney disease	63.0	(18.2)	76.3	(18.4)	13.3	(23.6)	0.004

Data were presented as mean (standard deviation).

¹Paired *t*-test. Δ: Differences in KDQOL–36 scores between week 0 and week 12; KDQOL: Kidney disease quality of life instrument; SF: Short form health survey.

occurring in more than 10% of the patients, were exit site infection/inflammation and edema.

None of the AEs led to discontinuation or modification of the study treatment. Most events (32/39), including all SAEs, were improved or recovered. There was no new or unexpected safety signals observed.

Table 6 Adverse events (*n* = 37)

Adverse events	No. of patients (%)	No. of events
Total	18 (48.65)	39
Blood and lymphatic disorders		
Bicytopenia ¹	1 (2.70)	1
Gastrointestinal disorders		
Diarrhea	1 (2.70)	1
Nausea	1 (2.70)	1
Infections and infestations		
Exit site infection/inflammation	6 (16.22)	6
Pneumonia ¹	2 (5.40)	2
Eosinophilic peritonitis	2 (5.40)	2
Injury, poisoning and procedural complications		
Closed fractures of femur ¹	1 (2.70)	1
Accidental tear small bowel ¹	1 (2.70)	1
Investigations		
Hyperkalemia	1 (2.70)	1
Hypokalemia	1 (2.70)	1
Hyperphosphatemia	1 (2.70)	1
Metabolism and nutrition disorders		
Hypoglycemia	2 (5.40)	2
Musculoskeletal and connective tissue disorders		
Acute arthritis	1 (2.70)	1
Nervous system disorders		
Headache	1 (2.70)	1
Dizziness	1 (2.70)	1
Renal and urinary disorders		
Volume overload ^{1,2}	1 (2.70)	1
Respiratory, thoracic and mediastinal disorders		
Chest discomfort	1 (2.70)	1
Bronchospasm	1 (2.70)	1
Pleural effusion ¹	1 (2.70)	1
Skin and subcutaneous tissue disorders		
Edema	4 (10.81)	4
Paleness	1 (2.70)	2
Cellulitis	1 (2.70)	1
Itching from dry skin	1 (2.70)	1
Surgical and medical procedures		
Catheter malfunction/ malposition ³	2 (5.40)	2
Vascular disorder		
Hypertensive urgency ^{1,4}	2 (5.40)	2

¹Serious adverse event.

²Severe adverse event.

³Only one out of two events were serious adverse event.

⁴The causality was deemed as probable.

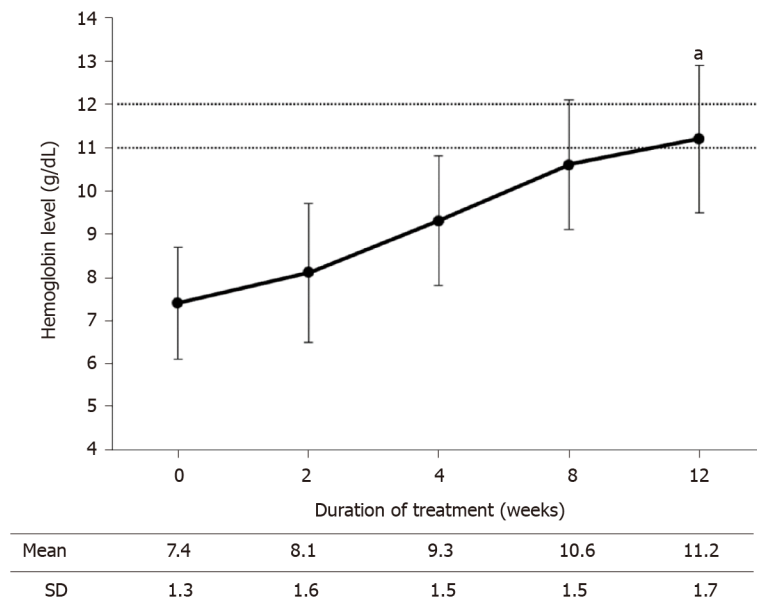


Figure 2 Mean hemoglobin levels throughout the study ($n = 30$). ^a $P < 0.001$ vs week 0, paired t -test.

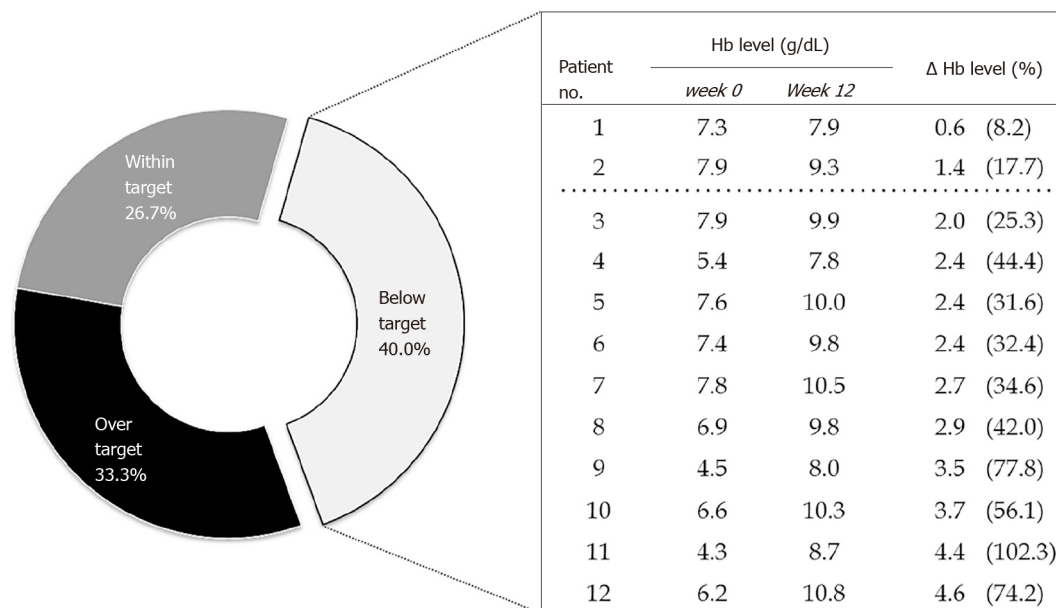


Figure 3 Changes from baseline of hemoglobin levels among patients with below-the-target hemoglobin levels at week 12 ($n = 12$). Δ : Differences between Hb level at week 0 and week 12; Hb: Hemoglobin.

DISCUSSION

The treatment of anemia in patients with CKD with ESAs has provided the following known beneficial effects: A reduced requirement for blood transfusions and the associated complications, improvement of heart failure symptoms and regression of left ventricular hypertrophy, improved QoL, decreased hospitalizations and reduction of overall healthcare costs[4,5,21].

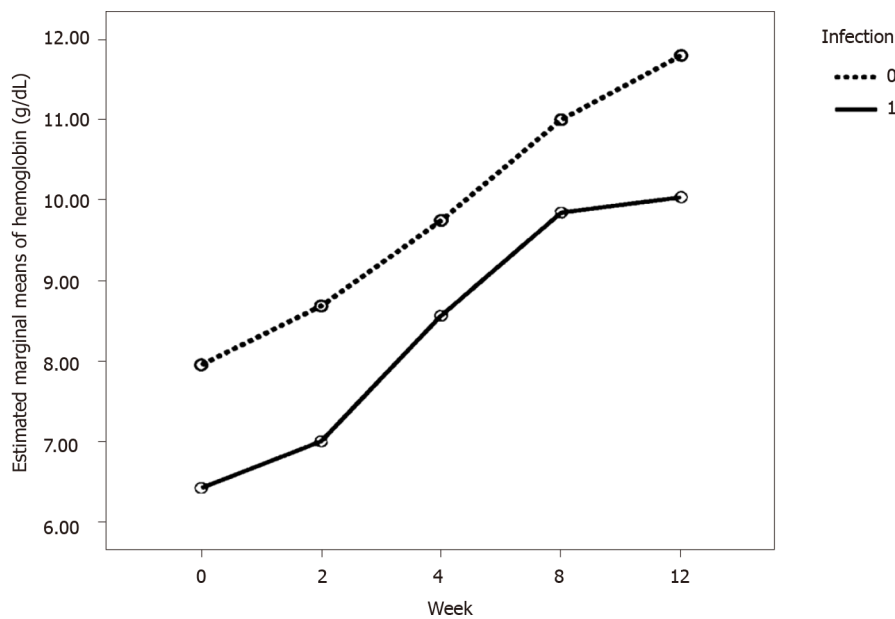


Figure 4 Estimated marginal means of hemoglobin levels from baseline to week 12 by infection using repeated measure ANOVA.

It is difficult to predict dose requirements of ESA in individual patients who have high comorbidities, diabetes, other disorders, and inflammation. Hb should be increased slowly between 1.0–2.0 g/dL (10–20 g/L) *per* month during the initial ESA therapy (correction phase), so as to avoid adverse effects like hypertension, seizures, vascular access thrombosis, and possible cardiovascular events. However, it is recommended that the starting dose of epoetin alpha should be 20–50 IU/kg weight thrice every week with Hb target of 11.0–12.0 g/dL. Dose adjustment should be determined by the patient's Hb level, the target Hb level, the observed rate of increase in Hb level and clinical circumstances[20,22].

Results from the present study showed that subcutaneously administered Hema-Plus at the doses and frequencies used in this patient population for treatment of anemia in CKD patients with PD significantly increased Hb levels over 12 wk. More than half of the study patients (60%) had Hb levels within (26.67%) or higher (33.33%) than the target range (11–12 g/dL)[1] at week 12 with percentages of change ranging from 8.22% to 134.62%. In addition, there were significant improvements in the QoL scores in all domains between baseline and week 12. The previous studies about QoL in PD patients have also shown that anemia was a significant factor in lowering the patients' QoL[23–25]. Access to medicines is a significant factor to ensure healthy lives and promote well-being of all people of all ages[26]. The Hema-Plus, which is a locally made recombinant human erythropoietin (rHuEPO) with lower cost, might help Thai people to gain more accessibility to epoetin alfa in Thailand.

This present study showed that the patients with infection had a significantly lower Hb level when compared to the patients without infection. This result was consistent with several studies that have indicated that markers of inflammation have an association with decreased response to EPO[27]. In this present study, only infection had a certain variation which was adequate to test for statistical significance. There are a lot of factors that influence the response to rHuEPO to keep in mind[27], such as iron deficiency[28–30], oxidative stress[31–33], hyperparathyroidism[34], and angiotensin-converting enzyme inhibitors[35,36].

In terms of safety, epoetin alpha is generally well tolerated. The most frequently reported AEs from studies of epoetin alpha in phase I trials are headache, polycythemia, tiredness, common cold, diarrhea, nausea, stomach pains, chest pressure sensation, back pain, leg pain, and dizziness[37]. In this present study there were 38 AEs experienced by patients exposed to Hema-Plus treatment for 12 wk. The majority of AEs were mild to moderate with 1 AE (volume overload) which was severe in intensity. The highest rate of AE was exit site infection/inflammation, followed by edema, catheter malfunction, pneumonia, hypoglycemia, and hypertensive urgency, respectively. All of the AEs were very unlikely to be related to study drug, except two SAEs (hypertensive urgency) which were deemed to be probably related to Hema-Plus according to investigators assessment. A multicenter study[38] analyzed the effectiveness of administering relatively high doses of rHuEPO subcutaneously in 41

patients CAPD by giving once every week dosing for 8 wk (initial phase) followed by once every 2 wk dosing for 12 wk (maintenance phase). The highest dose of rHuEPO within the initial 8 wk was 12000 IU once *per* week and within the maintenance phase was 12000 IU twice weekly. The results from this study showed that administration of the relatively high doses of rHuEPO was safe and potentially an effective administration plan for the correction of renal anemia. However, there were 2 patients who developed treatable hypertension with mild headache in the study[38]. Therefore, blood pressure should be closely monitored when patients are receiving high dose high frequency of rHuEPO. In the present study, there was no PRCA, a rare but serious complication related to epoetin[7,8], reported during the 12-wk administration of the study drug.

Limitations

Our study had some limitations that require attention. This study was an open-label single group study which did not directly compare with other epoetin alfa medications. The study design of this study intended to evaluate efficacy and safety during the correction phase of the study drug, and did not include maintenance therapy. The study treatment was 12 wk in which the long-term safety might not be concluded. In addition, a large numbers of subjects were required to study PRCA event because the PRCA incidence rates were very low[39]. The longer period study is suggested to determine whether use of Hema-Plus could maintain the Hb level with acceptable safety profile.

CONCLUSION

In conclusion, this study demonstrates that Hema-Plus administered for 12 wk was effective in correcting anemia in CKD patients undergoing PD with significantly improved QoL. The safety profile was acceptable and also looked comparable to epoetin alfa.

ARTICLE HIGHLIGHTS

Research background

The Hema-Plus is a locally made recombinant human erythropoietin (rHuEPO) that may help Thai people to gain more accessibility to epoetin alfa in Thailand due to lower costs.

Research motivation

There are no publicly available studies of Hema-Plus in Thai chronic kidney disease (CKD) patients on peritoneal dialysis (PD). The results from this study may be used as an evidence and information for considering to use Hema-Plus, locally made rHuEPO in these patients.

Research objectives

This study aimed to evaluate the efficacy and safety of Hema-Plus for treatment of anemia during correction phase in Thai patients with Stage V CKD on PD.

Research methods

An open-label, multi-center study of Hema-Plus in patients was used to assess the efficacy, *i.e.*, mean change in hemoglobin (Hb) level from baseline, safety, and changes in quality of life (QoL) after receiving the study drug for 12 wk.

Research results

Efficacy analysis comprised 30 patients. At the end of 12 wk-treatment, mean Hb was statistically significantly increased from baseline. Two hypertensive urgency events were observed probably related to study medication. QoL scores were significantly increased from baseline.

Research conclusions

Hema-Plus administered for 12 wk for treatment of anemia in CKD patients on PD effectively could increase Hb levels, and QoL with acceptable safety profile.

Research perspectives

This study results could be used as an evidence for efficacy and safety information of the locally made rHuEPO, Hema-Plus for anemia correction phase. Longer study duration is suggested to ensure long-term safety and efficacy.

ACKNOWLEDGEMENTS

Thanks to Mr. Stephen Pinder a medical-English specialist for English proofreading of this manuscript. We are also grateful to Siriraj Hospital, Mahidol University for permission to use the validated KDQOL-36 in Thai Kidney Disease Patient Questionnaire in this study.

REFERENCES

- 1 **Locatelli F**, Del Vecchio L. Optimizing the management of renal anemia: challenges and new opportunities. *Kidney Int Suppl* 2008; S33-S37 [PMID: 19034323 DOI: 10.1038/ki.2008.525]
- 2 **Segal GM**, Eschbach JW, Egrie JC, Stueve T, Adamson JW. The anemia of end-stage renal disease: hematopoietic progenitor cell response. *Kidney Int* 1988; **33**: 983-988 [PMID: 3392887 DOI: 10.1038/ki.1988.97]
- 3 **Mara NB**. Anemia in Patients With Chronic Kidney Disease. *Dia Spec* 2008; **12** [DOI: 10.2337/diaspect.21.1.12]
- 4 **Lankhorst CE**, Wish JB. Anemia in renal disease: diagnosis and management. *Blood Rev* 2010; **24**: 39-47 [PMID: 19833421 DOI: 10.1016/j.blre.2009.09.001]
- 5 **Evans RW**, Rader B, Manninen DL. The quality of life of hemodialysis recipients treated with recombinant human erythropoietin. Cooperative Multicenter EPO Clinical Trial Group. *JAMA* 1990; **263**: 825-830 [PMID: 2404150]
- 6 **Potasman I**, Better OS. The role of secondary hyperparathyroidism in the anemia of chronic renal failure. *Nephron* 1983; **33**: 229-231 [PMID: 6843752 DOI: 10.1159/000182958]
- 7 **Locatelli F**, Aljama P, Bárány P, Canaud B, Carrera F, Eckardt KU, Hörl WH, Macdougall IC, Macleod A, Wiecek A, Cameron S; European Best Practice Guidelines Working Group. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. *Nephrol Dial Transplant* 2004; **19** Suppl 2: ii1-ii47 [PMID: 15206425 DOI: 10.1093/ndt/gfh1032]
- 8 **Perlman RL**, Finkelstein FO, Liu L, Roys E, Kiser M, Eisele G, Burrows-Hudson S, Messina JM, Levin N, Rajagopalan S, Port FK, Wolfe RA, Saran R. Quality of life in chronic kidney disease (CKD): a cross-sectional analysis in the Renal Research Institute-CKD study. *Am J Kidney Dis* 2005; **45**: 658-666 [PMID: 15806468 DOI: 10.1053/j.ajkd.2004.12.021]
- 9 **Taylor and Francis Group**. Hema-Plus 2000 IU, 4000 IU, 10000 IU Package Insert 2011. [cited 10 April 2021]. Available from: <https://www.taylorfrancis.com/chapters/mono/10.1201/9781482295467-17/iu-iu-andrew-peacock>
- 10 **Johnson DW**, Pollock CA, Macdougall IC. Erythropoiesis-stimulating agent hyporesponsiveness. *Nephrology* 2007; **321** [DOI: 10.1111/j.1440-1797.2007.00810.x]
- 11 **KDOQI**. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis* 2006; **47**: S11-145 [PMID: 16678659 DOI: 10.1053/j.ajkd.2006.03.010]
- 12 **von Elm E**, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014; **12**: 1495-1499 [PMID: 25046131 DOI: 10.1016/j.ijsu.2014.07.013]
- 13 **Levey AS**, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604-612 [PMID: 19414839 DOI: 10.7326/0003-4819-150-9-200905050-00006]
- 14 **KDOQI**. KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *Am J Kidney Dis* 2007; **50**: 471-530 [PMID: 17720528 DOI: 10.1053/j.ajkd.2007.06.008]
- 15 **Thaweethamcharoen T**, Srimongkol W, Noparatayaporn P, Jariyayothin P, Sukthinthai N, Aiyasanon N, Kitisriworapan P, Jantarakana K, Vasuvattakul S. Validity and Reliability of KDQOL-36 in Thai Kidney Disease Patient. *Value Health Reg Issues* 2013; **2**: 98-102 [PMID: 29702860 DOI: 10.1016/j.vhri.2013.02.011]
- 16 **Hays RD**, Kallich JD, Mapes DL, Coons S, Amin N, Carter WB, Kamberg C. Kidney Disease Quality of Life Short Form (KDQOL-SF™), Version 1.3: A Manual for Use and Scoring. Santa Monica, CA: RAND Corporation; 1997
- 17 **Thanakitcharu P**, Siriwiwatanakul N. Hemoglobin response and influence on left ventricular hypertrophy after 24-week treatment of a biosimilar epoetin-alfa in hemodialysis patients with

- anemia. *J Med Assoc Thai* 2007; **90**: 2574-2586 [PMID: 18386706]
- 18 **Besarab A**, Salifu MO, Lunde NM, Bansal V, Fishbane S, Dougherty FC, Beyer U; Ba16285 Study Investigators. Efficacy and tolerability of intravenous continuous erythropoietin receptor activator: a 19-week, phase II, multicenter, randomized, open-label, dose-finding study with a 12-month extension phase in patients with chronic renal disease. *Clin Ther* 2007; **29**: 626-39 [PMID: 17617286 DOI: 10.1016/j.clinthera.2007.04.014]
- 19 **Nissenson AR**, Korbet S, Faber M, Burkart J, Gentile D, Hamburger R, Mattern W, Schreiber M, Swartz R, Van Stone J. Multicenter trial of erythropoietin in patients on peritoneal dialysis. *J Am Soc Nephrol* 1995; **5**: 1517-1529 [PMID: 7703390 DOI: 10.1681/ASN.V571517]
- 20 Chapter 3: Use of ESAs and other agents**Excluding iron which is discussed in Chapter 2. to treat anemia in CKD. *Kidney Int Suppl* 2012; **2**: 299-310 [DOI: 10.1038/kisup.2012.35]
- 21 **Eschbach JW**, Abdulhadi MH, Browne JK, Delano BG, Downing MR, Egrie JC, Evans RW, Friedman EA, Graber SE, Haley NR. Recombinant human erythropoietin in anemic patients with end-stage renal disease. Results of a phase III multicenter clinical trial. *Ann Intern Med* 1989; **111**: 992-1000 [PMID: 2688507 DOI: 10.7326/0003-4819-111-12-992]
- 22 **Locatelli F**, Del Vecchio L. Erythropoiesis-stimulating agents in renal medicine. *Oncologist* 2011; **16** Suppl 3: 19-24 [PMID: 21930831 DOI: 10.1634/theoncologist.2011-S3-19]
- 23 **Lew SQ**, Piraino B. Quality of life and psychological issues in peritoneal dialysis patients. *Semin Dial* 2005; **18**: 119-123 [PMID: 15771655 DOI: 10.1111/j.1525-139X.2005.18215.x]
- 24 **Furuland H**, Linde T, Ahlmén J, Christensson A, Strömbom U, Danielson BG. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. *Nephrol Dial Transplant* 2003; **18**: 353-361 [PMID: 12543892 DOI: 10.1093/ndt/18.2.353]
- 25 **Liu H**, Yao Y, Cao Y, Yang X, Huang B, Han X, Ren C. Anemia management trends in patients on peritoneal dialysis in the past 10 years. *Int J Clin Exp Med* 2015; **8**: 18050-18057 [PMID: 26770400]
- 26 **Singh PK**. Make medicines accessible for all. [cited 10 April 2021]. Available from: <https://www.who.int/southeastasia/news/opinion-editorials/detail/make-medicines-accessible-for-all> 2017
- 27 **Kwack C**, Balakrishnan VS. Managing erythropoietin hyporesponsiveness. *Semin Dial* 2006; **19**: 146-151 [PMID: 16551293 DOI: 10.1111/j.1525-139X.2006.00141.x]
- 28 **DeVita MV**, Frumkin D, Mittal S, Kamran A, Fishbane S, Michelis MF. Targeting higher ferritin concentrations with intravenous iron dextran lowers erythropoietin requirement in hemodialysis patients. *Clin Nephrol* 2003; **60**: 335-340 [PMID: 14640239 DOI: 10.5414/cnp60335]
- 29 **Aronoff GR**. Safety of intravenous iron in clinical practice: implications for anemia management protocols. *J Am Soc Nephrol* 2004; **15** Suppl 2: S99-106 [PMID: 15585604 DOI: 10.1097/01.ASN.0000143815.15433.87]
- 30 **Fishbane S**, Galgano C, Langley RC Jr, Canfield W, Maesaka JK. Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. *Kidney Int* 1997; **52**: 217-222 [PMID: 9211366 DOI: 10.1038/ki.1997.323]
- 31 **Himmelfarb J**. Uremic toxicity, oxidative stress, and hemodialysis as renal replacement therapy. *Semin Dial* 2009; **22**: 636-643 [PMID: 20017834 DOI: 10.1111/j.1525-139X.2009.00659.x]
- 32 **Roob JM**, Khoschsorur G, Tiran A, Horina JH, Holzer H, Winklhofer-Roob BM. Vitamin E attenuates oxidative stress induced by intravenous iron in patients on hemodialysis. *J Am Soc Nephrol* 2000; **11**: 539-549 [PMID: 10703678 DOI: 10.1681/ASN.V113539]
- 33 **Kato A**, Odamaki M, Hishida A. Blood 8-hydroxy-2'-deoxyguanosine is associated with erythropoietin resistance in haemodialysis patients. *Nephrol Dial Transplant* 2003; **18**: 931-936 [PMID: 12686667 DOI: 10.1093/ndt/gfg070]
- 34 **Goicoechea M**, Gomez-Campdera F, Polo JR, Tejedor A, Ruiz MA, Vazquez I, Verde E, Valderrabano F. Secondary hyperparathyroidism as cause of resistance to treatment with erythropoietin: effect of parathyroidectomy. *Clin Nephrol* 1996; **45**: 420-421 [PMID: 8793241]
- 35 **Albitar S**, Genin R, Fen-Chong M, Serveaux MO, Bourgeon B. High dose enalapril impairs the response to erythropoietin treatment in haemodialysis patients. *Nephrol Dial Transplant* 1998; **13**: 1206-1210 [PMID: 9623555 DOI: 10.1093/ndt/13.5.1206]
- 36 **Azizi M**, Rousseau A, Ezan E, Guyene TT, Michelet S, Grognet JM, Lenfant M, Corvol P, Ménard J. Acute angiotensin-converting enzyme inhibition increases the plasma level of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline. *J Clin Invest* 1996; **97**: 839-844 [PMID: 8609242 DOI: 10.1172/JCI118484]
- 37 **Strengers PFW**, Twuijver Ev. Chapter 33-Blood, blood components, plasma, and plasma products. In: Aronson JK, editor. *Side Effects of Drugs Annual*: Elsevier; 2009: 527-546
- 38 **Nomoto Y**, Kawaguchi Y, Kubota M, Tagawa H, Kubo K, Ogura Y, Shoji T, Kawada Y, Koshikawa S, Mimura N. A multicenter study with once a week or once every two weeks high-dose subcutaneous administration of recombinant human erythropoietin in continuous ambulatory peritoneal dialysis. *Perit Dial Int* 1994; **14**: 56-60 [PMID: 8312416]
- 39 **McKoy JM**, Stonecash RE, Cournoyer D, Rossert J, Nissenson AR, Raisch DW, Casadevall N, Bennett CL. Epoetin-associated pure red cell aplasia: past, present, and future considerations. *Transfusion* 2008; **48**: 1754-1762 [PMID: 18482185 DOI: 10.1111/j.1537-2995.2008.01749.x]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

