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Fluid balance concepts in medicine: Principles and practice

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Abstract

The regulation of body fluid balance is a key concern in health and disease and comprises three concepts. The first concept pertains to the relationship between total body water (TBW) and total effective solute and is expressed in terms of the tonicity of the body fluids. Disturbances in tonicity are the main factor responsible for changes in cell volume, which can critically affect brain cell function and survival. Solutes distributed almost exclusively in the extracellular compartment (mainly sodium salts) and in the intracellular compartment (mainly potassium salts) contribute to tonicity, while solutes distributed in TBW have no effect on tonicity. The second body fluid balance concept relates to the regulation and measurement of abnormalities of sodium salt balance and extracellular volume. Estimation of extracellular volume is more complex and error prone than measurement of TBW. A key function of extracellular volume, which is defined as the effective arterial blood volume (EABV), is to ensure adequate perfusion of cells and organs. Other factors, including cardiac output, total and regional capacity of both arteries and veins, Starling forces in the capillaries, and gravity also affect the EABV. Collectively, these factors interact closely with extracellular volume and some of them undergo substantial changes in certain acute and chronic severe illnesses. Their changes result not only in extracellular volume expansion, but in the need for a larger extracellular volume compared with that of healthy individuals. Assessing extracellular volume in severe illness is challenging because the estimates of this volume by commonly used methods are prone to large errors in many illnesses. In addition, the optimal extracellular volume may vary from illness to illness, is only partially based on volume measurements by traditional methods, and has not been determined for each illness. Further research is needed to determine optimal extracellular volume levels in several illnesses. For these reasons, extracellular volume in severe illness merits a separate third concept of body fluid balance.

Key words: Body fluids; Body water; Extracellular volume; Hypertonicity; Hypotonicity; Congestive heart failure; Hepatic cirrhosis; Sepsis; Nephrotic syndrome

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Core tip: The regulation and clinical disturbances of body fluid and its compartments are traditionally consigned to two concepts. The concept of tonicity of body fluids is critical in the regulation of the volume of body cells. Disturbances in tonicity result from abnormalities in the relation between body water and body solute. The concept of extracellular volume plays a critical role in the regulation of perfusion of body cells and organs. Disturbances in extracellular volume result primarily from abnormalities in sodium salt balance. Various methods for measuring body water and extracellular volume have been extensively applied in clinical practice. However, precise determination of the optimal body fluid volumes

encounters difficulties which are greatly accentuated in severe illnesses, because several other factors interacting with extracellular volume in determining tissue perfusion, including cardiac output, capacity of the blood vessels, and Starling forces, are significantly altered in these illnesses. The aforementioned factors cause changes in the extracellular volume and create the need for optimal levels of this volume that are higher than those of healthy individuals and the need for newer methods for evaluating body fluid volumes. Thus, fluid regulation in severe illness represents an evolving concept of body fluid balance separate from the two traditional concepts. Important questions about this third concept remain unanswered underscoring the need for further research.

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INTRODUCTION

Fluid balance is critical in health^[1] and disease^[2,3]. Its management is required in a variety of instances. These include stress that healthy individuals may experience at certain times, *e.g.*, during intense exercise^[4], development of various acute or chronic diseases^[5-7], and complication of the course of several diseases^[3,8,9]. Proper fluid balance is a key management target for groups of individuals experiencing difficulties in maintaining normalcy with regard to it, *e.g.*, those with cognition disorders^[10], the very young^[11,12], and the very old^[13,14]. Less well known is the fact that disorders of fluid balance are encountered in conditions common in the general population, *e.g.*, obesity^[15] or hypertension^[16-18].

Distinguishing normal from abnormal fluid balance in one's medical practice can be challenging. The diagnosis of fluid balance abnormalities requires the informed and reasoned interpretation of clinical and laboratory information^[14,19]. However, few would argue with the contention that the diagnostic accuracy of these methods is weak in general^[14,19-21] and is further complicated by the indiscriminate and inappropriate use of terms when expressing aspects of fluid balance. For example, the terms "hydration", "dehydration", and "overhydration" are often loosely used to express not one, but two fluid balance concepts, specifically body water balance and extracellular volume (ECFV) balance^[22,23]. The need to distinguish between pure water deficit and ECFV depletion has been stressed in the literature^[24-26]. The use of the term "dehydration" to indicate water deficit or ECFV depletion causes confusion among health care practitioners^[27].

The traditional approach to understanding disorders

of fluid balance has been to compare measured or estimated TBW and ECFV between the patients being studied and the corresponding “normal” values. However, this approach has three limitations: First, identifying “normal values” is fraught with ambiguity. Second, abnormalities in TBW and ECFV often coexist. Finally, optimal values of TBW and especially ECFV differ considerably between patients with serious illnesses vs normal individuals. This last difference justifies the introduction of a third approach to fluid balance, namely fluid balance in severe illness. Our aim in this report is to review the methods of measuring TBW and ECFV, the uses and limitations of these methods, and the methods of evaluating fluid balance in patients with severe illness.

BODY FLUID BALANCE AS A FUNCTION OF WATER BALANCE

Parameters characterizing water balance

The concept of water balance as applied in clinical practice refers to the relationship between total TBW and body solute. Osmolality, which expresses the total solute concentration in a fluid, is the core parameter of this concept^[28]. The principal physiologic function that depends on this first fluid balance concept is the maintenance of stable volume of the body cells. Stable body cell volume is critical for cell function and survival and is based on two membrane-related phenomena, active solute transport mechanisms of the cell membranes, mainly mediated by sodium-potassium ATPase, and high permeability of cell membranes to water^[29]. This second process has two fundamental consequences: (1) Osmolality is equal between the intracellular and extracellular compartment in the steady state^[30]; and (2) the distribution of TBW between the intracellular and extracellular compartments is determined by the total solute in each compartment^[31].

Certain solutes dissolved in body fluids are distributed almost exclusively in the intracellular or the extracellular compartment, while other solutes are distributed in TBW. Changes in the amount of solutes distributed in TBW (urea, ethanol, and other alcohols, *e.g.*, methanol and propyl alcohol) will lead to parallel changes in osmolality of all body fluids, but will not cause any change in cell volume. In contrast, changes in the amount of solutes distributed, by and large, in one of the two major body fluid compartments will lead to parallel changes in body fluid osmolality and opposite sign changes in cell volumes. For example, a decrease in the amount of an extracellular solute causes a decrease in body fluid osmolality and an increase in cell volume.

Tonicity is the portion of osmolality contributed by solutes distributed in one major body fluid compartment^[29]. The terms “hypotonicity” and “hypertonicity” should be used to denote, respectively, relative excess or relative deficit of water in place of the ambiguous

terms “overhydration” and “dehydration”. Serum sodium concentration ($[Na]_s$) is the most widely applied index of tonicity and is accurate except when there is an excess of exogenous extracellular solutes, other than sodium salts, or in the presence of falsely low laboratory values of $[Na]_s$ (pseudohyponatremia) resulting from measurement of $[Na]_s$ by indirect potentiometry when serum water fraction is decreased secondary to an increase in serum solid (proteins or lipids) concentration^[32].

Determinants of body fluid tonicity

The quantitative approach to clinical aspects of the first concept of fluid balance is based on the pivotal work of Edelman *et al.*^[33]. These researchers established the relationship between solutes involved in the function of tonicity and TBW using dilution of radio-isotopic markers in various clinical states potentially associated with dystonicity. Their work established the fact that $[Na]_s$ represents the fraction: Sum of exchangeable sodium plus exchangeable potassium over body water^[33]. A simplified expression of this fraction, used extensively in treating disorders of tonicity is as follows: $[Na]_s = (\text{Exchangeable Na} + \text{Exchangeable K})/\text{TBW}$. In this fraction, exchangeable sodium represents the extracellular solute while exchangeable potassium represents the intracellular solute^[29]. Abnormal values of the measured $[Na]_s$, or serum osmolality, or of serum tonicity calculated as the sum of the osmotic equivalents of $[Na]_s$ plus serum glucose concentration^[34], indicate that there is a discrepancy between TBW and effective body solute; however, they provide no information about excesses or deficits of any of the particular determinants of tonicity. In fact, TBW may be low, normal, or excessive in patients with either hypertonicity^[34-37] or hypotonicity^[38-43]. Figure 1 shows changes in extracellular and intracellular volumes in euvoletic, hypovolemic and hypervolemic hyponatremia.

Establishing the presence and degree of excess or deficit of the components that determine tonicity is critical for the rational management of disorders of tonicity. Assessing body water balance is the first step in the management of tonicity disturbances. A detailed review of the physiology and pathophysiological disturbances of body water is beyond the scope of this report; however, Schrier has provided an insightful review of this topic^[44]. Determining whether TBW is abnormal or not in a patient presenting with dystonicity requires a comparison of this patient's TBW and the “normal” value of TBW.

Measuring body water

“Normal” TBW values were first established as the weight differences between fresh and desiccated animal carcasses^[45]. Subsequently, TBW was measured by dilution of injected markers. Elkington and Danowski provide a useful explanation of this methodology^[46]. The TBW markers most widely applied in research studies include tritiated water ($^3\text{H}_2\text{O}$)^[47], deuterium oxide-heavy water ($^2\text{H}_2\text{O}$)^[48] and antipyrine^[49]. Other markers, *e.g.*, urea, thiourea and ethanol, have enjoyed only limited application. Heavy water does not subject patients to

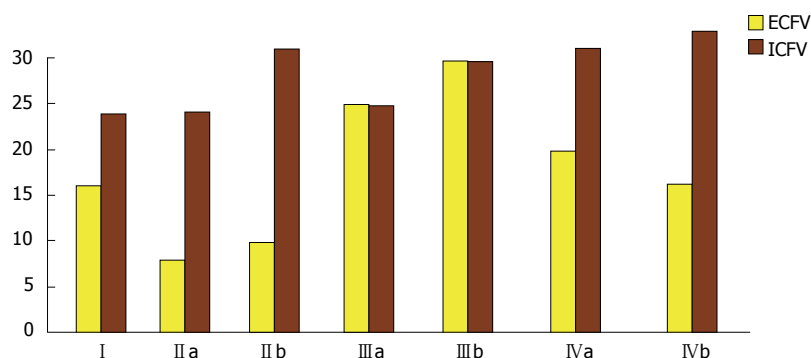


Figure 1 Body compartment volume (L) in the three categories of hyponatremia. I: Normal state: ECFV = 16 L, ICFV = 24 L, serum sodium concentration ($[Na]_s$) = 140 mmol/L. II: Hypovolemic hyponatremia; IIa: Loss of 8 L of isotonic sodium solution: ECFV = 8 L, ICFV = 24 L, $[Na]_s$ = 140 mmol/L; IIb: Gain of 8 L of water; ECFV = 10 L, ICFV = 30 L, $[Na]_s$ = 112 mmol/L. III: Hypervolemic hyponatremia; IIIa: Gain of 8 L of isotonic sodium solution; ECFV = 24 L, ICFV = 24 L, $[Na]_s$ = 140 mmol/L; IIIb: Gain of 8 L of water; ECFV = 28 L, ICFV = 28 L, $[Na]_s$ = 120 mmol/L. IV: Euvolemic hyponatremia manifested in the syndrome of Inappropriate ADH secretion, which combines water gain and sodium loss^[38,39]; IVa: Gain of 8 L of water; ECFV = 19.2 L, ICFV = 28.8 L, $[Na]_s$ = 116.7 mmol/L; IVb: Loss of 560 mmol of monovalent sodium salt (*e.g.*, NaCl); ECFV = 16 L, ICFV = 32 L, $[Na]_s$ = 105 mmol/L. ECFV: Extracellular fluid volume; ICFV: Intracellular fluid volume.

radiation and is the main reference method for measuring TBW^[50,51]. Water labeled with the stable oxygen isotope ^{18}O ($H_2^{18}O$) has also been used to estimate TBW^[52]. Both tracer hydrogen (^2H) and tracer oxygen (^{18}O) exchange with various compounds in the body, thereby causing small overestimates of body water by dilution of ^2H_2O or measurement of $H_2^{18}O$. Hydrogen of water molecules exchanges with labile protons in protein molecules, while oxygen of water molecules exchanges into inorganic pools during formation of ester bonds^[53]. Since the rate of exchange of ^2H with nonaqueous hydrogen slightly exceeds the rate of exchange of ^{18}O with nonaqueous oxygen in body tissues, body water estimates from ^2H_2O dilution space are approximately 3.5% higher than those obtained using $H_2^{18}O$ ^[53].

Efforts to develop non-invasive measurements of TBW applicable to clinical states have applied newer techniques that target body composition; these include: Dual-energy X-ray absorptiometry (DEXA)^[54], air displacement plethysmography^[55], nuclear magnetic resonance spectroscopy^[56], and bioelectrical impedance analysis (BIA)^[57-59]. This last technique is relatively inexpensive and simple to use. Because of these advantages, BIA has been extensively applied in clinical settings requiring precise knowledge of the state of water balance, *e.g.*, in populations on chronic dialysis. The newer methods^[54-57] estimate TBW using empirical equations derived from comparisons of their measurements to measurements made using reference methods. The reliability of these newer methods depends on the accuracy of certain assumptions made during construction of the equations^[60,61]. Findings from these techniques may disagree in subjects who do not fulfill the assumptions on which these equations are based^[62].

Comparisons by statistical regression methods of measurements of TBW by reference methods to known factors affecting body composition has led to the development of anthropometric formulas estimating TBW as a function of height, body weight, age, gender and ethnicity in subjects with normal water balance.

Of these formulas, three have been extensively used in adults^[63-65] and one in children^[66]. Figure 2 shows TBW values derived using the three formulas for adults, which provide comparable values of body water in most cases^[67]. Estimates from one of these formulas should provide more acceptable values of TBW than the older methods used to estimate TBW for the computation of the volume of the replacement fluids in dystonicity states. These older methods accounted only for body weight and gender; for example, TBW was computed as 0.6 of body weight in men and 0.5 of body weight in women. However, the existing anthropometric formulas can give misleading results for several reasons. The first source of inaccuracy is that they do not account for all the determinants of body composition. The degree of obesity varies substantially between subjects with the same height, age, gender, ethnicity and body weight. The anthropometric formulas will compute the same value of TBW for all these subjects. However, since body fat contains minimal amounts of water, TBW is less in obese than lean subjects with the same anthropometric characteristics. This is evident in the large standard errors of these formulas, which suggest a potential variation of several liters of estimates of TBW in subjects with the same age, height, weight, and ethnicity, and no water balance abnormalities.

A second source of inaccuracy of the anthropometric formulas is the presence of abnormal water balance, which creates the potential of even greater error of the formulas. Gains or losses of water result in equal magnitude gains or losses in body weight. The coefficients assigned to body weight in anthropometric formulas can be used to predict the direction of their error in subjects with water balance abnormalities. These coefficients are substantially lower than 0.5 L/kg in all formulas resulting in decreasing values of body water content (the fraction TBW over body weight) as weight increases and increasing values of water content as weight decreases^[68]. These changes in water content are appropriate for subjects with increasing weight due to

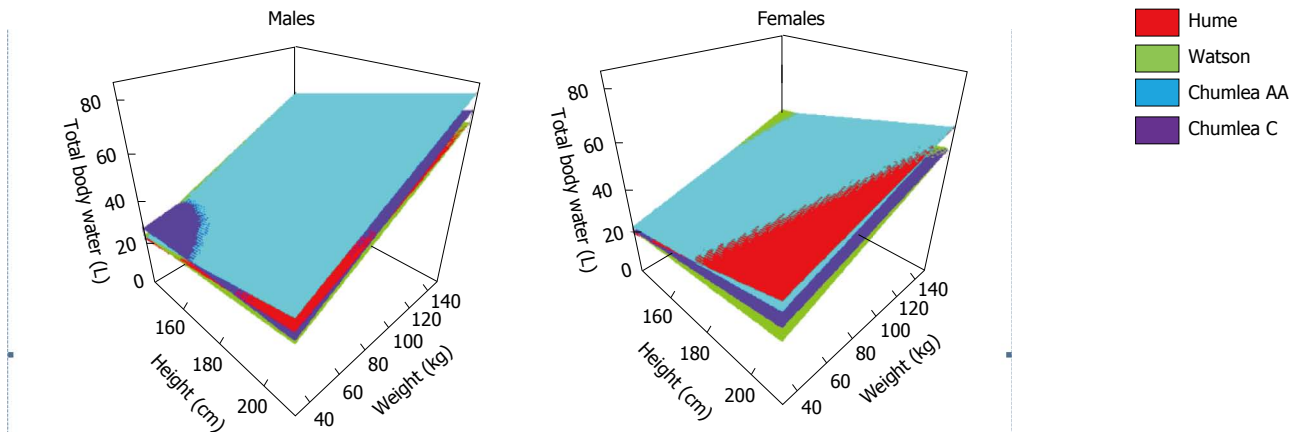


Figure 2 Total body water estimates from anthropometric formulas. Estimates of total body water computed by the Hume *et al.*^[63], Watson *et al.*^[64] and Chumlea *et al.*^[65] anthropometric formulas for men and women with the same age (40 years) and varying height and weight. AA: African American; C: Caucasians.

obesity or decreasing weight due to loss of body fat^[68]. However, body water content mathematically increases in subjects gaining weight because of fluid retention and decreases in subjects losing body fluids^[69,70]. The Chertow anthropometric formula^[71] was derived from measurements of TBW pre-hemodialysis, when patients routinely present with fluid gains. This formula provides higher estimates of TBW than the other anthropometric formulas^[67]. In addition, the Chertow formula accounts for one determinant of body composition (diabetes mellitus) not included in the other formulas^[63-65], and contains coefficients that take into consideration interactions between age and gender, age and weight, and height and weight^[71]. The main drawback of the Chertow formula is that it computes TBW for only the average fluid gain in the dialysis population that is being studied. Johansson *et al.*^[72] developed anthropometric formulas estimating TBW in peritoneal dialysis patients. Table 1 shows the anthropometric formulas estimating TBW in normal adults, normal children and patients on dialysis.

Determining whether there is water excess or water deficit in an individual patient, regardless of tonicity issues, can be challenging. Analyses of the components of body composition^[73] have the potential to reveal whether TBW is normal or not. According to Siri's simplest model of body composition^[74], the body has two components: Fat and fat-free mass. Body water occurs almost exclusively in the fat-free mass component. When the water balance is normal, the water content of fat-free mass is at or very close to 73%^[75-77]. Thus, determining whether TBW is within the normal range or not requires measurement of both fat-free mass and TBW.

Methods for measuring TBW and their limitations were discussed previously in this report. Fat-free mass is routinely measured by BIA or DEXA; however, these methods have hidden drawbacks. For example, an important assumption of the DEXA measurement of fat-free mass is that it contains 73% water^[60]. The measurement of fat-free mass by reference methods, *e.g.*, measurement of total body potassium (TBK) in a total body counter^[78], is generally not available for routine

clinical practices. Therefore, measuring TBW accurately and determining whether body water content is normal or not in individual patients require further research efforts.

Treatment of dystonicity states

Hyperglycemic crises are associated with hypertonicity and severe deficits of body water, sodium, potassium, and other electrolytes^[79]. The principles and quantitative aspects of treatment of these crises are detailed in several reports^[37,79-81]. Herein we will present the principles of management of true (hypotonic) hyponatremia^[43] and hypernatremia^[37].

Extensive guidelines delineating the treatment of hypotonic hyponatremia have been published recently^[82,83]. Treatment is guided by the severity and the pathophysiologic mechanism of hyponatremia^[43]. Severe cases with profound hyponatremia or symptoms attributed to it require infusion of hypertonic saline. The infused volume of saline is determined by formulas. The Adrogué-Madias formula^[41] has been successfully used to guide the treatment of hyponatremias. This formula calculates the increase in $[Na]_s$ after infusion of one liter of saline with sodium concentration higher than that in the serum and accounts for the original $[Na]_s$, the sodium concentration of the infusate, the original TBW and the volume of the infusate. A formula for calculating the volume of hypertonic saline required to raise $[Na]_s$ to a desired value, based on the same principles as the Adrogué-Madias formula, was published subsequently^[84]. These two formulas are shown in Table 2^[41,84].

General therapeutic measures applicable to all hypotonic hyponatremias include restriction of fluid intake and steps directed towards increasing renal water excretion, such as administration of loop diuretics or solute (salt tablets, urea)^[43]. Specific interventions for the management of hyponatremia are predicated on the pathophysiologic mechanism of the condition, and include: (1) Isotonic saline infusion to restore the ability of the kidneys to excrete large volumes of water in hypovolemic hyponatremia; (2) vasopressin 2 (V2) receptor antagonists to restore the renal diluting capacity

Table 1 Anthropometric formulas estimating body water

Adults, normal body water values
Hume and Weyers formulae ^[63]
Women: TBW = $-35.270121 + 0.344547H + 0.183809W$
Men: TBW = $-14.012934 + 0.194786H + 0.296785W$
Watson <i>et al</i> ^[64] formulae
....Women: TBW = $-2.097 + 0.1069H + 0.2466W$
Men: TBW = $2.447 - 0.09516A + 0.1074H + 0.3362W$
Chumlea <i>et al</i> ^[65] formulae
Women, African American: TBW = $-16.71 - 0.05A + 0.24H + 0.22W$
Women, Caucasian: TBW = $-10.50 - 0.01A + 0.18H + 0.20W$
Men, African American: TBW = $-18.37 - 0.09A + 0.25H + 0.34W$
Men, Caucasian: TBW = $23.04 - 0.03A + 0.50W - 0.62BMI$
Children, normal body water values
Mellits, Cheek formulae ^[66]
Girls, $H \leq 110.8$ cm: TBW = $0.076 + 0.013H + 0.507W$
Girls, $H > 110.8$ cm: TBW = $-10.313 + 0.154H + 0.252W$
Boys, $H \leq 132.7$ cm: TBW = $-1.927 + 0.045H + 0.465W$
Boys, $H > 132.7$ cm: TBW = $-21.993 + 0.209H + 0.465W$
Adults, pre-hemodialysis
Chertow <i>et al</i> ^[71] formula
TBW = $0.07493713A - 1.01767992G + 0.57894981D + 0.12703384H - 0.04012056W - 0.00067247W2 - 0.03486146 (A \times G) + 0.11262857 (G \times W) + 0.00104135 (A \times W) + 0.00186104 (H \times W)$
Adults, peritoneal dialysis
Johansson <i>et al</i> ^[72] formulae
Women: TBW = $-29.994 - 0.004A + 0.294H + 0.214W$
Men: TBW = $-10.759 - 0.078A + 0.192H + 0.312W$
.... All patients: TBW = $-42.879 - 0.033A + 0.372H + 0.274W$

Note that the Watson formula for men has an age term while the Watson formula for women has no age term. Age effects on body water are more pronounced in men than in women. This is clearly indicated by the coefficients for age in the Chumlea and Johansson formulas. TBW: Total body water (L); H: Height (cm); A: Age (yr); BMI: Body mass index (kg/m^2); G: Gender (male = 1, female = 0); D: Diabetes (present = 1, absent = 0).

in the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH); and (3) available specific treatments to correct conditions causing hyponatremia^[43].

The osmotic demyelination syndrome can result from too rapid correction of hyponatremia. To prevent the development of this syndrome, the general aim of treatment is to achieve a maximal increase in $[\text{Na}]_s$ equal to 6 mmol/L over 24-h. Exceptions to this recommendation are cases with persistence of severe clinical manifestations from hyponatremia, when an even greater rate of increase in $[\text{Na}]_s$ is required^[43]. In certain circumstances, foremost after restoration of the urinary diluting capacity during correction of hypovolemic hyponatremia by adequate volume replacement or after correction of SIADH by administration of V2 receptor antagonists, dangerous rises in $[\text{Na}]_s$ can develop. Frequent measurement of $[\text{Na}]_s$, *e.g.*, every 2 to 4 h, and, in selected cases, of urine flow rate and urine sodium and potassium concentrations, is critical for prevention of osmotic demyelination^[85]. Prevention of formation of large volumes of dilute urine by infusion of desmopressin can prevent excessive rises in $[\text{Na}]_s$ in patients in whom correction of the condition causing the hyponatremia, *e.g.*, SIADH or hypovolemia, restores the urinary diluting mechanism^[86,87].

Hypernatremia is correctable by infusion of either water in the form of 5% dextrose solution or, if hypovolemia is present, hypotonic saline. Formulas used to calculate the volumes of water or hypotonic saline

required to obtain the desired decrease in $[\text{Na}]_s$ are based on the same principles as those used to treat hyponatremia^[37]. Table 2 shows these formulas. Too rapid decline in $[\text{Na}]_s$ increases the risk of severe neurological manifestations^[37].

Clinicians should be aware that in addition to the occasional uncertainty associated with estimating TBW by means of formulas, formulas for calculating infusion volumes for treating dysnatremias carry several other potential sources of error^[42,43]. These formulas do not account for changes in the determinants of $[\text{Na}]_s$ during treatment, such as water and electrolyte losses in the urine during treatment^[37,84,85], potential release of sodium stored in interstitial glycosaminoglycan (GAG) networks^[88], and changes in intracellular organic osmolytes^[89]. For these reasons, changes in $[\text{Na}]_s$ during treatment of dysnatremia must be monitored. Clarification of the quantitative impact of these other determinants on changes in $[\text{Na}]_s$ during treatment of dysnatremias could lead to the development of more accurate predictive formulas. However, accurate prediction of the magnitude of urinary losses of water, sodium and potassium is exceedingly difficult. Monitoring of the clinical status of the patients and frequent measurements of $[\text{Na}]_s$ will remain the critical step of the treatment of all dysnatremias treated with saline or dextrose solutions^[43,84,85,88,89]. Water bound to hydrophilic surfaces^[90] is another elusive factor that can complicate the treatment of dystonicity using quantitative tools.

Table 2 Formulas for treatment of dysnatremias with saline or water infusions**Hypotonic hyponatremia**

Change in sodium concentration after infusion of 1 L of saline. Adrogue-Madias formula^[41]:

$$[\text{Na}]_{\text{Final}} - [\text{Na}]_{\text{Initial}} = ([\text{Na}]_{\text{Infusate}} - [\text{Na}]_{\text{Initial}}) / (\text{TBW}_{\text{Initial}} + 1)$$

Volume of saline required for a targeted serum sodium concentration^[84]:

$$V_{\text{Infusate}} = \text{TBW}_{\text{Initial}} \times ([\text{Na}]_{\text{Targeted}} - [\text{Na}]_{\text{Initial}}) / ([\text{Na}]_{\text{Infusate}} - [\text{Na}]_{\text{Targeted}})$$

Hypernatremia

Volume of D5/W required for a targeted serum sodium concentration^[37]:

$$V_{\text{Infusate}} = \text{TBW}_{\text{Initial}} \times ([\text{Na}]_{\text{Initial}} - [\text{Na}]_{\text{Targeted}}) / ([\text{Na}]_{\text{Targeted}} - [\text{Na}]_{\text{Infusate}})$$

Volume of hypotonic saline required for a targeted serum sodium concentration^[37]:

$$V_{\text{Infusate}} = \text{TBW}_{\text{Initial}} \times ([\text{Na}]_{\text{Initial}} - [\text{Na}]_{\text{Targeted}}) / ([\text{Na}]_{\text{Targeted}} - [\text{Na}]_{\text{Infusate}})$$

$[\text{Na}]_{\text{Final}}$: Final serum sodium concentration after infusion of 1 L of saline with a sodium concentration higher than the initial serum sodium concentration; $[\text{Na}]_{\text{Initial}}$: Initial serum sodium concentration; $[\text{Na}]_{\text{Infusate}}$: Sodium concentration in the infused saline; $\text{TBW}_{\text{Initial}}$: Initial volume of body water; V_{Infusate} : Volume of infused saline or dextrose required for a targeted change in serum sodium concentration; $[\text{Na}]_{\text{Targeted}}$: Targeted value of serum sodium concentration.

However, the extent to which changes in tonicity alter the binding of water to hydrophilic surfaces is poorly understood and invites further investigation.

BODY FLUID BALANCE AS A FUNCTION OF EXTRACELLULAR FLUID VOLUME

When a body fluid abnormality secondary to a disturbance in ECFV is diagnosed, the terms “hypovolemia” and “hypervolemia” should be used instead of the ambiguous terms “dehydration” of “overhydration”, respectively. The regulation of ECFV is a critical body function.

Determinants of extracellular fluid volume

The three determinants of ECFV are TBW, total intracellular solute, and total extracellular solute. As noted earlier, TBW is partitioned between the intracellular and extracellular spaces in proportion to the amount of solute in each compartment. Changes in TBW unaccompanied by changes in solute will cause opposite changes in tonicity and in the volumes of body fluid compartments. An isolated gain in TBW will cause hypotonicity and hypervolemia in both the intracellular and extracellular compartments while an isolated loss of body water will have exactly the opposite effects. Abnormal gains in intracellular solute causing body fluid shifts into the intracellular compartment can be observed in serious disease states leading to cellular sodium gain, such as occur in patients with “sick cell syndrome”^[91]. Significant losses of intracellular solute, *i.e.*, potassium, are associated with fluid shifts into the extracellular compartment and hyponatremia^[92]. Large potassium losses, such as occur secondary to diuretics, may be associated with loss of extracellular solute and hypovolemia.

Most clinical ECFV disturbances are caused by changes in extracellular solute. Thus, the amount of solute in the extracellular compartment is critical in any analysis of factors affecting ECFV. Sodium salts, including sodium chloride and to a lesser degree sodium bicarbonate, constitute 90% or more of the extracellular

solute. In a real sense, sodium chloride defines ECFV and abnormalities in sodium salt balance are the major sources of ECFV disturbances^[22]. Gain in extracellular solutes other than sodium salts (*e.g.*, glucose) can also cause ECFV expansion. The kidneys are the end-organ that regulate ECFV. Complex circulatory and neuro-endocrine mechanisms play vital roles in this regulation, which has attracted a major part of the research in renal transport and excretion mechanisms in health and disease^[93-95]. Regulation of sodium is a high priority renal function. In various clinical conditions stimulating the renal mechanisms for sodium retention (*e.g.*, hypovolemia, cardiac failure, cirrhosis, *etc.*), potassium balance, acid-base balance and water balance are sacrificed to preserve body sodium. Renal tubular sodium transport processes account for the largest fraction of oxygen consumption in the kidneys^[96]. Details of the regulation of sodium balance are beyond the scope of this report.

Measuring extracellular fluid volume

Measurement of ECFV entails ambiguities exceeding those associated with the measurement of TBW. These ambiguities relate to both the concept of ECFV and the methods for measuring it. The conceptual difficulty is rooted in the definition of extracellular space. Intracellular space is defined as the space enclosed within the cell membranes and intracellular water is the portion of body water in the intracellular space. However, there is significant doubt whether all body fluid compartments outside the cell membranes should be considered as contributing to the ECFV. The fluid compartments in question, which were termed by Moore as the transcellular fluids^[97], include fluids in the gastrointestinal tract^[98], collagenous connective tissues^[99], serous and synovial cavities^[46], cerebrospinal space^[46], lower urinary tract^[46], and bile ducts^[46].

Measurement of ECFV by dilution of injected exogenous markers, *e.g.*, radioactive compounds^[100], added to the difficulties. Table 3 lists some of these markers^[46,101-113]. Several “extracellular” markers penetrate transcellular fluids and some, including the commonly used bromide

Table 3 Measurement of extracellular volume by tracer dilution

Extracellular marker	Ref.
Inulin	[101]
Sucrose	[102]
Thiosulfate	[103,104]
Mannitol	[105]
Radiosulfate (S ³⁵)	[106,107]
Bromide	[108,109]
Radiochloride (Cl ³⁸ , Cl ³⁶)	[109,110]
Stable chloride (Cl ³⁵)	[111]
Radiosodium (Na ²⁴)	[112]
Thiocyanate	[113]

salts, enter partially into the intracellular compartment^[46]. Consequently, there are substantial differences in the estimates of ECFV between these markers^[46].

Recently, several new technologies for measuring ECFV have been developed^[114]. Table 4 shows the principal techniques, which fall into the following three categories: (1) methods based on body composition, including BIA^[115-121] or bioelectrical impedance vector analysis (BIVA)^[122,123], DEXA^[124-132], and magnetic resonance imaging (MRI)^[133]; (2) simultaneous measurement of TBK in a total body counter measuring stable potassium (⁴⁰K) and TBW usually by ²H₂O dilution^[134-136]; and (3) estimation of glomerular filtration rate (GFR) using exogenous markers with extracellular distribution^[137-147]. The ECFV value is computed in the third category by either constant infusion^[138], or, more often, a single injection^[139] of the exogenous GFR marker. In the case of a single injection, the theoretical equilibrated initial concentration of the marker in the extracellular fluid is calculated by extrapolating its plasma disappearance curve to zero time (time of infusion of the marker)^[139].

The methodologies for measuring TBW and ECFV by these newer techniques were developed by comparing their performance to measurements from the older dilution techniques, mostly the ²H₂O and bromide dilution techniques^[116,117,126,130,134,148-156]. Figure 3 shows average ECFV values obtained by the older dilution techniques (Table 3) and several frequently used newer techniques (Table 4). The values resulting from the most commonly used newer techniques (BIA, DEXA) are, in most cases, close to those based on chloride or bromide space. Equations predicting normal ECFV values from simple anthropometric measurements, for example as a fraction of body weight, were developed using ECFV measurements by one of the newer methods^[144,157]. However, these equations are not accurate in patients with ECV disturbances. Finally, techniques for measuring ECFV in diseased organs or tissues, for example in malignant tumor-bearing organs, have also been developed^[158-160].

Clinical applications of extracellular fluid volume estimates

The main clinical application of measurements of ECFV is in conditions requiring precise management of

Table 4 Measurement of extracellular volume by newer methods

Methodology	Ref.
Methods evaluating body composition	
Bioelectrical impedance, bioelectrical impedance vector analysis	[115-123]
Dual-energy X-ray absorptiometry	[124-132]
Magnetic resonance imaging	[133]
Methods measuring total body water and intracellular volume	
Simultaneous measurement of total body water and potassium	[134-136]
Methods using GFR markers	
Inulin	[138,139]
Polyfructosan	[140]
51chromium ethylenediamine tetra-acetic acid (⁵¹ Cr-EDTA)	[141-143]
Iohexol	[144]
Technetium diethylene triamine penta-acetic acid (^{99m} Tc-DTPA)	[145,146]
Iothalamate	[147]

GFR: Glomerular filtration rate.

excesses or deficits of this volume. To quantify ECFV excess, Chamney *et al.*^[50] measured TBW by ²H₂O dilution, ECFV by NaBr dilution, and body fat by DEXA and air-displacement. These investigators developed a quantitative model of body fluids containing three compartments: Normally hydrated lean tissue, normally hydrated adipose tissue, and excess fluid. Chronic dialysis for end-stage kidney disease represents an example of Chamney's three-body fluid compartment approach. One of the main aims of the prescription of hemodialysis is achieving "dry weight" by computing prior to each hemodialysis session the volume of fluid that should be removed to return ECFV within its normal range^[161]. Although clinical criteria for ECFV excess or deficit are useful in monitoring the overall state of health of hemodialysis patients, they have low positive and negative predictive values and carry the risk of excessive volume removal and hypotension during a hemodialysis session. DEXA has been used to evaluate ECFV in a small number of studies^[162]. BIA and BIVA studies are simple, technically easy to conduct, and inexpensive. Studies conducted in various parts of the world have provided evidence that measurements of ECFV by BIA or BIVA improve the management of fluid balance in hemodialysis patients^[163-170].

Hyperglycemic crises represent another clinical state in which ECFV changes, along with changes in the relationship between TBW and body solute, cause severe clinical manifestations and play an important role in the prescription of fluid management^[37]. ECFV changes occur during both development and treatment of severe hyperglycemia and differ between subjects with preserved and severely impaired renal function. The increase in extracellular solute during development of hyperglycemia causes intracellular water to shift into the extracellular compartment. This osmotic fluid shift,

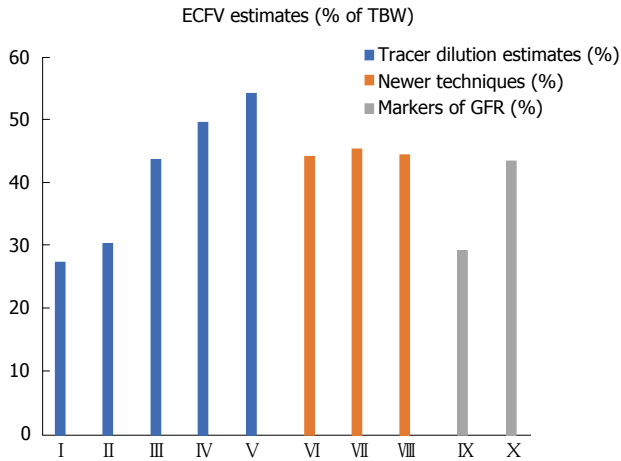


Figure 3 Average extracellular fluid volume estimates expressed as percentages of total body water. I - V: Tracer dilution estimates^[146]; I: Sucrose, thiosulfate; II: Mannitol, sulfate; III: Bromide, chloride; IV: Sodium; V: Thiocyanate; VI-VII: Newer techniques; VI: Dual-energy X-ray absorptiometry^[130]; VII: Bioelectrical impedance^[115]; VIII: Simultaneous determination of total body potassium and total body water^[195]; IX, X: Glomerular filtration rate markers; IX: Inulin^[139]; X: Iothalamate^[147]. ECFV: Extracellular fluid volume; TBW: Total body water.

which affects the estimation of the serum tonicity^[171], may cause volume overload symptoms in patients with advanced renal failure^[172]. The calculation of the magnitude of this shift requires knowledge of the amount of glucose added to the extracellular compartment, in addition to Edelman's three determinants of $[Na]_s$, which include body sodium, body potassium and TBW^[173,174]. The total amount of glucose in the body fluids is the product of the volume of distribution of glucose times the serum glucose concentration^[37].

Calculations of body fluid spaces made after a single glucose injection in normal individuals reported a glucose volume of distribution that was within the range of normal ECFV values^[175-177]. Insulin is usually the only treatment required for hyperglycemia in oligoanuric patients in whom correction of hyperglycemia reverses both hypertonicity and ECFV expansion^[172]. The reciprocal changes in $[Na]_s$ and serum glucose concentration during treatment of oligoanuric hyperglycemia with insulin only allow the calculation of the fraction ECFV/TBW at normoglycemia^[178]. Calculation of this fraction in hyperglycemic patients at their "dry weight" yielded ECFV/TBW values within the normal range^[178].

Both ECFV changes and tonicity differ in hyperglycemic patients with preserved renal function^[81,174,179]. These patients manifest osmotic diuresis secondary to glycosuria during development of hyperglycemia. The fluid loss from osmotic diuresis causes ECFV contraction and rise in tonicity far exceeding the rise from extracellular glucose gain. ECFV losses persist during treatment if glycosuria persists^[79]. In most cases, treatment of hyperglycemia in this patient group requires, in addition to insulin, infusion of large volumes of hypotonic saline and potassium salts and close monitoring of clinical status and laboratory values^[37]. The volume and composition of the replacement solutions is determined empirically

based on clinical manifestations and laboratory values. Selected cases where body weight measurements were recorded immediately before and during a hyperglycemic crisis allow more precise calculation of the volume and composition of the replacement solutions, but still require close monitoring^[81].

In addition to chronic dialysis and hyperglycemia, ECFV abnormalities and the need to monitor ECFV and its changes during treatment have been investigated in a variety of chronic and acute illnesses^[128,154,180-187]. Finally, another example of the potential clinical applications of ECFV and TBW measurements is in determining body composition. The components of body composition, particularly muscle mass and body fat, are major determinants of morbidity and mortality in the elderly, as well as in patients with various acute and chronic illnesses^[188,189]. Wang *et al.*^[190] developed sophisticated mathematical models of body composition using as their major parameter the ratio of extracellular to intracellular water. Measuring TBW and ECFV provides a reliable reference method for body composition analysis.

Limitations of extracellular fluid volume estimates

The efficacious application of measurements of ECFV in clinical practice relies on precise estimates of the normal values. Determination of the normal ECFV values has encountered significant limitations. The first limitation relates to the determination of the precision of ECFV measurement, which is established by frequent serial measurements^[191]. Burke and Staddon measured repeatedly over a six-week period TBW by ^3H_2O dilution and ECFV by radiosulfate dilution in 10 healthy subjects^[192]. These authors calculated a mean precision value of 2.63 L for TBW and 1.11 L for ECFV. The presence of disease raises an additional challenge to the precision of the ECFV measurements. Below we discuss the precision of three methods which have received extensive clinical applications: Namely chloride or bromide dilution, measurement of TBK and TBW, and BIA.

Estimates of ECFV based on chloride, or more frequently bromide, dilution are calculated as the fraction "amount of marker in the body" over "the equilibrated concentration of this marker in the extracellular fluid" and are routinely corrected for Gibbs-Donnan equilibrium and intracellular penetration of the markers^[193]. The Gibbs-Donnan equilibrium states that due to electrostatic forces, the concentration of a crystalloid anion is higher in interstitial fluid than in serum, which is rich in colloidal anions (*i.e.*, proteins)^[29]. The extracellular chloride or bromide concentration is calculated by multiplying the serum concentration by an empiric Gibbs-Donnan coefficient, which is usually 1.050^[193]. The magnitude of the error from this calculation in subjects with low plasma protein level or elevated interstitial protein concentration is unknown.

The calculated estimates of ECFV by bromide or chloride dilution are also corrected for intracellular penetration of the ECFV index by a reducing coefficient, usually 0.90^[193]. Penetration of reference extracellular

markers into the transcellular or intracellular compartment differs between healthy and severely ill subjects. Cunningham *et al.*^[194] analyzed the intracellular electrolyte composition of deltoid muscles in 7 normal subjects and 13 patients with various severe illnesses. Intracellular chloride concentration was 4.1 ± 1.5 mmol/L in the healthy subjects and 8.8 ± 3.6 mmol/L in the patients. Corresponding extracellular chloride concentrations were 104.4 ± 5.7 and 106.7 mmol/L respectively. Schober *et al.*^[195] measured TBW by $^3\text{H}_2\text{O}$ dilution and ECFV by radiobromide dilution in 10 normal subjects and 38 critically ill patients. TBW values were comparable between the two groups (536 ± 56 mL/kg in the healthy subjects and 505 ± 68 mL/kg in the critically ill patients). In contrast, bromide space as a fraction of body water was substantially higher in the critically ill patients (0.83 ± 0.17) than in the normal subjects (0.46 ± 0.04). These findings are consistent with substantially higher penetration of bromide into the intracellular compartment in critically ill patients than in normal subjects and raise serious concerns about the validity of ECFV measurements by bromide space in critically ill subjects.

The calculation of ECFV made by combining TBK and TBW values assumes that intracellular and extracellular potassium concentrations are constant, usually 152 and 4 mmol/L, respectively^[136]. The equation for calculating ECFV is as follows: $\text{ECFV} = (152 \times \text{TBW} / \text{TBK}) / 148$ ^[136,193]. Calculations of ECFV using this equation provided a reasonable agreement with calculations based on bromide space in the large number of subjects studied by Silva *et al.*^[193], with differences being more pronounced in obese subjects. ECFV calculations made using equations that combine TBW and TBK measurements will be subject to errors in subjects whose intracellular potassium concentration differs substantially from 152 mmol/L. Subjects with dystonicity in whom ECFV measurements may be required^[184], have an abnormal intracellular potassium concentration. Certain categories of patients with severe illness, *e.g.*, uremic patients, may also have low intracellular potassium concentration^[196].

The principles and limitations of measurements of TBW and its compartments by BIA have been reviewed^[61,118,167]. As stated above, BIA is widely used to investigate the status of body fluids in patients on dialysis. In patients undergoing hemodialysis, TBW measurements by BIA, which are used in the calculation of ECFV estimates, differed from $^2\text{H}_2\text{O}$ -based measurements by a margin of -3.4 to 20.3 L in one report^[197]. Another report found gross underestimation of TBW by BIA in a hemodialysis patient with extreme ascites and hydrothorax^[165]. In a study comparing measurements of TBW in hemodialysis patients by BIA and $^2\text{H}_2\text{O}$, Chan *et al.*^[198] concluded that BIA either underestimates systematically TBW or overestimates systematically intracellular water and that the differences between reference and BIA measurements of TBW increase as comorbidities increase.

Another difficulty in measuring ECFV is establishing normal values. This process is complicated by various

factors. In studies by Silva *et al.*^[136,199], the fraction ECFV/TBW increased progressively with age in men, while both African American men and women had higher values of this fraction compared to subjects from other ethnic backgrounds. Several studies have confirmed that women have higher ECFV/TBW values in comparison to age-matched men^[114,200-202]. Children have substantially different ECFV/TBW values than adults^[203], and obese children have higher ECFV/TBW values than non-obese children^[151]. These facts underscore the need for establishing normal ECFV values that are specific for gender, age, ethnicity and degree of obesity.

The importance of estimates of ECFV in various disease states, the various methods that are available for measuring ECFV, and the limitations and costs of these methods create the need to choose the best method of measurement. Shepherd *et al.*^[204] compared recently various methods of analyzing body composition in terms of cost, compliance, infrastructure, precision, quality control, training, trueness, and safety. The major limitation of all methods for measuring ECFV is encountered during severe acute or chronic illnesses. Several illnesses lead to both hypervolemia producing clinical manifestations and uncertainty about the desired values of ECFV. For these reasons, the challenge of optimal ECFV in severe illness merits a separate analysis as a fluid balance concept and is addressed in the next section.

BODY FLUID BALANCE IN SEVERE CHRONIC OR ACUTE ILLNESS

Concept and principles of management of fluid balance in illness

Disturbances of body fluid balance are cardinal manifestations of many severe acute or chronic illnesses^[205]. Precise management of these disturbances is critical^[206]. Fluid management must address both repletion of deficits and avoidance of excesses^[207] and requires understanding of the regulation and measurement of TBW and particularly ECFV. Adequate blood perfusion of organ systems is essential and is an indispensable role of ECFV. Normal cell function and survival require an uninterrupted supply of oxygen and nutrients, and removal of carbon dioxide and metabolic by-products. It has long been recognized that the optimal value of ECFV in critical illness may differ from a "normal" value^[208]. The term "obligatory edema" was used in the past to denote the need for an expanded ECFV in patients with hepatic cirrhosis, ascites and hypoalbuminemia. The term "effective blood volume" was coined by Peters to indicate the need for supranormal blood volume in certain disease states^[209,210]. More recently, the term effective arterial blood volume (EABV) has been used to indicate the state of organ perfusion^[95].

EABV is affected by several physiologic functions and biochemical parameters in addition to ECFV. Parameters related to either the composition of the

Table 5 Factors affecting cell- and organ-perfusion (effective arterial blood volume)

Blood volume
Red blood cell mass
Plasma volume
Cardiac output
Vascular capacity
Arterial resistance, total
Arterial resistance, regional
Venous capacity
Starling forces in blood capillaries
Endothelial barrier integrity
Gravity

blood, for example blood hemoglobin concentration and arterial blood gases, or the metabolic needs of diseased cells, are not directly correlated with ECFV. There are, however, several factors influencing EABV that interact directly with ECFV. Changes in these factors in disease states create the need for ECFV values that exceed normal values. Table 5 shows factors affecting organ perfusion that are interacting with ECFV^[211,212]. A brief discussion of these factors follows.

ECFV directly defines the plasma volume. Schrier explored the interaction between cardiac function, arterial tone, and ECFV regulation as well as the factors affecting this relationship^[213]. Starling forces in the blood capillaries and surrounding interstitial space dictate fluid exchanges between the intravascular and interstitial spaces. The importance of an effective capillary endothelial barrier to albumin transfer from the intravascular into the interstitial compartment is exemplified by patients who lose this barrier. Such patients require infusion of enormous volumes of albumin-containing fluid to maintain their intravascular volume^[214].

The effects of gravity on EABV and ECFV were studied during space flights. Absence of gravity causes large transfer of fluids from peripheral body parts (*e.g.*, limbs) into the central blood volume and decreases in the blood levels of vasopressin, renin and aldosterone, and causes profound diuresis of water and sodium salts^[215-217]. Gravity and “head-out” water immersion have similar effects on EABV and ECFV^[218]. This last observation may have clinical implications. The interactions between the factors indicated in Table 5 is the source of different optimal ECFV values in health and severe illness.

The aim of fluid management in severe illness is prevention of both organ hypoperfusion and circulatory overload. The methodology for evaluating EABV and determining whether clinical manifestations of low EABV are responding to volume replacement in critically ill patients is complex. The response of EABV to fluid challenges is monitored by a variety of invasive static (stroke volume, cardiac output, cardiac index) and dynamic (stroke volume variation, pulse pressure variation, change in the fraction “stroke volume”/“cardiac

index”) parameters^[219]. The uses and limitations of the patient’s history and clinical examination, chest X-ray and echocardiography, continuous dynamic evaluation of circulatory parameters during fluid administration, certain biochemical values, and BIVA in evaluating body fluid status were reviewed by Kalantari *et al.*^[207]. Adequate perfusion of the kidneys and prevention of acute kidney injury (AKI), which is both frequent in this clinical setting and an independent risk factor for mortality and prolonged hospital stay^[220-222], is a main target of this fluid management. Fluid management efforts in critical illness should be directed towards the interactions of systemic and renal hemodynamics, the preservation of the renal microcirculatory blood flow^[223], and the determination of indications for mechanical fluid removal^[224].

The mechanisms that underlie fluid imbalance and their treatment vary depending on the nature of critical illnesses. Palmer *et al.*^[95] analyzed the general mechanisms leading to decreased EABV and target ECFV values that are higher than normal. These mechanisms include: Fluid trapping in the interstitium or a preformed body cavity; reduced serum oncotic pressure; and vascular disturbances, *e.g.*, altered capillary filtration pressure due to low cardiac output, increased venous resistance, or endothelial dysfunction.

The clinical states discussed subsequently in this report illustrate the pathophysiologic mechanisms and the principles of fluid management in critically ill patients. The management of these conditions should address, in addition to ECFV, correction of abnormalities in the other factors specified in Table 5. However, ECFV estimates made using traditional methods have a limited role in this management. The clinical states we have chosen to illustrate the concepts of fluid imbalance secondary to EABV disturbances in severe illness include congestive heart failure (CHF), hepatic cirrhosis, and sepsis. Finally, nephrotic syndrome represents a unique state of disturbed fluid balance. The pathogenesis of fluid imbalance in nephrotic syndrome involves both a reduced EABV and primary sodium salt retention by the kidneys. The mechanisms of volume retention in nephrotic syndrome will be discussed briefly.

Congestive heart failure

Fluid retention characterizes the course of CHF, causes serious clinical manifestations, and is one of its main therapeutic targets. A decrease in cardiac output is the primary cause of fluid retention in CHF secondary to left ventricular failure (Table 5). Palmer *et al.*^[95] reviewed the complex mechanisms sensing decreased EABV and the effector mechanisms of renal retention of salt and water in CHF. The Frank-Starling law of the heart states that the stroke volume increases as end-diastolic volume increases when all other factors affecting myocardial performance are unchanged^[225]. In early-compensated stages of CHF, elevated left ventricular end diastolic volume secondary to both decreased

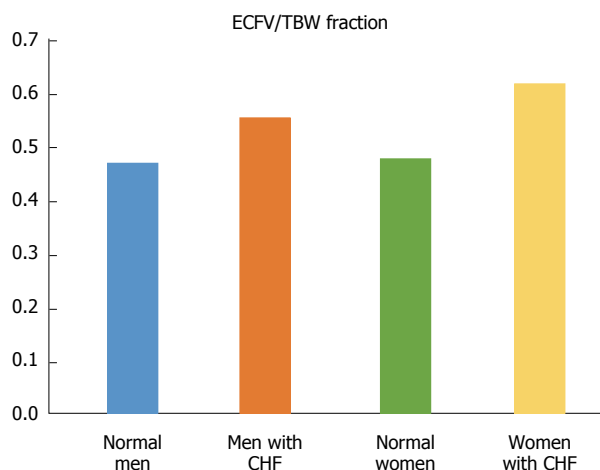


Figure 4 The fraction extracellular volume over total body water in elderly subjects with relatively compensated congestive heart failure and healthy controls. Mean values ECFV/TBW in the study of Sergi *et al.*^[228]. The mean ejection fraction of elderly patients with relatively compensated congestive heart failure (CHF) and absence of pleural effusion was 40%. Total body water (TBW) was measured by $^2\text{H}_2\text{O}$ dilution and extracellular volume (ECFV) by bromide dilution. The fraction ECFV/TBW was significantly higher in subjects with CHF.

cardiac performance and ECFV expansion leads to an increase in stroke volume and restoration of cardiac output. Figure 4 compares the fraction ECFV/TBW in elderly subjects with relatively compensated CHF and healthy controls^[226]. At this relatively early stage of CHF, ECFV/TBW was higher than normal. It is not clear whether the higher than normal ECFV in this stage of CHF is beneficial in the long term or not.

As CHF progresses, low EABV leads to progressive renal retention of salt and water^[227], which causes ECFV expansion and progressive distention of the myocardium with adverse effects on cardiac performance^[228]. Determining the optimal level of ECFV and maintaining the patient at that level are major management goals. Mechanisms of salt and water retention may differ between right and left ventricular failure^[229]. Myocardial dysfunction in valvular disease and “high-output” cardiac disease represent other categories of CHF in which the optimal levels of ECFV may differ from those in left ventricular failure.

Fluid overload therapy can be insufficient in many patients hospitalized with CHF. Incomplete fluid removal during the hospital stay coupled with the limitations of weight-based management to identify the recurrence of fluid retention post discharge leads to symptomatic elevated intracardiac right and left-sided filling pressures. In these patients, vigorous and timely reduction of the elevated filling pressures leads to improved prognosis, fewer hospitalizations and better outcomes. However, prevention of both symptomatic ECFV expansion and lower than optimal ECFV in CHF is important. In dilated CHF, forward flow is optimal at near-normal filling pressures, with minimized mitral regurgitation^[230]. In cases of acute CHF with persistent clinical manifestations, such as respiratory distress and impaired systemic perfusion, right heart catheterization is indicated. Fluid

management must incorporate a thorough clinical patient evaluation, use of appropriate diuretics, frequent follow-up, and daily weight measurement^[231]. Despite these measures, re-admissions are not prevented; thus, multiple approaches for monitoring outpatient fluid balance are being explored.

Natriuretic peptide biomarkers (BNP, B-type natriuretic peptide, NT-pro-BNP, N-terminal pro-B-type natriuretic peptide) are increasingly being used to diagnose and estimate the severity of CHF as well as for population screening purposes. Many other biomarkers have been implicated in CHF (markers of inflammation, oxidative stress, vascular dysfunction, and myocardial and matrix remodeling). Furthermore, biomarkers of myocardial fibrosis, soluble ST2 receptor, and galectin-3 are predictive of hospitalization and death and may provide supplemental prognostic value to BNP levels in patients with CHF^[231]. All these biomarkers have been used in assessing fluid balance status in patients with CHF.

BIVA has also been applied in assessing fluid balance status in patients with CHF^[130]. Valle *et al.*^[232] tested the hypothesis that achievement of adequate ECFV status with intensive medical therapy, modulated by combined BIVA and BNP measurement, optimizes the timing of discharge and improves the clinical outcomes of patients admitted with acutely decompensated heart failure (ADHF). Three hundred patients admitted for ADHF underwent serial BIVA and BNP measurements. Therapy was titrated to reach a BNP value < 250 pg/mL. Patients were categorized as early responders (rapid BNP fall below 250 pg/mL); late responders (slow BNP fall below 250 pg/mL, after aggressive therapy); and non-responders (BNP persistently > 250 pg/mL). Worsening of renal function was evaluated during hospitalization. Death and re-hospitalization were monitored with a 6-mo follow-up. This study confirmed the hypothesis that serial BNP/BIVA measurements help to achieve adequate fluid balance status in patients with ADHF and can be used to drive a “tailored therapy”, allowing clinicians to identify high-risk patients and possibly to reduce the incidence of complications secondary to fluid management strategies.

The combined use of BNP and BIVA for assessing and managing fluid overload, distinguishing cardiogenic from non-cardiogenic dyspnea, and improving management of CHF patients in Emergency Departments was tested in another report as well^[233]. This randomized controlled trial was designed to investigate whether fluid status monitoring with an automatically generated wireless CareAlert notification can reduce all-cause death and cardiovascular hospitalizations in a CHF population, compared with standard clinical assessment^[234]. The investigators found that fluid status telemedicine alerts did not significantly improve outcomes in patients with advanced CHF and implantable cardioverter defibrillators (ICDs). The problem of adherence to treatment protocols by physicians and patients might be compromising advances in the telemedicine field^[235].

The term Cardio-Renal Syndrome (CRS) defines disorders of the heart and kidneys whereby “acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other”^[236]. CRS requires a tailored approach to manage a patient’s underlying pathophysiology while optimizing the patient’s clinical picture and thus providing better outcomes. Precise prescription of fluid removal by diuretics or extracorporeal therapies is a key element of this approach. Adequate monitoring of fluid balance is essential for preventing worsening of renal function or other complications while delivering these therapies. Monitoring of extravascular fluid in the lungs by ultrasonography is helpful in fluid management^[237]. The range of optimal ECFV values appears to be very narrow in patients with CHF. Hypervolemia results in myocardial stretching and decompensation, whereas hypovolemia leads to low EABV that can result in organ damage. Therefore, in cases with CRS the “5B” approach has been suggested: Balance of fluids (reflected by body weight), blood pressure, biomarkers, BIVA, and blood volume^[236].

It has traditionally been presumed that patients with CHF benefit from a low-sodium diet. A recent review attempted to provide insight into the currently available evidence base for the effects of dietary sodium restriction in patients with chronic CHF. This review concluded that both observational and experimental studies have shown mixed results and that the effects of a low-sodium diet on clinical outcomes in patients with CHF remain controversial and unclear^[238]. However, the fact remains that most hospitalizations for CHF are related to sodium and fluid retention. Recent research suggests that not all sodium is distributed in the body solely as a free cation, but that some sodium is also bound in different tissues to large interstitial GAG networks that appear to have important regulatory effects on ECFV. In CHF, high sodium intake and neurohumoral alterations disrupt GAG structure, leading to loss of the interstitial buffer capacity for sodium and disproportionate interstitial fluid accumulation. Moreover, a diminished GAG network increases vascular resistance and interferes with endothelial nitric oxide production. Improved imaging modalities should help in the assessment of interstitial sodium levels and endothelial glycocalyx integrity. Furthermore, several therapies have been proven to stabilize interstitial GAG networks, *e.g.*, hydrocortisone, sulodexide, dietary sodium restriction, spironolactone). Hence, better understanding of this new sodium “compartment” might improve the management of CHF^[239].

Detailed guidelines for the diagnosis and treatment options of the various forms of CHF (acute or chronic, with reduced or not-reduced ejection fraction) are available^[231,240]. The patient who presents with suspected CHF should be assessed by clinical history and detailed physical examination. Chest X-ray, electrocardiogram and blood levels of natriuretic peptides are always useful. The next step is an echocardiogram. If CHF is confirmed, its etiology should be determined and appropriate

treatment initiated. At the end of these guidelines the authors discuss the missing pieces of information in the existing literature and offer thoughtful recommendations for future work. Since there is no exact method for estimating optimal ECFV in patients with CHF, future studies should address this knowledge gap.

Cirrhosis-ascites-hepatorenal syndrome

Decreased EABV is a cardinal feature of cirrhosis in which changes in multiple factors activate the mechanisms of sodium retention and ECFV expansion. Factors that lead to decreased EABV in cirrhosis are listed in Table 5 and include: Increase in overall arterial and venous capacity, decrease in Starling forces, and, in late stages of cirrhosis, decrease in cardiac output. The decrease in arterial and venous resistance is a strong stimulus for increased ECFV. Advanced cirrhosis is characterized by portal hypertension, arteriovenous fistulae, peripheral vasodilatation, and sequestration of plasma volume in the abdominal cavity and splanchnic venous bed^[241]. The “arterial vasodilation theory” is the most widely accepted explanation for the expansion of ECFV in cirrhotic patients^[242]. An alternative theory, designated the “hepatorenal reflex hypothesis”, suggests that vascular bed vasodilatation in cirrhosis is a consequence of the shunting of blood from the portal to the systemic circulations rather than an etiology for volume overload; however, further research is required to support this hypothesis^[243].

The widely recognized causes of vasodilatation in cirrhosis are: (1) Increased production or increased activity of vasodilating factors by hepatocytes and stellate cells (mainly nitric oxide, carbon monoxide, prostacyclin and endogenous cannabinoids); (2) reduced response to vasoconstrictor factors; (3) mesenteric neoangiogenesis; (4) compromise of cardiac output as cirrhosis progresses probably due to cirrhotic cardiomyopathy; and (5) systemic inflammatory response with increased production of pro-inflammatory cytokines (IL-6, TNF- α) and vasodilating factors due to translocation of bacteria and their products across the intestinal barrier to mesenteric lymph nodes^[244-247]. In addition, markers of oxidative stress such as oxidized albumin have been shown to increase in decompensated cirrhosis^[242]. The exact cellular and molecular mechanisms implicated in the phenomenon of bacterial translocation in cirrhosis have not been fully elucidated^[246]. Hypoalbuminemia, another feature of advanced cirrhosis, decreases intracapillary colloid-osmotic forces and increases fluid translocation from the intravascular into the interstitial compartment leading to further decreases in EABV. Circulatory abnormalities in cirrhosis define the stages of progression of cirrhosis that ultimately culminate in hepatorenal syndrome (HRS). Cardiac output is not a cause of clinical manifestations in early compensated stages, but is increased in advanced cirrhosis, and may decrease in its later stages and thus contribute to the decreased EABV. Cirrhotic vasodilatation stimulates the arterial stretch receptors in the carotid sinus and

aortic arch, producing a baroreceptor response and activation of compensatory vasoconstricting mechanisms including the renin-angiotensin-aldosterone system, the sympathetic nervous system, and the non-osmotic hypersecretion of vasopressin^[248]. Stimulation of these systems contributes to maintenance of blood pressure by modulating decreases in the systemic vascular resistance and increasing cardiac output^[248].

The so-called "hyperdynamic syndrome" in cirrhosis is a consequence of portal hypertension and involves complex humoral and neural mechanisms. This syndrome is hemodynamically characterized by high cardiac output, increased heart rate and total blood volume, reduced total systemic vascular resistance and normal or decreased blood pressure^[245]. Arterial blood volume is shunted to the splanchnic vessels at this stage, while the central arterial blood volume (heart, lungs, and central arterial tree blood volume) is often decreased^[245]. At a later stage, the hyperdynamic syndrome leads to cardiac dysfunction (cirrhotic cardiomyopathy), pulmonary dysfunction (hepatopulmonary syndrome) and renal dysfunction (HRS), in addition to reduced survival^[249].

The function of the cardiovascular system is disturbed in cirrhosis due to decreased vascular reactivity and a universal endothelial and autonomic dysfunction^[249]. Cirrhotic cardiomyopathy is characterized by impaired myocardial contractility with systolic and diastolic dysfunction in combination with electromechanical abnormalities, such as prolongation of the Q-T interval, in the absence of any other cardiac disease^[249]. Some degree of diastolic dysfunction may be present in > 50% of cirrhotic patients regardless of the presence or extent of ascites. No correlation has been found between HRS and diastolic dysfunction^[242]. A study of the role of cardiac abnormalities in the pathogenesis of circulatory and renal dysfunction in cirrhosis^[250] concluded that: (1) Diastolic dysfunction is frequent, but mild in most cases and does not increase the pulmonary artery pressure to abnormal levels. This may be due to the central hypovolemia of cirrhosis and probably accounts for the lack of symptoms associated with this condition; (2) diastolic dysfunction is unrelated to circulatory dysfunction and ascites; and (3) in cirrhosis, there is a lack of response of the left ventricular systolic and chronotropic function to peripheral arterial vasodilatation and activation of the sympathetic nervous system. This feature is an important contributory factor to the progression of circulatory dysfunction and the pathogenesis of HRS, which constitutes the last stage of the circulatory disturbances in cirrhosis^[244,247,248]. Other systems are affected as well including: The femoral and brachial vessels (producing cramps), the immune system, the adrenal glands, and the vessels in the brain (playing a role in encephalopathy)^[247,249].

The vasoconstrictive compensation in cirrhosis includes the renal vessels and negatively affects renal function, resulting in sodium and solute-free water retention, edema, and eventually renal failure. Patients with advanced cirrhosis exhibit a shift in the renal autoregulation curve, which means that for a given

level of perfusion pressure, renal blood flow is lower compared to that of patients with compensated cirrhosis; a decrease in GFR leading to HRS ensues. HRS is almost exclusively of a functional nature and usually without discernable histologic abnormalities in the kidneys^[242,245]. However, in some reports the kidneys of cirrhotic patients with presumed HRS showed histologic evidence of AKI. Immunologic mechanisms are apparently important in mediating the renal injury and hemodynamic factors do not operate in isolation^[251].

HRS is classified into two subgroups, HRS 1 and HRS 2. The rate of deterioration of renal function is rapid, within 2 wk, in HRS 1 and slower in HRS 2, occurring over several months^[244]. HRS must routinely be differentiated from two other conditions that cause AKI frequently in cirrhotic patients, namely acute tubular necrosis and prerenal azotemia. AKI in cirrhosis carries a high risk for mortality^[252], with HRS or acute tubular necrosis having substantially higher mortality rates compared to prerenal azotemia^[252]. Urinary biomarkers can be helpful in differentiating between HRS and acute tubular necrosis. Urinary neutrophil gelatinase-associated lipocalin (NGAL) activity was shown to be highly accurate in identifying patients with acute tubular necrosis and was incorporated into a proposed diagnostic algorithm^[253]. Other biomarkers that were shown to be useful in the diagnosis of acute tubular necrosis include interleukin-18 (IL-18), albumin, trefoil-factor-3 (TFF-3) and glutathione-S-transferase- π (GST- π)^[253].

NGAL is not helpful in differentiating between prerenal azotemia and HRS^[247]. Also, biochemical analytes indicative of tubular function do not distinguish between prerenal azotemia and HRS; in both conditions, the decrease in GFR is associated with intact tubular function as reflected by a very low urinary sodium concentration and high urine to plasma (U/P) creatinine ratio. The response of renal dysfunction to expansion of the intravascular space with colloid or saline solutions constitutes the key differentiating feature between the two conditions. Prerenal azotemia is reversed with adequate fluid replacement and no other measures. In contrast, reversal of HRS requires administration of fluid plus vasoconstrictors.

In addition to pre-renal azotemia and acute tubular necrosis due to hypovolemia (bleeding, diarrhea, excessive use of diuretics), several other clinical conditions may cause AKI in patients with advanced cirrhosis. These conditions include: (1) Bacterial infections with or without septic shock (such as spontaneous bacterial peritonitis); (2) use of nephrotoxic medications such as non-steroidal anti-inflammatory drugs or aminoglycosides; (3) abdominal compartment syndrome from tense ascites; and (4) intrinsic renal diseases (hepatitis-B or C associated glomerulonephritis, glomerulonephritis in alcoholic cirrhosis)^[240,244,252]. The initial management of cirrhotic patients with AKI should address all these conditions. This management is therefore complex, but depends primarily on accurate assessment of the status of EABV. Physical examination and invasive measurements, such as

central venous pressure, often do not reflect intravascular volume status. Point-of-care echocardiography can be effective in guiding the timing of large volume abdominal paracentesis and optimizing the hemodynamic status in decompensated cirrhotic patients with AKI, which in turn can improve venous return and promote recovery of renal function^[254].

First-line treatment of patients with cirrhosis and ascites consists of sodium restriction and application of diuretics. However, the main thrust for preventing and managing HRS is directed towards expanding ECFV with albumin infusions and correcting the splanchnic vasodilatation by vasoconstrictors, including octreotide, sympathomimetic agents (*i.e.*, midodrine), and vasopressin analogues (*i.e.*, terlipressin). Oral midodrine has been shown to improve clinical outcomes and survival in patients with refractory ascites^[255]. In patients with stable hypotension, midodrine may improve splanchnic and systemic hemodynamic variables, renal function, and sodium excretion. In patients without HRS, midodrine was shown to increase urinary volume, urinary sodium excretion, and mean arterial pressure and was associated with a reduction in overall mortality^[256].

Terlipressin and albumin administration can reverse HRS and reduce the associated short-term mortality rate^[257,258]. Terlipressin alone is effective in reversing HRS in a smaller number of patients (40%-50%). In the REVERSE study, terlipressin plus albumin was associated with greater improvement in renal function vs albumin or terlipressin alone in patients with HRS-1, whereas rates of HRS reversal were similar with terlipressin or albumin alone^[259].

Based on four small studies, norepinephrine appears to be an attractive alternative to terlipressin in the treatment of HRS, in part because it is associated with fewer adverse events^[260]. Infusion of albumin plus norepinephrine may be beneficial in HRS 1^[255]. Albumin has dose-dependent effects in both increasing survival and reducing complications in cirrhotic patients with HRS^[261]. The beneficial effects of albumin infusion are not due solely to its oncotic properties. In patients with advanced cirrhosis, several albumin functions, such as binding of toxins, drugs and drug metabolites, are depressed because of molecular alterations of the compound, *e.g.*, to oxidized albumin. Replacement of the altered albumin molecules by the infused albumin has beneficial effects^[262]. Predictors of the clinical response to terlipressin and albumin treatment are the serum bilirubin and creatinine levels along with the increase in blood pressure and the presence of systemic inflammatory response syndrome^[258].

Another approach to the management of HRS, namely "head-out" water immersion, has confirmed the importance of low EABV in this syndrome. Two studies have investigated water immersion as a means of increasing central blood volume in patients with HRS^[241,263]. In both studies, water immersion resulted in marked natriuresis and diuresis, and a decrease in plasma levels of renin and aldosterone. In the study by

Bichet *et al.*^[241], although a five-hour water immersion in one patient with HRS resulted in central blood volume expansion and a modest decrease in serum creatinine concentration, it did not reverse the HRS. In a study by Yersin *et al.*^[263], two patients with HRS underwent repeated two-hour daily courses of water immersion for a week; in both patients, significant decreases in serum creatinine concentration were noted.

In a recent therapeutic algorithm for HRS 1, the use of the combination of octreotide, midodrine and albumin without vasoconstrictors was discouraged because of low efficacy^[255]. The use of vasopressin for the treatment of HRS-1 was also not recommended, due to several adverse effects and the lack of randomized, clinical trials supporting this use^[257]. Other treatments for HRS have also been assessed and include dopamine, transjugular intrahepatic portosystemic shunt, and renal and liver replacement therapy. However, current thinking is that liver transplantation is the only curative option and should be considered in all patients^[247,257].

The evaluation of EABV in patients with cirrhosis, especially with regard to the differential diagnosis of AKI, is based on their response to infusion of albumin and vasopressors. Traditional laboratory techniques have also been employed for the evaluation of the status of fluid balance in these patients. The BNP and its prohormone (pro-BNP) are elevated in patients with cirrhosis as well as those with CHF, thereby rendering it difficult from a single plasma BNP measurement to accurately differentiate between ascites due to CHF and ascites due to cirrhosis^[264]. Elevated plasma BNP confirms CHF with high probability, but is of limited value in evaluating EABV in cirrhosis^[265,266].

Methods evaluating body composition have also been employed for evaluating fluid balance status in cirrhotic patient. BIA studies have been employed in evaluating the volume of the ascetic fluid^[267] and the changes in ECFW/TBW in various parts of the body as cirrhosis progresses^[267,268]. Further work is needed to evaluate the role of body composition analysis in assessing fluid balance in cirrhotic patients.

CHF and cirrhosis both usually cause ECFV expansion. Whether a modest degree of ECFV expansion is beneficial in early compensated stages of CHF has yet to be determined. ECFV expansion is deleterious in advanced stages of CHF; however, a modest degree of ECFV expansion appears to be beneficial in cirrhosis. The treatment of advanced cirrhosis, especially HRS, is based on further ECFV expansion by means of albumin-containing solutions. ECFV levels optimal for these conditions remain to be established. In addition to ECFV excesses, both advanced CHF and advanced cirrhosis are often associated with relative water excess leading to hypotonic hyponatremia. Unlike hypervolemia, which at least in cirrhosis may have beneficial effects, hyponatremia is an independent predictor of adverse outcomes in both CHF^[269,270] and cirrhosis^[271]. Current management guidelines call for aggressive treatment of hyponatremia in both clinical conditions^[82].

Sepsis

The definition of sepsis and the methods for determining its degree of severity have undergone changes recently. Two degrees of severity are currently recognized, namely sepsis and septic shock. The older degree “severe sepsis” was deemed redundant. Sepsis is defined as life-threatening organ dysfunction secondary to a response to infection involving both pro-inflammatory and anti-inflammatory immunological responses and reactions in non-immunological cardiovascular, neuronal, hormonal, metabolic, bio-energetic, and coagulation pathways^[272]. Septic shock is a subset of sepsis characterized by profound circulatory, cellular, and metabolic abnormalities and a heightened mortality risk^[272]. Severe hypotension and greatly elevated serum lactate levels are the defining criteria of septic shock.

Sepsis accounts for about 2% of all hospital admissions and 10% of intensive care unit (ICU) admissions in the United States^[273]. Several organ systems develop severe dysfunction during sepsis, the respiratory and cardiovascular systems being the most commonly affected. Other frequently affected organ systems include: The central nervous system, kidneys, peripheral nervous system, muscles, gastro-intestinal tract, and thyroid gland^[273]. The development of AKI in sepsis is associated with a 70% mortality rate^[274].

The pathogenesis of sepsis involves different mechanisms that have been investigated by various teams of researchers^[272-274]. Unraveling these mechanisms has led to novel strategies, some of which are still in the research stage, for managing sepsis^[275]. In this review, we focus on fluid balance issues. Sepsis causes profound disturbances in at least three of the determinants of EABV listed in Table 5: Vascular capacity, cardiac output, and capillary endothelial barrier. Sepsis can be considered as the prototype of an acute illness causing life-threatening decreases in EABV. In sepsis, ECFV values above the normal range are associated with favorable outcomes.

Increased vascular capacity is a primary cause of low EABV in sepsis. Pro-inflammatory cytokines released in sepsis cause arterial vasodilatation and decrease peripheral vascular resistance. Several metabolic pathways mediate vasodilatation. Upregulation of the inducible nitric oxide synthase and profound release of nitric oxide is a potent vasodilatory pathway^[274]. Vasodilatation is manifested primarily in the splanchnic vascular bed, the muscles and the skin, while the renal vascular bed exhibits vasoconstriction^[274]. Compensatory mechanisms for vasodilatation include activation of the sympathetic nervous system and the renin-angiotensin-aldosterone axis, release of vasopressin, and increase in cardiac output^[274]. Renal vasoconstriction results from high levels of the compensatory hormones which include catecholamines and vasopressin.

One of the mechanisms for compensating for low EABV in sepsis is an increase in cardiac output. However, cardiac output may be depressed in severe septic episodes leading to decreased ejection fraction in approximately 50% of the cases^[276]. Studies in a

murine model also revealed adverse effects of sepsis on heart rate, heart rate variability and electrical impulse conduction^[277]. Reversal of cardiac dysfunction in sepsis survivors after several days suggests that the mechanism of dysfunction was functional rather than structural^[276,278]. However, structural cardiac abnormalities, including mononuclear cell infiltrates, edema, fibrosis, disruption of mitochondria, myocardial cell death and apoptosis were found in the hearts of humans or experimental animals dying from sepsis^[279]. A variety of mechanisms leading to myocardial dysfunction in sepsis have been proposed^[276,278,279]. Therapeutic interventions directed to specific mechanisms are at the stage of pre-clinical trials in experimental sepsis models^[280].

Disruption of the blood capillary endothelial barrier is the third major mechanism leading to low EABV in sepsis. Starling forces regulate fluid transfers between the intravascular and interstitial compartment and play an important role in the maintenance of the intravascular blood volume and EABV. In animal studies reviewed by Schrier and Wang^[274], vasodilatation caused albumin and fluid transfer from the intravascular into the interstitial compartment. Generalized capillary protein leakage was documented in septic patients by Ishihara and coinvestigators^[281]. The endothelial barrier defect is not the exclusive result of arterial vasodilatation. A variety of mediators of endothelial barrier damage in sepsis, including the complement components C3 and C5a, bradykinin, platelet activating factor (PAF), pro-inflammatory cytokines, and many others have been identified^[282,283]. Endothelial barrier disruption is considered a key step in the development of septic shock^[283].

Collectively, vasodilatation, myocardial dysfunction, and impairment of the endothelial barrier lead to decrease in EABV and render imperative the need for administration of large volumes of fluid and vasoconstrictors, which are mainstays of treatment in sepsis. However, impaired cardiac and endothelial barrier function increase the risks of fluid administration in septic patients^[274,284] and narrow its therapeutic margins. Recent therapeutic trials and meta-analyses^[285-294] have addressed the issue of the volume of fluids administered to septic patients among other issues.

A prospective randomized trial of aggressive treatment by infusion of fluids based on invasive monitoring of central venous pressure in septic patients prior to their admission to the ICU showed advantages in survival and improvement in important biochemical parameters including central pressure oxygen saturation, serum lactate concentration and metabolic acid-base values^[285]. Subsequently, three large prospective randomized studies compared goal-directed early (pre-ICU) resuscitation and routine management of septic shock^[286-288]. In all three studies, patients assigned to early goal-directed care routinely received larger volumes of fluids and higher doses of vasoconstrictors than those assigned to routine care. No difference in mortality and most other secondary outcomes was noted in any of these studies;

however, one study computed a higher cost for the early, goal-directed group of patients^[288]. A metaanalysis of 11 randomized trials concluded that early-goal directed therapy for septic shock is not associated with early (28 d) or late (90 d) mortality improvement^[289].

Fluid balance during treatment of sepsis or septic shock was addressed in three recent reports. One study found no difference in volume of fluid gained during treatment of septic shock between surviving and deceased patients^[290]. The second study found significantly lower mortality in patients with sepsis or septic shock receiving less than 5 L than in those receiving more than 5 L of fluids in the first day of treatment and an increase in mortality by 2.3% for each liter of administered fluid in excess of 5 L^[291]. The third study analyzed risks for mortality from sepsis associated with a completion within three hours of a protocol calling for blood cultures, administration of antibiotics and administration of 30 mL of crystalloids per kilogram. This study reported an increased risk for longer waiting until administration of antibiotics, but not for longer time to completion of the fluid bolus^[292].

Finally, two randomized studies addressed two other issues related to fluid balance and EABV during treatment of septic shock. The first study found similar mortality rates in patients with targeted mean arterial blood pressure of 80 to 85 mmHg and those with targeted pressure of 60 to 65 mmHg^[293]. Mean fluid volume administration was similar in the two groups while the higher blood pressure group received higher doses of norepinephrine and for a longer time. The second study found similar mortality rates in patients with targeted blood hemoglobin level above 9 g/dL and those with targeted level above 7 g/dL^[294]. The international guidelines for management of sepsis and septic shock recommend a minimal initial intravenous crystalloid fluid bolus of 30 mL/kg within the first three hours followed by additional fluid administration guided by hemodynamic monitoring and maintenance of mean arterial blood pressure above 65 mmHg by vasoconstrictors as needed^[295]. The guidelines highlight all three recommendations as “strong” and the quality of evidence as “weak” for the first recommendation, “best practice evidence” for the second and “moderate” for the third.

Infusion of large volumes of fluid is one of the key therapeutic modalities in sepsis and septic shock; however, the literature provides ample evidence indicating that the safety margin of fluid infusion in sepsis is narrow. The optimal level of volume expansion will need further research to be determined. The need for volume replacement in sepsis is not determined by measurements of ECV, but by clinical, laboratory and hemodynamic criteria. Calculation of blood volume, by adding plasma volume measurements obtained by dilution of injected albumin labelled with radioactive iodine (¹³¹I-albumin) and red cell mass computed from either hematocrit and plasma volume [Blood volume = plasma volume/(1 | Hematocrit)], or measured simultaneously with plasma volume by injected red blood

cells (RBCs) labelled with radioactive chromium (⁵¹Cr-RBC) has found wider application than the measurement of TBW or ECV in critically ill patients with conditions leading to blood loss^[296,297].

Nephrotic syndrome

Heavy albuminuria, hypoalbuminemia and pronounced salt retention leading to ECFV expansion and edema, but typically not to hypertension, characterize the nephrotic syndrome. The cardinal complaint of patients suffering from nephrotic syndrome is edema^[298]. The pathogenesis of edema formation has been disputed^[299]. Two theories, the underfill and overflow or overfill theories, explaining the fundamental mechanism of salt retention and edema formation in nephrotic syndrome have been proposed^[300,301]. The underfill theory places the focus of salt retention on the nephrotic hypoalbuminemia which causes through Starling forces decreased blood volume and EABV and stimulation of neurohumoral pathways leading to renal salt and water retention^[300,302]. A subset of patients with severe nephrotic syndrome and profound hypoalbuminemia exhibit elevated serum levels of indicators of hypovolemia, including vasopressin, renin, aldosterone and norepinephrine; “head-out” water immersion of nephrotic patients with these features resulted in pronounced natriuresis and diuresis and substantial decreases in the levels of all four indicators of hypovolemia^[303]. Decreases in interstitial colloid-osmotic pressure accompanying decreases in plasma albumin concentration and colloid-osmotic pressure modulate the loss of intravascular fluid into the interstitial compartment in nephrotic syndrome^[304].

The overflow theory states that patients with nephrotic syndrome have an expanded plasma volume, and that the retention of sodium leading to edema formation in these patients is the result of an intrinsic defect in renal salt excretion. The first evidence against the underfill theory was provided by Meltzer *et al*^[305] who noticed that serum renin and aldosterone levels were not elevated in a subset of patients with nephrotic syndrome. Other important observations arguing against the underfill theory include the following: (1) Animals and humans with congenital analbuminemia rarely develop edema^[306,307]; (2) blood volume is increased in a subset of edematous patients with the nephrotic syndrome^[308]; (3) volume expansion with hyperoncotic albumin in edematous patients with nephrotic syndrome and various underlying renal histologic pictures, including minimal change disease, results in normal suppression of plasma renin activity and aldosterone, without significantly increasing urinary sodium excretion^[309]; (4) medications blocking the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors, do not increase natriuresis in nephrotic patients^[310]; (5) adrenalectomy does not prevent edema formation in laboratory animals with nephrotic syndrome^[311]; and (6) natriuresis in the recovery phase of nephrotic syndrome in children starts before serum albumin is normalized^[312]. These observations suggested

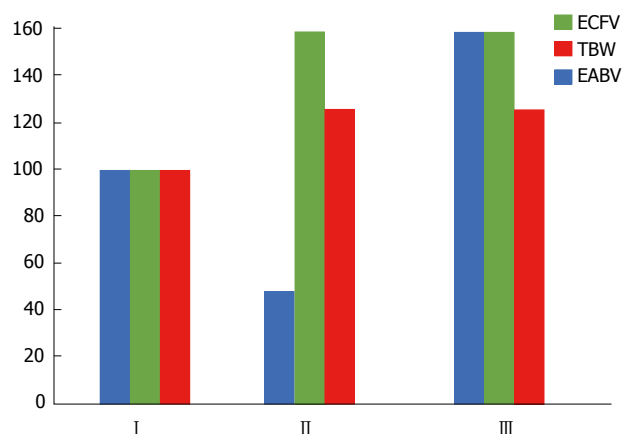


Figure 5 Percent changes from normal of body fluid compartments in hypervolemic states. I: Normal body fluid state; II: Congestive heart failure, hepatic cirrhosis, nephrotic syndrome with underfill mechanism of fluid retention; III: Nephrotic syndrome with overfill mechanism of fluid retention. EABV: Effective arterial blood volume; ECFV: Extracellular fluid volume; TBW: Total body water.

that the renal retention of sodium salts in some patients with nephrotic syndrome results not from low EABV, but from a primary renal retention of sodium^[313,314].

Ichikawa *et al.*^[315] reported primary renal retention of salt in a unilateral model of puromycin-induced nephrotic syndrome in rats. Subsequently, Kim *et al.*^[316] demonstrated increased expression and apical targeting of the epithelial sodium channel (ENaC) in the distal convoluted tubule, connecting tubule, and collecting duct of rats with puromycin-induced nephrotic syndrome. Increased synthesis of the sodium-potassium ATPase (Na,K-ATPase) was also observed in the collecting ducts of rats with puromycin-induced nephrotic syndrome^[317]. Serine proteases, which are present in high concentrations in the glomerular filtrate of nephrotic patients, play a major role in the activation of ENaC by cleaving certain channel-protein subunits and removing certain inhibitory peptides from the channel thus increasing its open probability^[318]. A landmark study by Senningsen *et al.*^[319] showed that urine from laboratory animals and patients with nephrotic syndrome can activate ENaC and promote sodium retention. In this study, mass-spectrometry analysis identified plasmin, an abnormally filtered enzyme, as the serine protease responsible for ENaC activation.

The widely accepted current view is that sodium retention develops in all subtypes of the nephrotic syndrome because of ENaC activation in the collecting ducts regardless of EABV^[320,321]. Other mechanisms, including a proposed increase in the permeability of blood capillaries^[321,322], decrease in the renal response to atrial natriuretic peptide (ANP), decreased conversion of pro-ANP to ANP in the kidneys, and decreased expression of nitric oxide synthase in the kidneys^[323], are also likely contributors to salt retention and edema formation in the nephrotic syndrome. Underfilling represents an additional mechanism of edema formation in some nephrotic patients^[314]. Hypovolemia and underfilling are pronounced

in nephrotic subjects with very low serum albumin levels, e.g., children with minimal change disease^[323]. BIA studies have been employed in assessing fluid balance in patients with the nephrotic syndrome^[324-326]. Figure 5 shows changes in EABV and ECF in the chronic conditions, including CHF, cirrhosis and nephrotic syndrome, discussed in this report.

CONCLUSION

The traditional concepts of body fluid balance encompass the regulation and perturbations of the relation between TBW and effective body solute (tonicity), and the regulation, measurement, and disturbances of ECFV. Severe acute and chronic illnesses cause disturbances that affect both fluid balance concepts. However, while the disturbances in tonicity have always adverse effects and require aggressive treatment, modest excesses in ECFV can be beneficial in some illnesses (e.g., cirrhosis, sepsis) and represent targets of the fluid management. The optimal ECFV in these illnesses is greater than the normal ranges of ECFV in healthy individuals because disease states produce changes in several factors that interact with ECFV in regulating EABV. These other factors are subjects of intense research and constitute therapeutic targets along with fluid treatment of ECFV. It is important to distinguish between fluid retention that results from low EABV, as in CHF or cirrhosis, and fluid retention that results from either low EABV or primary renal salt and water mechanisms, as in nephrotic syndrome. The traditional methods for measuring ECFV are associated with greater sources of error in patients with severe illness than in normal individuals. The management of fluid balance in patients with severe illness clearly needs further research. Two key questions regarding fluid balance should be addressed in these patients: (1) Are factors other than ECFV affecting EABV (Table 5) disturbed causing, in addition to the need for their proper management, the need for ECFV values different from the normal values? (2) If fluid retention is a feature of these illnesses, is it a consequence of decreased EABV from a disturbance of the factors shown in Table 4 or of primary renal retention of salt? For these reasons, severe illness with fluid disturbances justifies a separate concept of body fluid balance.

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Immunoglobulin G4-related kidney diseases: An updated review

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Abstract

This review will encompass definition, pathogenesis, renal clinical manifestations and treatment of immunoglobulin G4-related diseases (IgG4-RDs). IgG4-RD is a recently recognized clinical entity that often involves multiple organs and is characterized by high levels of serum immunoglobulins G4, dense infiltration of IgG4⁺ cells and storiform fibrosis. Cellular immunity, particularly T-cell mediated immunity, has been implicated in the pathogenesis of IgG4-RDs. The most frequent renal manifestations of IgG4-RD are IgG4-related tubulointerstitial nephritis, membranous glomerulopathy and obstructive nephropathy secondary to urinary tract obstruction due to IgG4-related retroperitoneal fibrosis. IgG4-RD diagnosis should be based on specific histopathological findings, confirmed by tissue immunostaining, typical radiological findings and an appropriate clinical context. The first line treatment is the steroids with two warnings: Steroid resistance and relapse after discontinuation. In the case of steroid resistance, B cell depleting agents as rituximab represent the second-line treatment. In the case of relapse after discontinuation, steroid treatment may be associated with steroid sparing agents. Since the disease has been only recently identified, more prospective, long-term studies are needed to an improved understanding and a more correct and safe treatment.

Key words: Immunoglobulin G4-related disease; Storiform fibrosis; Lymphoplasmacytic infiltration; Tubulointerstitial nephritis; Steroid treatment; B cell depleting agents

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Core tip: Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized clinical entity that often involves

multiple organs; it is characterized by high levels of serum immunoglobulin G4, dense infiltration of IgG4+ cells, and storiform fibrosis. Cellular immunity, particularly T cell-mediated immunity, has been implicated in the pathogenesis of IgG4-RD. The most frequent renal manifestations of IgG4-RD are IgG4-related tubulointerstitial nephritis, membranous glomerulonephropathy and obstructive nephropathy secondary to urinary tract obstruction due to IgG4-related retroperitoneal fibrosis. In IgG4-membranous glomerulopathy, proteinuria can be in the nephrotic range. Steroid treatment is the first-line therapy. For relapsing or refractory cases, immunosuppressants could be combined with steroids.

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INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a recently identified systemic fibroinflammatory condition that mimics several autoimmune, malignant and rheumatologic diseases. IgG4-RDs may affect several organs as recognized since the 1st international symposium held in Boston in 2011^[1] (Table 1). To date the diagnosis of IgG4-RDs unifies several pathologic conditions previously considered well-defined and distinct disorders and now recognized as organ manifestations of IgG4-RD^[2-4] (Table 2). Other diseases merely mimic IgG4-RD and hence should be considered and classified separately because they represent diseases with distinct features (Table 3).

Consequently, the classification is rather confusing; hence the American College of Rheumatology recently recommended a revised nomenclature of IgG4-RD and its individual organ system manifestations^[5].

Basing on clinical presentation per site of involvement IgG4-RD may be classified as in Table 4.

In this review, following the description of the hallmarks characteristic of IgG4-RD, its epidemiology and its pathophysiology, we principally highlight the so-called IgG4-related kidney disease (IgG4-RKD), its clinical and histological manifestations, the diagnostic criteria and treatment.

RESEARCH METHODOLOGY

We have analyzed the available papers on IgG4-RD pathogenesis, IgG4-RKD clinical and diagnosis and IgG4-RD therapy by a review of the currently available papers. A literature search was performed using PubMed (NCBI/NIH) with the search words "IgG4-RD pathogenesis", "IgG4-RKD clinical and diagnosis", "IgG4-RD treatment", "IgG4-RD classification". As first line research the papers published in the last three years were examined. Paper

selection has been made according the relevance of the journal, the authors, and the dimension of the study and the novelty of the findings. So doing 40 papers recently published have been selected, then we proceeded in a backward way and studies previously published have also been included.

HISTOLOGICAL ASPECTS OF IgG4-RD

The major histopathological features associated with IgG4-RD are represented in Table 5.

Pathological features of IgG4-RD may vary according to the organ involved. Obliterative arteritis and neutrophilic infiltration rarely occurs. When present they are characteristic of lung lesions and occur in the alveolar spaces^[6]. Absence of storiform fibrosis and lack of obliterative phlebitis may be observed in diseases involving the salivary glands, lymph nodes and kidney^[7].

Hallmarks of the diseases are a lymphoplasmacytic infiltrate enriched with IgG4 plasma cells, a storiform pattern of fibrosis and obliterative phlebitis^[3,8]. The pattern is often similar to a cartwheel with the bands of fibrosis emanating from the center representing the spokes of the wheel. Immunoperoxidase staining revealed that nearly all plasma cells are strongly positive for IgG4, whereas the small lymphocytes are negative. A total obliteration of venous channels (obliterative phlebitis) may be present. Eosinophils and fibroblasts are present as well^[9,10].

Several caveats must be considered in the interpretations of tissue lesions and particularly IgG4 positive plasma cells: (1) IgG4 positive plasma cells are generally present in the lesions, but focal aggregations of IgG4-positive cells are atypical; (2) The absolute number of IgG4 positive plasma cells should be interpreted according to the specific tissue^[8]; (3) The ratio of IgG4 to IgG positive plasma cells must be at least 40%; and (4) IgG4-RD cannot be diagnosed on the basis of infiltration by IgG4-positive plasma cells alone because these cells may also be present in other inflammatory or neoplastic disorders^[11].

EPIDEMIOLOGY

IgG4-RD was first recognized as a systemic entity in the early 2000s, when autoimmune pancreatitis (AIP) type I patients demonstrated similar conglomerations of fibroinflammatory tissue in other organs or lesions, such as retroperitoneal and mediastinal fibrosis, inflammatory pseudo tumor of lung and liver as well as interstitial nephritis^[12-14]. Due to the relatively recent discovery, minimal epidemiological data exist. The majority of the patients reported in the literature are from Japan^[15]; however, to date it is not clear whether this higher prevalence is due to genetic or environmental causes or simply because the disease was specifically investigated within this population. The average age of disease onset is between 61 and 70 years and there is a clear male

Table 1 Representative organ manifestations in IgG4-related disease

Organs adopted at the 1 st International symposium in Boston in 2011	
Pancreas	Lymphoplasmacytic sclerosing pancreatitis
Eye/orbit/lacrimal glands	Dacryadenitis/orbital inflammation/pseudotumour
Salivary glands	Sialoadenitis/Mikulicz disease/Küttner's tumor
Aorta/arteries	Aortitis/periaortitis/arteritis
Mediastinum/retroperitoneum	Mediastinitis/retroperitoneal fibrosis/mesenteritis
Kidney	Tubulointerstitial nephritis/renal pyelitis
Pachimeninges/hypophysis	Pachimeningitis/hypophysitis
Lung	Lung disease/inflammatory pseudotumor
Pleura/pericardium	Pleuritis/pericarditis
Breast	Mastitis
Bile ducts/gall bladder/ liver	Sclerosing cholangitis/cholecystitis/hepatopathy
Prostate	Prostatitis
Skin	Skin disease/pseudolymphoma
Lymph node	Lymphadenopathy
Organs newly recognized after the Boston meeting	
Nerve	Infraorbital nerve swelling
Paranasal sinus	Chronic rhinosinusitis
Testis/paratestis	Paratesticular pseudotumour
Ureter	Ureteritis
Urethra	Urethritis
Urinary bladder	Interstitial cystitis

Table 2 Conditions once regarded as individual disorders now recognized to be part of IgG4-related disease

Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
Eosinophilic angiocentric fibrosis (affecting the orbits and upper respiratory tract)
Fibrosing mediastinitis
Hypertrophic pachymeningitis
Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs)
Küttner's tumor (affecting the submandibular glands)
Mikulicz's disease (affecting the salivary and lacrimal glands)
Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)
Periaortitis and periarteritis
Inflammatory aortic aneurysm
Retroperitoneal fibrosis (Ormond's disease)
Riedel's thyroiditis
Sclerosing mesenteritis

Table 3 Mimickers of immunoglobulin G4-related disease

Autoimmune	Malignancy	Other
Antineutrophil cytoplasmic antibody-associated vasculitis	Adenocarcinoma and squamous cell carcinoma	Castleman's disease
Granulomatosis with polyangiitis	Extranodal marginal zone lymphoma	Cutaneous plasmacytosis
Eosinophilic granulomatosis with polyangiitis	Inflammatory myofibroblastic tumor	Erdheim-Chester disease
Microscopic polyangiitis	Lymphoplasmacytic lymphoma	Inflammatory bowel disease
Sarcoidosis	Lymphoproliferative disease	Perforating collagenosis
Sjogren's disease	Follicular lymphoma	Primary sclerosing cholangitis
		Rhinosinusitis
		Rosai-Dorfman disease
		Splenic sclerosing angiomatoid nodular transformation
		Xanthogranuloma

predilection with the exception of the forms involving the head and neck^[16,17].

PATHOPHYSIOLOGY

Several immune-mediated mechanisms are involved

in the pathophysiology of IgG4-RD. They are divided into: (1) Initiating mechanisms; and (2) specific disease pathways.

Potential initiating mechanisms

Genetic background: In Japanese populations, the

Table 4 Clinical presentation of immunoglobulin G4-related disease per site of involvement

Organ system	Nomenclature	Clinical features
Orbit	IgG4-related ophthalmic disease IgG4-related orbital inflammatory pseudo-tumor IgG4-related pan-orbital inflammation IgG4-related orbital myositis	Swelling of orbital tissue and proptosis
Lacrimal gland	IgG4-related dacryadenitis	Bilateral swelling of the glands and impaired production of secretion
Salivary gland	IgG4-related sialoadenitis IgG4-related parotitis IgG4-related submandibular gland disease	Bilateral swelling of the glands and impaired production of secretion
Thyroid	IgG4-related thyroid disease	Hypothyroidism, neck pain, dysphagia, dyspnea
Liver	IgG4-related hepatopathy	Jaundice, right upper quadrant mass
Biliary tract and gall bladder	IgG4-related sclerosing cholangitis IgG4-related cholecystitis	Jaundice, pruritus, cholestasis
Blood vessels	IgG4-related aortitis/periaortitis IgG4-related periarteritis	Chest pain, dyspnea
Retroperitoneal fibrosis	IgG4-related retroperitoneal fibrosis	Flank pain, obstructive symptoms, peripheral edema
Kidneys	IgG4-related kidney disease Tubulo-interstitial nephritis secondary to IgG4-related disease	Hematuria, proteinuria, hypocomplementemia, chronic renal failure
Skin	IgG4-related skin disease	Papulonodular lesions, plaques, purpura

Table 5 Major histopathological features associated with immunoglobulin G4-related disease

Dense lymphoplasmacytic infiltrate
Fibrosis, arranged at least focally in a storiform pattern
Obliterative phlebitis
Phlebitis without obliteration of the lumen
Increased number of eosinophils

frequencies of human leukocyte antigen (HLA) serotypes DRB1*0404 and DRB1*0401 are significantly higher in patients with AIP, a common manifestation of IgG4-RD^[18].

Non-HLA genes with single nucleotide polymorphisms (SNPs) are also involved in the expression of disease encoding proteins, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), tumor necrosis factor alpha (TNFα) and Fc receptor like 3, expressed on B cells (FCRL3)^[19-21].

Bacterial infection and molecular mimicry: Homologies existing between human carbonic anhydrase II and the alpha carbonic anhydrase of *Helicobacter pylori* (*H. pylori*), as well as between the plasminogen binding protein of *H. pylori* and the ubiquitin-protein ligase E3 component n-recogin 2 expressed on pancreatic cells have raised the question of a possible pathogenetic role of molecular mimicry involving *H. pylori*^[22,23]. The contribution of the innate immune response to IgG4-RD is highlighted by the fact that various species of bacteria may induce the stimulation of toll-like receptor ligand in the production of IgG4 and interleukin-10 (IL-10) from peripheral blood mononuclear cells (PBMCs)^[24].

Autoimmunity: The involvement of autoimmunity in activating Th cells in IgG4-RD is suspected because of the presence of auto antibodies against carbonic anhydrases, lactoferrin, pancreatic secretory trypsin

inhibitors and trypsinogens^[25-27]. In addition, electron-dense deposits have been observed in the renal tubular membrane and pancreatic ducts of patients affected by IgG4-RD^[28].

Specific disease pathways

Th cells and regulatory immune reaction: T cells may ultimately be implicated in the pathogenesis of IgG4-RD. Potential triggers, such as foreign pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) may be recognized by Toll-like receptors (TLR), which may induce the production of IgG4 by CD19⁺^[29]. More importantly these triggers by activating the innate immune system, may determine the state of polarization of T helper cells in IgG4-RD. Treg cells are also activated, as indicated by the high expression levels of forkhead box P3 (FOXP3) mRNA in the tissue^[30].

Activated T helper cells and Treg cells may produce inflammatory cytokines, including interferon gamma (IFNγ), IL-4, IL-10, IL-5 and IL-13. IL-4 and IL-10, possibly produced by T follicular helper cells, and may cause class switching of auto reactive B cells to IgG4 and IgE and induce differentiation and expansion of IgG4 plasma cells^[31,32]. IL-5, IL-13 and tumor growth factor beta (TGFβ) may lead to the recruitment of eosinophils and the activation of fibroblasts^[4,33]. IFNγ may also contribute to the activation of macrophages that induce fibrosis^[4] and induce a dense storiform fibrosis. On the other hand, B cells that recognize self antigens are capable of efficient antigen presentation to auto reactive T cells, thereby mediating a vicious cycle between T and B lymphocytes^[34].

Role of IgG4 antibodies: It is likely that IgG4 per se have a poor role in generating IgG4-RD. The IgG4 antibodies bind weakly to complement C1q and Fcγ receptors. As a consequence, they are not involved

in antibody-dependent cell-mediated cytotoxicity^[35]. Additionally, IgG4 form half antibodies through the process of Fab arm exchange^[35]. The consequence is a reduced ability to bind to the antigen and to generate immune complexes. Moreover, IgG4 antibodies seem to be stronger suppressors than inducers of inflammation^[33].

All the aforementioned mechanisms and pathways are summarized in fig. 1, which unifies all the different mechanisms. Auto-antibodies may drive the Th2-cell response. Molecular mimicry as well as microbial components may also act as triggers for IgG4-RD, wherein they may stimulate innate immune mechanisms by activating nucleotide-activating factors belonging to the tumor necrosis factor (TNF) family (NODR) and the toll-like receptor 2 (TLR2) to produce B cell activating factor (BAFF) and a proliferative-inducing ligand (APRIL), which leads to B cell modifications in a T cell-independent manner. An expansion in Treg cells may contribute to both B-cell Ig class switching and fibrosis. A treatment sensitive expansion in circulatory plasma blasts is present in the active disease.

IgG4-KIDNEY RELATED DISEASES

The kidney may be affected by different histopathologic lesions in the course of IgG4-KRD. This fact represents a peculiarity with respect to other organs that may be affected by IgG4-RD.

The kidney may be affected directly by histopathologic lesions affecting the parenchyma or indirectly as in the case of retroperitoneal fibrosis, which causes renal function impairment because of the obstruction of the urinary tract.

IgG4-related tubulointerstitial nephritis (TIN) represents the parenchymal lesions more often affecting the kidney. The other more frequent lesion is represented by membranous glomerulopathy, in which lymphoplasmacytic infiltrate and storiform fibrosis, typical of IgG4-RD are not present. Other types of glomerular lesions, such as Schonlein Henoch purpura nephritis, may be infrequently observed during the course of IgG4-RD. When present, it is often associated with TIN^[36,37]. IgA nephropathy, membrano-proliferative glomerulonephritis and minimal change disease have also been described^[38]. Recently, a case of AA Amyloidosis affecting the kidney in the course of IgG4-RD has been reported^[39]. Altogether, renal involvement in the course of IgG4-RD occurs in approximately 15% of patients.

IgG4 RELATED TIN

As mentioned above, IgG4-TIN is the most common renal manifestation of IgG4-RD, and the majority of data concerning this lesion come from two series of biopsies: A Japanese cohort^[40] and an American cohort^[41].

IgG4-related TIN is often diagnosed in the setting of already known extra renal disease. The most common

associated manifestations are sialoadenitis, lymphadenopathy, type I AIP and dacryadenitis. When IgG4-KRD with TIN is the only manifestation, the diagnosis is made by a renal biopsy performed because of acute or progressive renal failure.

The Japanese Society of Nephrology proposed a useful algorithm for the diagnosis of IgG4-related TIN^[42]. According to the algorithm, in the case of abnormal renal function, principally when associated with high serum IgG or serum IgE, after exclusion of secondary diseases, such as lupus, vasculitis, *etc.*, and with serum IgG4 higher than 135 mg/dl, characteristic radiologic findings, such as multiple low density lesions, diffuse kidney enlargement and/or solitary hypovascular mass should be looked for and renal histology should be performed.

Laboratory findings

In addition to signs of renal dysfunction, nearly all patients with IgG4-related TIN have elevated serum concentrations of IgG and IgG4. Sixty percent of the patients have hypocomplementemia. Peripheral eosinophilia is observed in approximately 40% of the patients and positive anti-nuclear auto antibodies (ANA) are observed in 32%^[43,44].

Radiologic features

Multiple hypodense lesions are the most common observation^[40,41]. Such lesions were present in 69.6% of the Japanese cohort and in 78.3% of the Mayo Clinic cohort. Using diffusion-weighted magnetic resonance imaging (MRI), a recent study reported 100% sensitivity with respect to computed tomography (CT)^[45]. However, a caveat is that when a solid mass is observed, it may be misdiagnosed as a malignant neoplasm and lead to an unnecessary nephrectomy^[46,47].

Histopathological features

Plasma cell-rich TIN with fibrosis and often infiltrating eosinophils represent the typical histopathologic appearance^[8,48]. This aspect represents the gold standard for diagnosis and allows for filtering out malignancies and other mimicking diseases^[49] (Figure 1). Fibrosis often has a storiform pattern. In IgG4-TIN, fibrosis is generally more severe than the fibrosis observed in other forms of TIN^[1]. Obliterative phlebitis, a critical pathological feature of IgG4-RD is rarely observed in IgG4-TIN, probably because of the lack of veins in the biopsy specimen^[8,41]. Other histopathological features are represented by the fact that affected and unaffected areas are clearly demarcated^[50]. Additionally, sometimes the lesions infiltrate the renal capsule and beyond^[51].

Overall there is a spectrum of microscopic appearances, which includes TIN with minimal fibrosis, interstitial fibrosis with marked inflammatory infiltrate and an extensive tubular destruction and atrophy^[41,52]. More recently, according to the Mayo Clinic series, 3 histological patterns of IgG4-TIN were described: (1) Acute TIN with minimal interstitial fibrosis; (2) chronic TIN with expansive interstitial fibrosis; and (3)

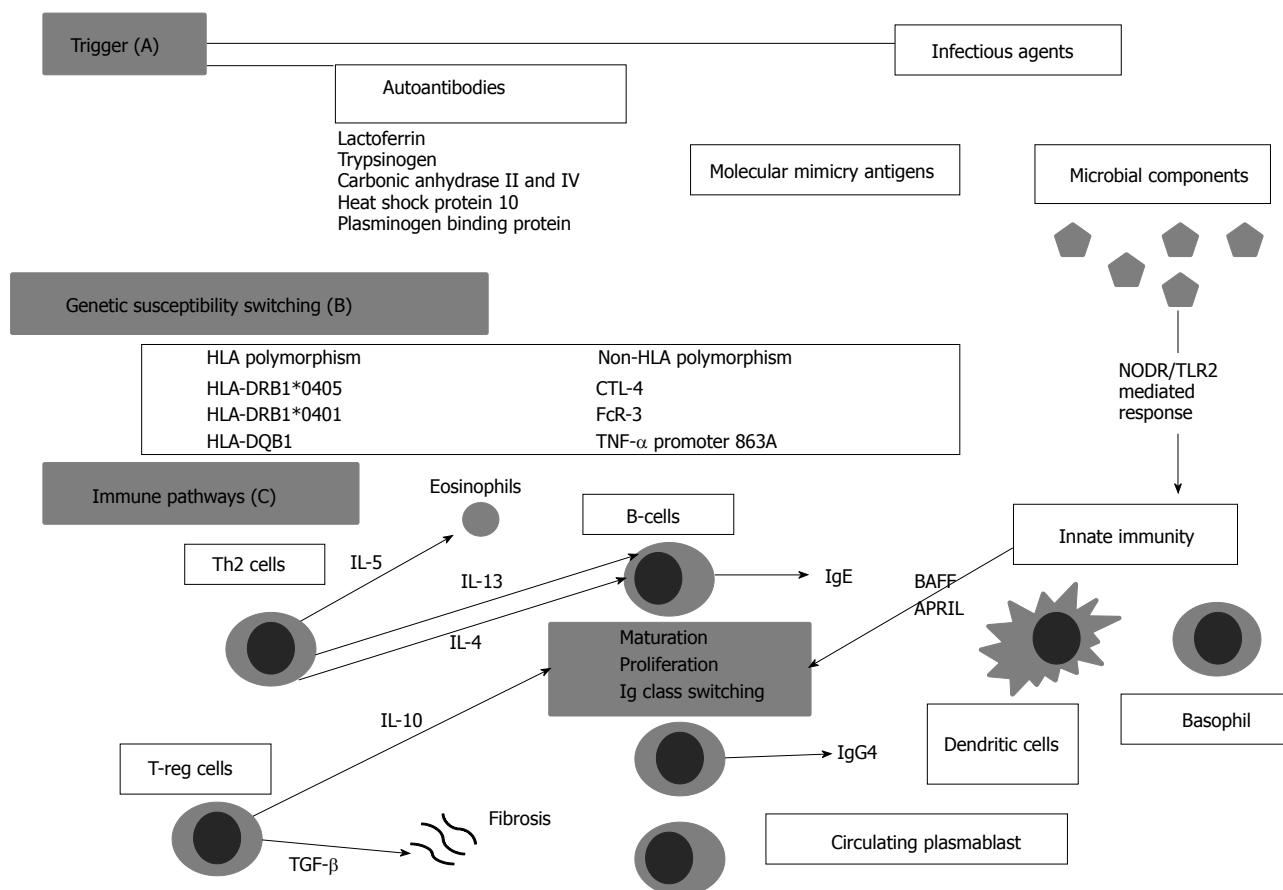


Figure 1 Pathogenesis of immunoglobulin G4-related disease. CTL-4: Cytotoxic T-lymphocyte-associated antigen 4; FcR-3: Fc receptor like 3; TNF α : Tumor necrosis factor alpha; NODR: Nucleotide-activating factor belonging to the tumor necrosis factor (TNF) family; TLR2: Toll-like receptor 2; BAFF: B cell activating factor; APRIL: A proliferative-inducing ligand; TGF β : Tumor growth factor beta.

advanced sclerosing pattern^[43].

Immunohistochemical staining for IgG4 reveals IgG4⁺ plasma cells, even if the increased number of interstitial IgG4⁺ plasma cells is not specific for IgG4-TIN and 80% of patients have granular IgG and C3 deposits along the tubular basement membrane (TBM)^[41]. Deposits of immune complexes have been observed as electron dense deposits in the TBM^[41,53]. Because IgG4 cannot activate the complement system, other subclasses, such as IgG1, may play a role in activating complement and forming immune complexes.

Diagnosis and differential diagnosis

In order to diagnose IgG4-TIN, two sets of diagnostic criteria have been proposed as shown in Table 6. The criteria proposed by Raissian^[41] require a TIN with > 10 IgG4⁺ plasma cells per high-power field (HPF) in addition to either elevated serum IgG4 or evidence of extra renal IgG4-RD. Moreover, Kawano^[54] classified patients with features of IgG4-TIN into three categories: Definite, probable and possible.

Contrasted enhanced computed tomography (CT) is widely used to identify radiographic abnormalities in IgG4-TIN^[55], even though MRI has a higher sensitivity^[45]. The most common finding in CT are bilateral, hypo-dense lesions often multiple that involve the renal cortex and may have the aspect of small peripheral cortical

nodules, well or poorly defined round lesions and diffuse patchy lesions^[55].

Differential diagnosis of IgG4-TIN includes distinction from allergic TIN, chronic pyelonephritis, granulomatosis with polyangiitis, Castleman disease and other autoimmune TINs. Allergic TIN does not have storiform fibrosis and does not have as many plasma cells in the infiltrate.

Chronic pyelonephritis has several neutrophils in the infiltrate and a typical radiographic pattern. Granulomatosis with polyangiitis has necrotizing vasculitis or granuloma. Moreover, ANCA antibodies in the serum are not present in IgG4-TIN.

Differential diagnosis with Castleman disease may be difficult, and recently, two cases of Castleman disease with kidney involvement closely mimicking IgG4-TIN have been reported^[56]. Finally, TIN due to other autoimmune diseases demonstrates clinical and laboratoristic signs of the autoimmune disease, such as lupus or Sjogren syndrome^[41].

GLOMERULAR NEPHROPATHIES RELATED TO IgG4-RD

The most important and frequent glomerular lesion is membranous glomerular nephropathy (MGN), which

Table 6 Two proposed criteria for IgG4-TIN by the Mayo Clinic and the Japanese Society of Nephrology

Criterion	The Mayo Clinic criteria	JSN criteria
Histology	Plasma cell-rich TIN with > 10 IgG4+ plasma cells/HPF in the most concentrated field (mandatory criterion) TBM immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy	Dense lymphoplasmacytic infiltrate with > 10 IgG4+ plasma cells/HPF and/or IgG4/IgG+ plasma cell ratio of > 40%; Characteristic storiform fibrosis
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement	Multiple low-density lesions or enhanced CT, diffuse kidney enlargement, hypovascular solitary nodule, hypertrophic lesion of the renal pelvic wall
Serology	Elevated serum IgG4 or total IgG level	Elevated serum IgG4 or total IgG level
Clinical features	None	Clinical or laboratory evidence of kidney damage
Other organ involvement	Characteristic findings of IgG4-RD in other organs	Characteristic findings of IgG4-RD in other organs
Definite IgG4-TIN	The histologic feature and at least one other feature from imaging, serology or other organ involvement	The histologic feature (a and b) and at least two of other features from imaging, serology or other organ involvement

IgG4-RD: Immunoglobulin G4-related disease; IgG4-TIN: Immunoglobulin G4-related tubulointerstitial nephritis; CT: Computed tomography.

represents 7% of all IgG4-RKD cases according to the two largest biopsy series^[40,41]. Other rare glomerular lesions are classified into two subgroups according to the prevalence of a Th2 response. Henoch Schonlein purpura nephritis and minimal change syndrome are associated with a prevailing Th2 response^[38,57], whereas IgA nephropathy and membranoproliferative glomerulonephritis are associated with a poor Th2 response^[58,59].

Clinical and laboratory features

IgG4-related MGN occurs principally in males. Other extra renal manifestations of IgG4-RD are often present^[60]. Heavy proteinuria with nephritic syndrome is the principal clinical feature. Half of the patients have concomitant TIN. In these patients, TIN is probably the cause of renal dysfunction^[61].

Renal histopathology

All patients exhibit sub-epithelial deposits in a membranous pattern. Immunofluorescence demonstrated IgG4 to be the prevailing immunoglobulin. No anti phospholipase A2 receptor (PLA2r) antibody has been observed in IgG4-MGN. Some patients affected by IgG4-MGN also had mesangial and sub-epithelial deposits^[41]. Whether the target antigen in IgG4-MGN is located in the podocytes, as in idiopathic MGN, is not known.

RENAL AMYLOIDOSIS RELATED TO IgG4-RD

To date only one case of renal AA amyloidosis associated with extra-renal IgG4-RD has been described^[39].

Clinical features

The patient suffered from a mesenteric IgG4-RD with involvement of the lymph nodes. AA amyloidosis developed after 16 years; however, whether or not the treatment of IgG4-RD caused a delay in the development of AA amyloidosis, is not known.

RETROPERITONEAL FIBROSIS

Compared to the described renal diseases, wherein

renal dysfunction is caused by parenchymal lesions, retroperitoneal fibrosis causes renal dysfunction by obstruction of the urinary tract.

Pathogenesis

Development of retroperitoneal fibrosis in the periaortic and periiliac retroperitoneum results in hydronephrosis and inflammatory abdominal aortic aneurysm^[62,63].

Hydronephrosis is caused by the diffusion of the periaortic inflammation to the ureter, resulting in its obstruction. Involvement of both kidneys may result in end-stage renal failure.

TREATMENT

The optimal treatment for IgG4-RD is unknown. Indeed, to date, there have been no randomized clinical trials that have evaluated and compared the effectiveness of different treatment regimens^[33]. Although some patients affected by IgG4-RD may have spontaneous remission and do not require treatment^[64], a prompt treatment is generally recommended to avoid deleterious complications and consequences of the evolving disease.

Glucocorticoids are currently the first line treatment for IgG4-RD^[65,66] and IgG4-RKD^[33,42]. An alternative are the B depleting agents as rituximab (RTX), which is still under investigation in clinical trials^[67,68]. An international panel of experts developed recommendations for the management of IgG4-RD and recommended steroids as first line agents for remission induction, while there was low agreement on the use of RTX^[49].

IgG4-RD may affect several organs. Recently, Della Torre *et al.*^[69] categorized six principal clinical phenotypes.

In all the phenotypes the authors confirmed the efficacy of a 4- to 6-mo course of glucocorticosteroids. In the case of steroid toxic effects or steroid resistance, steroid sparing agents or RTX may be considered. According to the aforementioned international consensus^[49] IgG4-RD treatment should comprise the following three steps^[70]: (1) Induction treatment (prednisolone 40 mg/d). Consider B cells depletion therapy if patient is resistant or intolerant to glucocorticosteroids; (2) Tapering treatment with a

duration of 3-6 mo; and (3) Maintenance treatment (low dose prednisolone associated or not with azathioprine or other agents, such as cyclophosphamide, mycophenolate mofetil or calcineurin inhibitors). Maintenance is necessary only in multiorgan disease, elevated serum IgG4, and relapse).

A prompt response to corticosteroid therapy is characteristic of IgG4-RD and renal involvement is not an exception^[41]. In patients with renal dysfunction, a recovery of renal function after glucocorticoid therapy has been documented^[71]. Data on the use of steroids in IgG4-TIN are principally reported by the Japanese and the Mayo Clinic series^[41]. Data on long-term outcomes of IgG4-TIN treated with steroids are available from a retrospective analysis of 40 patients^[72]. These data confirm the beneficial effects of corticosteroids in a majority of the patients. However, 60% of the patients who underwent CT imaging during follow up exhibited evidence of a notable renal atrophy. For these disappointing results, a multicenter phase II prospective clinical trial of glucocorticoid for patients with untreated IgG4-RD is to date ongoing^[73].

Data on IgG4-MGN are limited to a retrospective analysis of seven patients^[60]. Steroid treatment seems to be effective in these patients; however, the retrospective study has several limitations: Some patients had a concomitant IgG4-TIN and other patients received other immunosuppressants in addition to steroids.

AA renal amyloidosis merits few comments. Only one patient has been reported^[39], and because of the long-standing IgG4-RD, the authors argue that the treatment of IgG4-RD with steroids not only ameliorated the symptoms but also modulated inflammatory effects and delayed secondary amyloidosis.

Retroperitoneal fibrosis is also treated successfully with steroids, but with a relevant warning. Hydronephrosis is often associated with aortic aneurysm. The latter represents a critical contraindication to steroid treatment because it may cause aneurysm rupture.

Altogether, steroid treatment of IgG4-RD has the limitation that needs a long-term course and has unavoidable side effects. Additionally, a number of patients are steroid-resistant or steroid-relapsing.

For such patients other immunosuppressants, such as azathioprine, mycophenolate mofetil (MMF) should be considered; however, their effectiveness and safety remains to be established^[65].

International consensus is to take a pragmatic approach: Start to taper the drug after two to four weeks of induction dosing and aim to stop treatment within three to six months^[74]. In the case of relapse, depletion of B cells by RTX should be attempted. In the early phase, two trials have been demonstrated to be highly effective^[49,68]. RTX may dramatically decrease the circulating plasma blasts that represent an index if IgG4-responders^[75].

In the case of IgG4-RKD, particularly TIN, renal atrophy developed in a number of patients treated with steroids, principally in cases where treatment was

started late. Relapse of renal dysfunction following steroid tapering or withdrawal is also frequently observed among patients with IgG4-TIN.

In patients with IgG4-TIN, B cell depletion with RTX may provide a durable response; however, this hypothesis requires confirmation in controlled trials^[72].

The first suggestions on the efficacy of RTX in patients affected by IgG4-RD have been reported in patients affected by IgG4-associated cholangitis, AIP, and ocular involvement resistant to steroids^[76].

The first, randomized, clinical trial on the efficacy of RTX on IgG-RD was performed at the Massachusetts General Hospital and the Mayo Clinic (Clinical Trials.gov identifier NCT01584388)^[68]. Disease response occurred in 97% of the patients and overall, RTX appeared to be an effective treatment for IgG4-RD. Unfortunately, only 4 patients were affected by IgG4-TIN. Recently, McMahon *et al.*^[77] reported successful treatment with RTX in one patient affected by IgG4-TIN who was steroid resistant.

Beneficial effects of B cell depletion were observed by other investigators confirming its significant role in this condition^[78]. In clinical practice RTX is usually considered the first steroid sparing agent after relapse in patients treated with steroids.

Other biologic agents, such as Bortezomib, Abatacept and Infliximab have been used in IgG4-RD refractory to steroids and with a particular disease severity^[79-81]. To date their use in IgG4-TIN is not recommended, based on clinical experience.

CONCLUSION

IgG4-RDs have only been recently recognized, and several features, principally concerning nomenclature, pathophysiology and treatment still remain to be completely defined.

Nomenclature

To better recognize which diseases should be included under the umbrella of IgG4-RDs, a consensus statement was held in Boston in 2011, which provided a set of guidelines for the diagnosis of IgG4-RDs^[8]. As the spectrum of this group of diseases is continuously expanding, the committee advocated the use of strict criteria for accepting newly proposed entities as components of the group.

As a consequence, in 2015^[1] (Table 1), new organs affected by the disease were recognized in addition to the organs identified in the Boston consensus conference. Additionally, pathologic conditions previously considered as well-defined disorders are now recognized as organ manifestations of IgG4-RD^[3] (Table 2).

On the other hand, several conditions have been identified, which only mimic IgG4-RDs but should be classified separately because they represent diseases with distinct and different features^[49] (Table 3). This point is principally relevant for IgG4-related TIN because a number of TINs have been observed, which are

not related to IgG4-RDs^[82]. The American College of Rheumatology recently^[5] edited the recommendations for an improved nomenclature of IgG4-RDs.

Pathogenesis

Pathogenesis of IgG4-RD is poorly understood and controversial. IgG4 antibodies do not seem to be pathogenetic in this disease; rather they mediate a down-regulatory response to other processes^[4]. In addition, IgG4s are only half-antibodies and are unable to bind the complement proteins. Several findings concerning IgG4-RD pathogenesis are consistent with both an autoimmune disorder^[83,84] and an allergic disease^[85].

Autoimmunity is principally evident in patients with type 1 AIP^[83]. Auto antibodies have been described in IgG4-RDs but an evidence for an autoimmune disease is lacking. Cytokines and increased IgE have been described in affected tissues^[85]; however, recent studies^[10,57] have documented that circulating Th2 in IgG4-RDs are restricted to a subset of patients affected by atopy.

An improvement in the understanding of the physiopathology of IgG4-RD is represented by the identification of a cytotoxic CD4 T cell. These cells may produce granzyme B and perforin as well as IL-1 and TGF- β , which are important mediators of fibrosis. Moreover, these T cells are continuously stimulated by the antigen presentation by B cells and plasma blasts^[10], and this fact highlights the importance of a cross-talk between innate and acquired immunity in the pathogenesis of IgG4-RD^[86].

Treatment

The optimal treatment for IgG4-RD has not yet been established. Indeed, to date, there have been no randomized clinical trials that have evaluated and compared the effectiveness of different treatment regimens^[33]. An international consensus among experts^[49] recommended steroids as first line treatment. Due to some disappointing results with the long-term use of corticosteroids, a multicenter phase II prospective clinical trial with steroids is currently ongoing^[73].

Steroid treatment has several drawbacks: (1) Steroid resistance or relapse at discontinuation; and (2) Long-term undesirable steroid side effects. In the case of steroid resistant patients or frequently relapsing patients, B cell depleting agents may represent an effective treatment. RTX is the most used agent and a clinical trial on the use of RTX has been conducted in the United States^[68].

To avoid long-term steroid related side effects, other steroid sparing agents, such as azathioprine, MMF and cyclophosphamide, are reasonable choices for second-line agents; however, once again, their effects have not yet been adequately evaluated in IgG4-RD.

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Observational Study

Awareness, self-management behaviors, health literacy and kidney function relationships in specialty practice

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Abstract

AIM

To determine the relationship between chronic kidney disease (CKD) awareness (CKD-A), self-management behaviors (CKD-SMB) knowledge, performance of CKD-SMBs, health literacy (HL) and kidney function.

METHODS

Participants were eligible patients attending an outpatient nephrology clinic. Participants were administered: Newest Vital Sign to measure HL, CKD self-management

knowledge tool (CKD-SMKT) to assess knowledge, past performance of CKD-SMB, CKD-A. Estimated GFR (eGFR) was determined using the MDRD-4 equation. Duration of clinic participation and CKD cause were extracted from medical charts.

RESULTS

One-hundred-fifty patients participated in the study. eGFRs ranged from 17-152 mL/min per 1.73 m². Majority (83%) of respondents had stage 3 or 4 CKD, low HL (63%), and were CKD aware (88%). Approximately 40% (10/25) of patients in stages 1 and 2 and 6.4% (8/125) in stages 3 and 4 were unaware of their CKD. CKD-A differed with stage ($P < 0.001$) but not by HL level, duration of clinic participation, or CKD cause. Majority of respondents ($\geq 90\%$) correctly answered one or more CKD-SMKT items. Knowledge of one behavior, "controlling blood pressure" differed significantly by CKD-A. CKD-A was associated with past performance of two CKD-SMBs, "controlling blood pressure" ($P = 0.02$), and "keeping healthy body weight" ($P = 0.01$). Adjusted multivariate analyses between CKD-A and: (1) HL; and (2) CKD-SMB knowledge were non-significant. However, there was a significant relationship between CKD-A and kidney function after controlling for demographics, HL, and CKD-SMB ($P < 0.05$).

CONCLUSION

CKD-A is not associated with HL, or better CKD-SMBs. CKD-A is significantly associated with kidney function and substantially lower eGFR, suggesting the need for focused patient education in CKD stages 1.

Key words: Chronic kidney disease awareness; Health literacy; Kidney function; Self-management behaviors; Self-management behavior performance; Epidermal growth factor receptor; Chronic kidney disease knowledge

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Core tip: Chronic kidney disease (CKD) awareness has not been examined in a specialty clinic environment. This study examined the associations between CKD awareness, health literacy, CKD self-management behaviors, past performance of self-management behaviors, and kidney function. We found that majority of the participants in our study were aware of having CKD. CKD awareness increased as CKD worsened; however, nearly 40% of patients in CKD stages 1 and 2 and about 6% of patients in CKD stages 3 and 4 were unaware of having CKD. CKD awareness was not related to health literacy, self-management behavior knowledge, or past performance of behaviors.

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INTRODUCTION

Chronic kidney disease (CKD) is marked by slow and progressive decline in kidney function, leading to end stage renal disease (ESRD), a condition associated with high morbidity, mortality, and economic burden^[1]. The prevalence of CKD in the United States is approximately 15%^[2] and rising^[1]. Despite this, CKD awareness (CKD-A) is low among primary care patients, ranging from 6% to 9%^[3-6], with greater awareness in more advanced stages of CKD^[7,8]. Improving CKD-A is the goal of public health initiatives such as Kidney Early Evaluation Program^[8] and National Kidney Disease Education Program^[9].

Awareness of CKD is an essential step for patient adherence to multiple CKD-specific health behaviors to slow further renal function deterioration. Behavioral management of CKD is complex and includes managing blood pressure (BP), weight, cholesterol, blood glucose levels in those with diabetes, fluid intake, dietary modifications, medication adherence, and engaging in physical activity^[10]. Optimal performance of these health behaviors requires patients to be knowledgeable and health literate about these behaviors. Knowledge and health literacy (HL) are closely related, though distinct concepts, as health knowledge, while essential for adequate HL^[11], does not ensure that an individual is health literate. Low HL is a significant problem impacting 23%-28% of patients with CKD^[12,13]. Low HL has been linked to poor kidney function^[14,15] and lower kidney disease knowledge^[16]. A review by Mackey *et al.*^[17] examining the relationship between HL and development of self-management skills, concluded that low HL presents a significant issue in development of self-management skills.

Previous research examining relationships between CKD-A and clinical risk reduction targets, clinical markers, and specific health behaviors^[3,6,18] found no relationship between CKD-A and most clinical markers or targets and with two out of three health behaviors. However, since these studies were based on larger databases designed for other purposes, they may not capture the entire range of patient-reported CKD-specific self-management behaviors. Previous work has not examined whether CKD-A is associated with HL, and importantly, with actual performance of behaviors, a vital issue in CKD self-management. While previous work has shown that there is greater awareness at higher CKD stages^[7,8], these have not been examined in the context of patients participating in a specialty nephrology clinic.

The purpose of this study was to examine the relationship between CKD-A and: (1) Knowledge of current CKD self-management behaviors (CKD-SMB); (2) performance of CKD-SMB in previous three months as a measure of engagement in behavior; (3) HL; and (4) kidney function (eGFR) in patients attending a specialty nephrology clinic.

MATERIALS AND METHODS

The study was conducted at an outpatient specialty

nephrology clinic at the University of New Mexico Health Sciences Center (UNM HSC) between April and August 2012. Inclusion criteria included: (1) At least 21 years of age; (2) English-speaking; (3) having CKD stages 1-4; and (4) one prior visit at the outpatient nephrology clinic. Exclusion criteria included acute kidney injury, and cognitive impairment. Patients were excluded if they had acute kidney injury and if their medical charts showed signs of poor cognitive functioning. Cognitive impairment was further assessed using the six item screener, a psychometrically valid and reliable tool to identify patients with cognitive impairment^[19]. Patients with a score of less than 4 were excluded. Visual acuity was measured using the pocket vision screener (Rosenbaum, Graham-Field Surgical Co Inc., New York, NY, United States)^[20]. Those with visual acuity worse than 20/100 were also excluded. Patients were given a \$20 merchandise gift card as compensation for participating, irrespective of whether they met vision or cognitive screening tests. Individuals who consented to participate were evaluated for cognitive impairment and visual acuity. Detailed description of the study methodology is provided elsewhere^[14].

Eligible patients who consented were administered the following instruments by trained interviewers: (1) Newest Vital Sign (NVS) a validated HL instrument^[21]; (2) CKD-SMKT, a 10 item CKD self-management knowledge tool measuring patients' knowledge about common CKD SMBs^[22]. After responding to the knowledge aspect for each CKD-SMKT behavior item, respondents indicated whether they had performed the respective behavior in the previous three months using a dichotomous (Yes/No) response. This instrument has been content validated^[20] and reported in a previous study^[14]; and (3) one question about CKD awareness, "Have you ever been told that you have weak or failing kidneys (excluding kidney stones, bladder infections, or incontinence (*i.e.*, no bladder control))". This question is similar to previous studies that have assessed CKD awareness^[5,6,7,18,23]. Self-reported demographic data were also collected. We also extracted data on medically reported cause of CKD as well as patients' first visit date to the specialty clinic from medical records to determine the length of time attending specialty clinic. Kidney function was estimated using the Modification of Diet in Renal Disease (MDRD) equation (MDRD-4) traceable to IDMS, which uses serum creatinine concentration, age, gender, and race. Patients received a \$20 merchandise gift card for study participation. Approval to conduct the study was obtained from the institutional review boards of both Southern Illinois University Edwardsville and University of New Mexico Health Sciences Center.

Statistical analysis

Sample size calculations were based on the effect size for kidney function, with a power of 0.9, alpha of 0.05^[14]. Descriptive statistics were used for quantitative variables; frequencies and percentages were used for categorical variables. Duration of time attending the specialty clinic was calculated by determining the number of months

from the first visit date recorded in the specialty clinic and the date on which the survey was conducted. CKD-A was a dichotomous variable. HL derived from NVS scores, was combined into two categories: (1) limited HL (high likelihood and possible likelihood of limited HL); and (2) adequate HL. Knowledge of CKD-SMB was calculated as percent of correct CKD-SMB responses on the 10-item CKD-SMKT. eGFR was log transformed to address deviations from normality.

Chi-square contingency coefficient and Fisher's exact test were used for the following analyses: (1) demographics and CKD-A; (2) CKD-A and performance of each activity over the previous three months. Demographic categories were collapsed to reduce the number of cells with expected frequencies < 5. Median test was used to examine whether duration of participation in specialty clinic affected CKD awareness.

Hierarchical regression was performed to determine whether CKD-A was associated with knowledge of CKD-SMB (measured as percent knowledge) after controlling for demographics and HL. Logistic regression was used to examine the relationship between CKD-A and HL after controlling for demographics and knowledge of CKD-SMB. The relationship between CKD-A and kidney function after controlling for key demographics, and length of time attending clinic was examined using both logistic and hierarchical regression as appropriate. As age, gender, and race are used to calculate eGFR, they were removed from multivariate analyses that involved eGFR, similar to a previously published study^[14]. Analyses were conducted using SPSS Inc. Released 2009 PASW statistical version 18.0 (SPSS Inc. Chicago, IL, United States). Results were considered statistically significant at $P < 0.05$ ^[14]. The statistical review of the study was performed by Dr. Junvie Pailden, from SIUE Department of Mathematics and Statistics.

RESULTS

Patients

Of the 181 patients approached, 150 met the eligibility criteria and participated in the study (83% participation rate)^[14]. Non-participants included 15 patients who declined to participate, and 16 patients who agreed to participate but failed to meet screening criteria. Among those who failed screening criteria, majority ($n = 15$) of the patients were excluded because they had a score of 4 or less on the six item screener (SIS), and one was excluded because they had recent acute kidney injury. Table 1 shows the demographics of the sample.

Participant demographics: Respondents were female (53%), white (40%) or Hispanic/Latin American (41%), over the age of 40 (90%), high school graduates or above (85%), with private or government insurance (63%), and earning up to \$30000 annually (74%). The majority of respondents had Stage 3 or 4 CKD (83%) and limited HL (63%), and were aware that they had CKD (88%). CKD-A differed by age ($P = 0.027$) with 67% (10/15) of patients in the 21-40 age group

Table 1 Sample demographics

Characteristic	Total <i>n</i> (%), <i>n</i> = 150	CKD aware <i>n</i> (%), <i>n</i> = 132 (88%)	CKD unaware, <i>n</i> = 18 (12%)	<i>P</i> value ^a
Gender				0.087
Male	70 (47)	65 (49)	5 (27)	
Female	80 (53)	67 (51)	13 (72)	
Race				0.625
White	60 (40)	54 (41)	6 (33)	
Native American	9 (6)	8 (6)	1 (6)	
Black	6 (4)	6 (4)	0 (0)	
Hispanic/Latin American	62 (41)	54 (41)	8 (44)	
Other ^b	13 (9)	10 (8)	3 (17)	
Age (yr, 21-90)				0.027
21-40	15 (10)	10 (8)	5 (28)	
41-60	67 (45)	61 (46)	6 (33)	
≥ 61	68 (45)	61 (46)	7 (39)	
Education				0.258
Some high school	22 (15)	21 (16)	1 (6)	
High school graduate or GED ^d	38 (25)	31 (61)	7 (39)	
Some college and above	90 (60)	80 (61)	10 (56)	
Health Insurance				0.437
Medicare	35 (23)	33 (25)	2 (11)	
Medicaid	12 (8)	11 (8)	1 (6)	
Medicare and Medicaid	18 (12)	17 (13)	1 (6)	
Private and Other	30 (20)	25 (19)	5 (28)	
Other ^c	55 (37)	46 (35)	9 (50)	
Annual household income				0.176
< \$15000	69 (46)	64 (48)	5 (28)	
\$15000-30000	42 (28)	34 (26)	8 (44)	
> \$30000	39 (26)	34 (26)	5 (28)	
CKD stage (KDOQI guidelines)				< 0.001
Stage 1	8 (5)	4 (3)	4 (22)	
Stage 2	17 (11)	11 (8)	6 (33)	
Stage 3	75 (50)	69 (52)	6 (33)	
Stage 4	50 (33)	48 (36)	2 (11)	
CKD cause				0.088
Hypertension	30 (20)	28 (21)	2 (11)	
Diabetes	19 (13)	18 (14)	1 (6)	
Diabetes and hypertension	28 (19)	25 (19)	3 (17)	
Glomerulonephritis	26 (17)	18 (14)	8 (44)	
Cystic disease	4 (3)	4 (3)	0 (0)	
Urologic disease	8 (5)	8 (6)	0 (0)	
Other	30 (20)	27 (21)	3 (17)	
Unknown	5 (3)	4 (3)	1 (6)	
Health literacy level				0.513
Low	95 (63)	84 (64)	11 (61)	
Adequate	55 (37)	48 (36)	7 (39)	

^a χ^2 contingency coefficient comparing demographics and CKD awareness; bold numerals, $P < 0.05$; ^bRace: Other: Asian 6 (4%) and other 3 (2%); ^cHealth insurance "Other": Uninsured 4 (3%), private 6 (4%), Indian Health Service 1 (0.7%), and other 51 (34%). CKD: Chronic kidney disease; GED: General Education Development; KDOQI: Kidney Disease Outcomes Quality Initiative.

compared to 90% (61/68) of patients over 60 years old being aware of having CKD. CKD-A was higher with higher CKD stage ($P < 0.001$). Fifty percent ($n = 4$) of those in CKD stage 1 were aware compared to 65% ($n = 11$) in stage 2, 92% ($n = 69$) in stage 3, and 96% ($n = 48$) in stage 4. CKD-A did not differ by HL level.

Association between CKD-A And CKD-SMB knowledge and performance

Table 2 shows the correct responses to each item in the CKD-SMB scale along with the comparison of each item by CKD-A. The majority of respondents (≥ 90 percent) correctly answered one or more items in the CKD-SMB scale. Only one item, "control my blood pressure,"

differed between those who were aware and those who were unaware ($P = 0.02$) with fewer CKD unaware correctly identifying controlling blood pressure being important to help their kidneys. Knowledge (determined as percent of CKD-SMB items answered correctly) did not differ by CKD-A ($t = 1.98$, $df = 146$, $P = 0.162$).

Table 3 describes whether each CKD-SMB performed in the past 3 mo differed by CKD-A. A significantly greater percent of respondents who were aware reported that they "controlled their BP" ($P = 0.02$) and kept a healthy body weight ($P = 0.013$) in the past three months compared to those who were unaware. Specifically, those who were aware were 5.9 times more likely to perform the activity of controlling blood pressure

Table 2 Correct responses to current chronic kidney disease self-management behaviors and comparison with chronic kidney disease awareness (*n* = 150)

CKD-self-management knowledge items	Correct answer; % (<i>n</i>)	Total aware, <i>n</i> = 132 Percent aware giving correct answer % (<i>n</i>)	Total unaware, <i>n</i> = 18 Percent unaware giving correct answer % (<i>n</i>)	Significance with CKD awareness ^a
To help my kidneys, I need to:				
Control my blood pressure	True; 93.3 (140)	96 (126)	78 (14)	0.020
Take my blood pressure medicine(s)	True; 90 (135)	91 (120)	83.3 (15)	0.390
Have my urine ("pee") tested	True; 93.3 (140)	93 (123)	94.4 (17)	0.657
Eat more salt	False; 95.3 (143)	96 (127)	89 (16)	0.199
Get my blood checked	True; 90.6 (136)	92 (122)	78 (14)	0.068
Keep a healthy body weight	True; 96.0 (144)	97 (128)	89 (16)	0.153
Not take some types of over-the-counter medicines (motrin, aleve, ibuprofen, naproxen)	True; 93.3 (140)	92 (122)	100 (18)	0.61
With diabetes	(Total <i>n</i> = 63)	(<i>n</i> = 57)	(<i>n</i> = 5)	
Keep track of my blood sugar	True; 95.2 (60)	97 (55)	100 (5)	1
Eat less sugar	True; 95.2 (60)	97 (55)	100 (5)	1
Take my diabetes medicine(s)	True; 96.8 (61)	93 (52)	100 (5)	1

^aFishers' exact test used as more than 20% of cells had expected frequency < 5, *P* < 0.05.

Table 3 Performance of chronic kidney disease self-management behaviors in previous three months compared with chronic kidney disease awareness (*n* = 150)

Items	Percent who performed the activity in the past 3 mo, % (<i>n</i>)	Total aware (<i>n</i> = 132) Percent aware that performed the activity in past 3 mo, % (<i>n</i>)	Total unaware (<i>n</i> = 18) Percent not aware that performed the activity in the past 3 mo, % (<i>n</i>)	Odds ratio (95%CI) ^b	<i>P</i> value ^a
Control my blood pressure	93 (139)	95.4 (125)	77.8 (14)	5.9 (1.5-23.7)	0.02
Take my blood pressure medicine(s)	88 (130)	88.5 (115)	83% (15)	1.5 (0.4-5.9)	0.46
Have my urine ("pee") tested	92 (138)	93.1 (122)	89 (16)	1.7 (0.3-8.5)	0.62
Eat more salt	9.4 (14)	9.2 (12)	11.1 (2)	0.8 (0.2-3.9)	0.67
Get my blood checked	98 (145)	98.5 (129)	94.1 (16)	4.0 (.3-47.0)	0.31
Keep a healthy body weight	68 (101)	72 (94)	39 (7)	4.0 (1.4-11.1)	0.013
Not take some types of over-the-counter medicines (motrin, Aleve, ibuprofen, naproxen)	89 (133)	90 (118)	83.3 (15)	1.8 (0.5-7.1)	0.41
Items included for those with diabetes	(<i>n</i> = 63)	(<i>n</i> = 58)	(<i>n</i> = 5)		
Keep track of my blood sugar	90 (55)	89 (50)	100 (5)	---	1
Eat less sugar	93.5 (58)	93 (53)	100 (5)		1
Take my diabetes medicine(s)	95 (57)	94.5 (52)	100 (5)		1

^a*P* < 0.05; ^bReference category: "Not performed activity" for odds ratio.

and four times more likely of "keeping a healthy body weight" over the past 3 mo.

eGFR ranged from 17 to 152 mL/min per 1.73 m². Approximately 17% of the eGFRs were 60 or above. Figure 1 shows the bivariate analysis of mean eGFR by awareness (*t* = -3.42, *df* = 18.82, *P* = 0.003) demonstrating increased CKD-A with more advanced CKD. We also examined CKD awareness by CKD stage (results not reported) and found similar results.

Multivariate analyses

Multivariate analysis examining the relationship between CKD-A and HL after controlling for demographics and CKD-SMB knowledge was non-significant (*P* > 0.05). Additionally, multivariate comparison of CKD-A and CKD-SMB knowledge after controlling for demographics and HL was not significant (*P* > 0.05). As the literature does not offer guidance on the directionality of the relationship between CKD-A and kidney function, we performed

multivariate analyses to examine the relationship between CKD-A and kidney function after controlling for demographics, and length of time attending clinic considering CKD-A as an independent as well as dependent variable. For both analyses, the overall model was significant. Hierarchical regression analyses with CKD awareness as independent variable and log eGFR as the dependent variable showed that CKD awareness predicted 29.4% of the variance in log eGFR. The relationship between CKD-A and log eGFR was negative suggesting a lower eGFR with awareness. Logistic regression results with awareness as a dependent variable, suggested the estimated odds ratio to be 0.926 (95%CI: 0.891-0.926, *P* < 0.05) suggesting a lower odds of awareness at higher eGFR.

CKD-unaware patients

We examined CKD unaware patients (*n* = 18) further to identify reasons for their unawareness despite

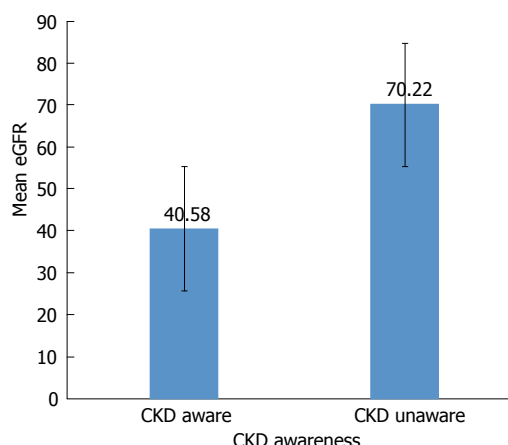


Figure 1 Comparison of mean eGFRs between those who are aware of their chronic kidney disease vs those who are unaware ($P = 0.003$)^a. ^aFigure shows mean eGFRs and standard errors for the chronic kidney disease (CKD) aware and CKD unaware group.

participation in specialty clinic. As reported in Table 1, majority of CKD unaware patients were female (72%) and Hispanic/Latin American (44%). Proportional comparison to the demographic characteristics of the overall sample showed that a greater percent of the CKD-unaware patients were in the 21-40 age group (33%), were high school graduates or GED (18.4%), had private or other insurance (33%), incomes between \$15000-\$30000 (19%), had CKD stages 1 and 2 (40%), and had adequate health literacy (12.7%). The primary medically reported cause for CKD unaware patients in the initial stages of CKD (stages 1 and 2) was glomerulonephritis. However, 4 out of 8 patients in stages 3 to 4 with diabetes and hypertension also indicated that they were unaware of having CKD. There were no patients with cystic or urologic disease who indicated that they were unaware of having CKD. Fourteen out of 18 CKD unaware patients were clinic patients for more than 6 mo.

Duration of participation in specialty clinic and medically reported cause of CKD were examined to further understand potential reasons for unawareness among patients visiting the specialty clinic. Duration of clinic participation ranged from 2 to 118 mo (media $n = 22.5$ mo). However, duration of participation in the clinic was not significantly different between those who were aware and those who were unaware (chi sq = 0.253, $P = 0.802$). Similar results were obtained for duration of clinic participation across different health literacy groups (chi sq = 0.258, $P = 0.735$). We also examined CKD awareness by comparing it with medically reported cause of CKD. No significant relationships were present (chi sq = 12.39, $df = 7$, $P = 0.088$).

DISCUSSION

This study examined CKD-A in patients with CKD stages 1-4 in a nephrology specialty clinic and as expected, found that awareness of having CKD was high among patients

in this outpatient nephrology specialty clinic. However, we found that 10/25 (40%) of patients in stages 1 and 2, and 8/125 (6.4%) in stages 3 and 4 were unaware of their CKD. We did not find any relationships between CKD-A and HL, and with most CKD-SMBs. No relationship between CKD-A and knowledge of CKD-SMBs and performance of the same in the previous three months was found either. However, similar to other studies, we found CKD-A was significantly higher with worse renal function^[12,24,25], and this relationship remained significant even after controlling for demographics and length of time attending clinic. This study extends findings from prior studies that focused only on knowledge of CKD-specific behaviors to an assessment of patient-reported engagement in behaviors. While previous studies examined the relationship of CKD awareness with clinical targets and markers as outcome measures^[3,6,18], our study examined patient-reported knowledge and performance of self-management behaviors as outcomes, which are more patient-centered outcomes. Nevertheless, our study corroborates prior research that showed non-significant relationships between CKD-A and outcomes.

While our study determined that there is a relationship between CKD awareness and kidney function (eGFR), the direction of this relationship is unclear. CKD-A can impact kidney function and it is possible that kidney function decline can promote awareness. Given the potential for a bi-directional relationship, we conducted analyses using CKD awareness as both a dependent as well as independent variable. While we can envision awareness to impact kidney function *via* self-management behaviors^[8] our study did not find such a relationship. It is possible that the cross-sectional nature of our study or small sample size limited our findings. Future longitudinal studies are needed to elucidate the pathway by which CKD awareness impacts kidney function.

The vast majority (88%) of patients in our study were aware that they had CKD, although the 40% unawareness in stages 1 and 2 in a specialty nephrology clinic setting is cause for concern and suggests an urgent need to improve awareness and education of CKD in the earlier stages of disease. This was expected as our study was conducted in a specialty nephrology clinic and the majority of our sample had stage 3 or 4 CKD. Even patients in stages 1 and 2 were mostly aware (60% aware), possibly due to having a primary renal disease (e.g., glomerulonephritis) requiring nephrology management. This contrasts with low awareness rates reported in other studies, which were conducted in primary care settings^[3-7].

Our study used the NHANES question to assess awareness. This question has been previously used to gauge CKD-A and has comparable sensitivity and specificity to other single item awareness questions, including a modified version to enhance sensitivity and specificity^[9]. Irrespective of the question used for gauging CKD-A, no association was found with clinical markers or specific CKD-SMBs^[3,18]. For example, one study examined the relationship of seven clinical markers

of renal dysfunction to awareness using the NHANES CKD-A question and determined that a high percentage of individuals with 4 to 5 clinical markers were unaware of their CKD^[6]. Another study examined three health behaviors, three clinical risk reduction targets, and their association with CKD-A using a different question^[3]. Only one clinical marker, albuminuria, and one health behavior, tobacco avoidance, was related to CKD-A. However, their study did not examine all CKD-specific behaviors or HL. Tuot *et al.*^[18], examined the relationship between CKD-A and specific clinical measures reporting no relationship between the two, and called for assessment of the relationship between awareness and behaviors related to CKD-A.

We found no relationship between CKD-A and HL, which suggests that people who are aware may be no more health literate than those who are unaware. Poorer HL has been linked to several important CKD outcomes such as lower eGFR, poor knowledge, poor referral for transplantation, and increased mortality in ESRD^[12]. While CKD-A may be the essential first step for patient engagement and adherence^[9,26], our results highlight the need for targeted HL interventions in order to realize the positive impact on patient outcomes, rather than assuming that awareness of having CKD would intrinsically motivate patients to become health literate.

Our finding of a lack of relationship between CKD-A and most of the recommended CKD-SMB knowledge items is noteworthy. Evidence from this study are counter to the commonly perceived notion that awareness of CKD is essential for patients to have greater knowledge of CKD-SMBs or to engage in CKD SMBs^[8,26]. In contrast to previous studies, the patients in our study were seen in a nephrology clinic and a majority were aware of having CKD, were knowledgeable about CKD-specific behaviors, were in the advanced stages of CKD (Stages 3 and 4) and reported performing many of the CKD SMBs in the previous three months. Yet, being aware of having CKD was not significantly associated with self-reported performance of majority of the CKD-SMBs, though the behaviors were performed at a relatively high (70%) rate regardless of awareness. One explanation for the lack of a significant association between most behaviors and CKD-A may be that patients perceived these as general or cardiovascular-related behaviors (*i.e.*, hypertension) rather than CKD-specific behaviors^[3]. This may explain the lack of relationships between CKD-A and performance of behaviors in the previous 3 mo. The finding of a relationship between CKD-A and performance of two specific behaviors, namely, "blood pressure control" and "maintaining healthy body weight" supports patients' thinking of these as cardiovascular or general health behaviors.

Previous studies examining CKD-A and BP control (measured clinically) have reported conflicting results^[18,27]. Our study asked patients about their maintenance of BP control as a useful behavior to protect their kidneys and found that a significantly greater percent of CKD aware patients performed the activity. This may be

associated with a greater percent of CKD aware patients self-reporting having hypertension and consequently recognizing that behavior as a cardiovascular-related behavior. Although providers at the nephrology clinic may have equally emphasized all key CKD-specific health behaviors, the frequent comorbidity of hypertension along with public health education about BP control may result in higher patient knowledge of the importance of optimal BP control. Greater educational efforts by providers to highlight the importance of other CKD-specific behaviors are needed if CKD-A is to translate into actual behavior performance. Nevertheless, from a clinical practitioner perspective, it is encouraging to note the high numbers of patients in both aware and unaware categories that performed most behaviors.

Other explanations of lack of relationship between CKD-A and CKD-SMBs may relate to the relative lack of symptoms in CKD, especially in early stages^[3], or that CKD SMBs may have been less familiar to patients who developed CKD caused by non-diabetes or non-hypertension causes (*e.g.*, glomerulonephritis). In our study, 18 (72%) of the 25 patients in CKD stages 1 and 2 had non-diabetes or non-hypertension CKD causes. Consistent with prior studies^[7,8], our study found that mean eGFR of those who were aware was significantly lower (worse CKD) than those who were unaware, suggesting that awareness increases with higher CKD stage or worse eGFR. The relationship with eGFR remained significant even after controlling for demographics and length of time attending clinic. Given that renal function trajectory is variable among individuals, affected by numerous factors^[28], and sometimes slow^[29], the relationship with kidney function offers promising opportunity for education about CKD-SMBs, especially if targeted in earlier CKD stages. Such tailored behavior education can improve adherence and slow the rate of eGFR loss^[30]. Clinicians may keep this in mind when counseling patients, and use different educational strategies for those with higher eGFRs. Also, telehealth technology such as text messaging and interactive voice response (IVR) systems have been recently suggested as ways to improve patient awareness and knowledge of CKD particularly in the earlier stages when minimal symptoms are experienced^[31].

We were surprised to find 8 out of 18 patients in stages 3 and 4 CKD, the majority of whom were seen in this specialty nephrology clinic for more than 6 mo, were unaware of having CKD. We do not have data about the number of visits that they made to the clinic over the duration of time that they participated in the clinic. Providers should not assume that the patients that they are seeing are aware of their disease and should proactively discuss and educate patients about their disease condition without assuming that their participation in the specialty clinic, or their performance of CKD-specific behaviors would imply awareness.

This study has several limitations, including that this was a relatively small cross-sectional study conducted at a single center. We were unable to include non-English speakers due to the nature of the study instruments.

While we used validated measures such as NVS, we were unable to evaluate critical or interactive HL^[14]. Also, construct validity of the CKD-SMB tool has not been established, although content validity of the instrument has been previously published^[22]. Further, the item in CKD SMKT that referred to taking BP medication, isn't relevant to those not taking BP medication. Nevertheless, as only 12% reported that they did not perform the activity, it implies that patients may have interpreted the item as "taking medication" rather than taking BP medication. Additionally, we were unable to confirm behaviors through chart review. Finally, we estimated eGFR using MDRD-4 equation, rather than the (more recent) CKD-EPI equation, which is more accurate at higher GFR^[32]. However, in a study examining CKD-A and healthy behaviors, sensitivity analyses performed using the MDRD equation showed that their study results remained unchanged irrespective of the type of equation used to assess eGFR^[3]. It is unlikely that the GFR estimating equation would have significantly influenced our results.

In conclusion, CKD-A was not associated with health literacy, did not translate into better CKD-SMB knowledge, or result in improved performance of CKD-SMBs even in worse stages of CKD. However, CKD-A did have a significant association with kidney function, especially with lower eGFR, which is consistent with existing literature. Future work should focus on targeted efforts to enhance education and training of CKD-SMBs differentiating it from behaviors for other related conditions such as hypertension, and beginning in the early stages of CKD. It is important to determine the effect of awareness on renal function and vice versa, as worse renal function may improve one's awareness, and, conversely, improved awareness may impact the trajectory of renal disease. Longitudinal research is essential to evaluate the impact of CKD-SMB education on renal function trajectory.

ARTICLE HIGHLIGHTS

Research background

Chronic kidney disease (CKD) awareness is low in the primary care patient population with greater awareness in the advanced stages of CKD. Awareness of CKD is the first step for patient adherence to the numerous CKD-specific health behaviors necessary for optimal management of CKD. In order for patients to perform these behaviors appropriately, it is necessary that they be knowledgeable and health literate about these behaviors. Previous studies on CKD awareness have been based on larger databases and have focused on clinical markers and only few health behaviors. Additionally, previous work has not studied whether CKD awareness is associated with health literacy, or with actual performance of self-management behaviors, particularly in a specialty nephrology clinical practice setting.

Research motivation

While it may be assumed that being aware of having CKD will motivate patients to improve their health outcomes particularly in a specialty nephrology clinic setting, it has never been previously studied within this setting. Additionally, CKD awareness and kidney function relationships have not been previously examined, nor has actual performance of CKD specific behaviors been previously examined. This study examines the relationships between CKD awareness, health literacy, kidney function, CKD self-management behavior knowledge and its performance in a specialty practice setting. Examining

these relationships will offer useful information to clinicians regarding how to design the best interventions for different stages of CKD, taking into account factors such as CKD awareness, health literacy, and self-management behavior performance.

Research objectives

The purpose of this study was to examine the relationship between CKD-A and: (1) Knowledge of current CKD self-management behaviors (CKD-SMB); (2) performance of CKD-SMB in previous three months as a measure of engagement in behavior c) HL, and d) kidney function (eGFR) in patients attending a specialty nephrology clinic. Learning more about these relationships will allow clinicians to use more targeted interventions with their patients.

Research methods

The authors used surveys to measure health literacy, self-management behavior knowledge, and performance, and CKD awareness. At the same time, the authors extracted information from medical records to determine CKD cause, serum creatinine levels, and length of time attending specialty clinic. Serum creatinine levels were converted to estimate glomerular filtration rates (eGFR) values using the MDRD-4 equation. The uniqueness of our study is that the authors used actual prospective data collection rather than retrospective data which most current studies in the literature have used.

Research results

This study examined CKD-A in patients with CKD stages 1-4 in a nephrology specialty clinic and as expected, found that awareness of having CKD was high among patients in this outpatient nephrology specialty clinic. However, the authors found that 10/25 (40%) of patients in stages 1 and 2, and 8/125 (6.4%) in stages 3 and 4 were unaware of their CKD. The authors did not find any relationships between CKD-A and HL, and with most CKD-SMBs. No relationship between CKD-A and knowledge of CKD-SMBs and performance of the same in the previous three months was found either. However, similar to other studies, the authors found CKD-A was significantly higher with worse renal function, and this relationship remained significant even after controlling for demographics and length of time attending clinic. Future efforts should include longitudinal studies that focus primarily on CKD-specific behaviors and beginning in the early stages of CKD. Also, since the authors saw that awareness was associated with kidney function, future work should determine the effect of awareness on renal function trajectory.

Research conclusions

Some new findings from our study include: (1) although awareness of CKD was high, it did not translate into better CKD self-management behavior knowledge or actual performance of behaviors even in worse stages of CKD; (2) the authors also found that awareness was significantly associated with kidney function but not with health literacy; (3) The authors found that large percent of patients reported being knowledgeable about CKD self-management behaviors, but there was no relationship between knowledge and performance of those behaviors. Based on this study, the authors theorize that among the several factors that affect kidney function, CKD awareness is a significant factor. However, the pathway by which awareness affects kidney function is unknown. It is possible that awareness arises only after kidney function decline, implying that raising awareness in the earlier stages of the disease may minimize the rate of kidney function decline. As health literacy and self-management behaviors are not associated with awareness, it suggests that just being aware of having CKD does not guarantee that individuals will perform self-management behaviors, or become health literate. The mechanisms to improve kidney function through awareness pathway need to be further assessed by longitudinal studies. CKD-A is not associated with HL, nor does it translate into better CKD-SMBs. CKD-A is significantly associated with kidney function, with awareness occurring with substantially lower eGFR. While the current literature indicates that CKD awareness is low, our study found a high level of CKD awareness. One reason for a high level of awareness may be that it was conducted in a specialty practice setting. Also, current literature does not address awareness and self-management behaviors or kidney function, both which our study addresses. The new hypothesis that this study proposes include: a) CKD awareness arises after kidney function decline. This study proposes examination of the relationship between CKD awareness and kidney function using longitudinal studies. Clinical practitioners should enhance and focus patient education of CKD in the earlier stages of CKD when awareness may be low. Also,

practitioners should differentiate between CKD-specific behaviors and general health behaviors, so that patients clearly understand the CKD-specific behaviors needed to prevent kidney function decline.

Research perspectives

A larger sample size would help confirm the study results. Also, conducting this study in multiple practice settings will help improve generalizability. Future research should be longitudinal in nature and examine the relationship between CKD awareness and renal function trajectory. Future research should be longitudinal with a larger sample size and multiple specialty clinics.

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Is serum copeptin a modifiable biomarker in autosomal dominant polycystic kidney disease?

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Abstract

The availability of disease-modifying drugs for the management of autosomal dominant polycystic kidney disease (ADPKD) has accelerated the need to accurately predict renal prognosis and/or treatment response in this condition. Arginine vasopressin (AVP) is a critical determinant of postnatal kidney cyst growth in ADPKD. Copeptin (the C-terminal glycoprotein of the precursor AVP peptide) is an accurate surrogate marker of AVP release that is stable and easily measured by immunoassay. Cohort studies show that serum copeptin is correlated with disease severity in ADPKD, and predicts future renal events [decline in renal function and increase in total kidney volume (TKV)]. However, serum copeptin is strongly correlated with creatinine, and its additional value as a prognostic biomarker over estimated glomerular filtration rate and TKV is not certain. It has also been suggested that copeptin could be a predictive biomarker to select ADPKD patients who are most likely to benefit from AVP-modifying therapies, but prospective data to validate this assumption are required. In this regard, long-term randomised clinical trials evaluating the effect of prescribed water intake on renal cyst growth may contribute to addressing this hypothesis. In conclusion, although serum copeptin is aligned with the basic pathogenesis of ADPKD, further rigorous studies are needed to define if it will contribute to enabling the delivery of personalised care in ADPKD.

Key words: Polycystic kidney disease; Copeptin; Biomarker

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Core tip: Serum copeptin is correlated with disease severity in autosomal dominant polycystic kidney disease (ADPKD), and predicts future renal events (decline in renal function and increase in total kidney volume). The aim of this review is to critically evaluate the role of copeptin as a prognostic biomarker of renal outcomes in ADPKD, and if it has potential as a predictive marker of treatment response.

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INTRODUCTION

The life-time risk for end stage kidney disease (ESKD) in autosomal dominant polycystic kidney disease (ADPKD) is characterised by high intra- and interfamilial variability^[1]. Epidemiological data indicates that only 50% of patients with ADPKD will develop ESKD by the age of 60^[2]. This variability in risk for ESKD is likely due to the interaction of genic factors^[3] with environmental variables^[4] that alter the expressivity of the clinical phenotype^[5,6]. Routine tests performed during the initial clinical evaluation of affected patients, such as estimated glomerular filtration rate (eGFR), lack sensitivity as prognostic markers in early disease^[7], and other clinical information (such as family history of early-onset of ESKD) do not have precision^[8]. The uncertainty in predicting renal prognosis causes tremendous anxiety to patients and their families^[9]. Furthermore, the introduction of disease-modifying drugs to treat ADPKD has catalysed an urgent need to identify and validate a panel of reliable and easily measurable clinical, genetic, molecular and imaging biomarkers in predicting the risk for ESKD^[10].

The arginine vasopressin (AVP)-cAMP signalling pathway has a central role in the initiation of lifetime growth of kidney cysts in ADPKD^[11]. Serum copeptin is a surrogate marker of AVP release^[12], and the availability of a sensitive commercially available immunoassay, has led to several cohort studies to evaluate its role as a prognostic biomarker in ADPKD. The role of copeptin as a clinical diagnostic test is also under evaluation in several other diseases including in the differential diagnosis of polyuria-polydipsia (where it is being considered as a replacement for the direct measurement of serum AVP)^[13,14], and in the diagnostic evaluation of other disorders (such as acute myocardial infarction^[15] and sepsis^[16]) where its potential utility is less certain. In this regard, to date, copeptin is not funded for reimbursement

for routine measurement in patients in ADPKD in any country, providing an indirect indicator that its value as a prognostic biomarker in this setting has also not been proven and that further data is needed. The aim of this review is to critically evaluate the role of copeptin as a prognostic biomarker of renal outcomes in ADPKD, and if it has potential as a predictive marker of treatment response.

ROLE OF AVP-CAMP SIGNALLING IN THE PATHOGENESIS OF RENAL CYST GROWTH IN ADPKD

The role of AVP in the pathogenesis of ADPKD has been reviewed elsewhere^[11], but briefly, it is considered to be the most important factor that determines the postnatal rate of renal cyst growth. The most compelling preclinical evidence to support this hypothesis is that the congenital deficiency of AVP almost completely abrogated the formation of renal cysts in the pck rat^[17]. Furthermore, in mouse models of PKD, small-molecule vasopressin-receptor antagonists were highly effective in reducing kidney cyst growth^[18]. In humans, the evidence is supported by the TEMPO 3:4 and REPRIS trials which collectively showed that tolvaptan (a highly specific vasopressin-receptor antagonist) reduced the rate of increase in total kidney volume (TKV) in early-stage ADPKD and also the decline in renal function in late-stage disease^[19,20]. Given its critical importance, it seems logical to consider markers of AVP release as potential biomarkers in ADPKD.

SYNTHESIS, FUNCTION AND DEGRADATION OF COPEPTIN

Synthesis of copeptin

As shown in Figure 1, copeptin is the C-terminal end of the AVP precursor molecule (pre-proAVP), a 164-amino acid peptide consisting of four segments: (1) The signal peptide at the N-terminus (amino acids 1-19); (2) AVP (amino acids 20-28); (3) neurophysin (amino acids 32-124); and (4) copeptin (amino acids 126-164), a 39-aminoacid glycopeptide that makes up the C-terminal part of pro-AVP. As summarised in Table 1, the precursor peptide (pre-proAVP) is produced in two anatomically distinct regions of the hypothalamus.

Function of copeptin

While the physiological function of AVP is well defined by its effects on tissue-specific receptors (V_{1a} receptor: mediates vasoconstriction and platelet aggregation; V_{1b} receptor: ACTH secretion; and V₂ receptor: water balance), the exact role of copeptin in normal physiology is unclear as it has no known receptors. In this regard, copeptin has been hypothesised to function as a chaperone for pre-proAVP release from the magnocellular

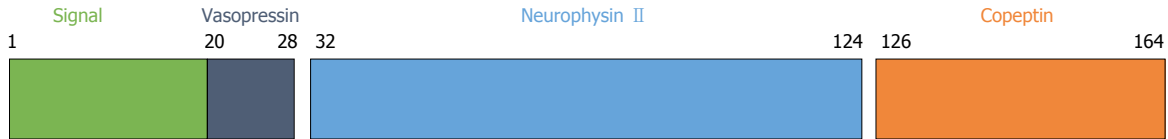


Figure 1 The precursor peptide of arginine vasopressin, also known as pro- arginine vasopressin. The indicative numbers of the amino acid positions of the peptide. Copeptin is the C-terminal peptide of pro-AVP and is released with AVP during precursor processing. Figure adapted from Reference^[22]. AVP: Arginine vasopressin.

Table 1 Distinct production sites of precursor arginine vasopressin in hypothalamus

Site of synthesis in hypothalamus	Magnocellular neurons (Supra-optic and paraventricular)	Parvocellular neurons
Processing of AVP	Occurs during axonal transport in the infundibulum with copeptin and neurophysin acting as chaperones for correct AVP folding	Occurs in the parvocellular neurons where it released with other releasing hormones, such corticotrophin releasing hormone
Storage	Posterior pituitary	Hypothalamus
Stimuli for release	Osmotic and haemodynamic stimuli from the posterior pituitary gland	Released in response to humoral stress together with CRH, which both act on the adrenal gland to release cortisol

AVP: Arginine vasopressin.

Table 2 Summary of vasopressin limitations compared to copeptin advantages as a biomarker using the thermo scientific B.R.A.H.M.S KRYPTOR assay (adapted from Thermo Fisher scientific)

Features	Limitations of measuring AVP	Advantages of CT-proAVP (Copeptin)
<i>Ex vivo</i> stability	Unstable (even at -20 °C)	Stable at > 3 d at room temperature
Sample volume required	400 L	50 µL
Time to results	3 working days	approximately 1 h
Sensitivity	Low (small molecule size, measured only by competitive immunoassay)	High (larger size, can be measured using a sensitive sandwich immunoassay)
Measuring range	1.15-73.8 pmol/L	0.7-500 pmol/L and up to 2000 pmol/L with automated dilution
Handling	Manual	Automatic

AVP: Arginine vasopressin.

neuron, but its role in peripheral tissues (if any) remains unknown. Thus, the literature has considered that copeptin is simply an inert biomarker with no direct role in the pathogenesis kidney cyst formation, but clearly further studies (such as gene knockout experiments in mice) are needed to evaluate this premise.

Degradation of copeptin

Another gap in knowledge is that little is known about the pharmacokinetics and degradation of copeptin. Available data suggests that it is rapidly cleared from the circulation either through the degradation by tissue-bound proteases, renal excretion and/or hepatic metabolism. New data on this topic are likely to emerge in the future and in this regard, a recent study reported that while the release of copeptin in response to elevation in the serum osmolality in healthy individuals was similar to AVP, its decay in the serum was two-fold longer than AVP^[21]. Understanding the clearance of copeptin also has major implications for interpreting values in the setting of renal impairment, as reduced glomerular filtration is associated with elevated serum copeptin and thereby, confounds its value as a unique prognostic biomarker in ADPKD (as discussed below).

ADVANTAGES AND DISADVANTAGES OF COPEPTIN MEASUREMENT IN THE LABORATORY

It is well known that the laboratory testing of AVP is time-consuming and not practical (primarily because it is rapidly removed from the circulation with a half-life of less than 30 min requiring a large volume of serum) and is unstable in serum^[22,23]. On the other hand, copeptin is released in equimolar amounts with AVP^[24], is stable for up to 14 d in serum at room temperature; can be rapidly measured (0.5-2.5 h); and requires only 50 L of serum, making it potentially suitable for a high-throughput clinical pathology laboratory^[12]. These analytical comparisons in methodology are summarised in Table 2.

The disadvantage of the copeptin assay is that in many countries, including in Australia, the most widely used and validated assay is a sandwich immuno-luminometric method by ThermoFisher Scientific which requires purchase of a specific instrument^[22]. As there is insufficient evidence for the use of copeptin in routine clinical practice, it is not currently provided by most clinical pathology laboratories and therefore, not readily

accessible. Other manufacturers other than Thermo-Fisher Scientific produce in-house ELISA kits^[25] to measure copeptin, and this might make it easier to access the assay, but this is suitable for the clinical setting and large numbers of samples need assayed using a standardised technique. In sum, insufficient clinical evidence has not allowed further development of copeptin for clinical use in ADPKD, and the assay remains primarily restricted to the research setting.

MULTIPLE LIFESTYLE FACTORS INFLUENCE THE BASAL LEVELS OF SERUM COPEPTIN

Several lifestyle factors modify the basal level of copeptin in an individual. The most well studied variable is fluid intake. In healthy individuals, a chronic increase in total fluid intake by approximately 1 L/d above baseline reduced serum copeptin from 5.18 to 3.90 pmol/L^[26]. Similarly, in patients with Stage 3 CKD ($n = 28$), the median copeptin level was 17 pmol/L and declined to 4.2 pmol/L with fluid intake over a 6-week period^[27], confirming that: (1) Patients with CKD have higher levels of copeptin; and (2) increasing fluid intake can attenuate long-term copeptin levels. The type of fluid consumed may also influence the change in copeptin, as preclinical data in rats shows that rehydration with 20% hypertonic fructose increased plasma osmolality, AVP release and oxidative renal injury in rats with mild dehydration, whereas this effect was not seen with plain water^[28].

Multiple other factors may influence the basal levels of copeptin. A cross-sectional analysis of the Groningen population-based cohort study ($n = 6801$) showed that in addition to low fluid intake, other dietary factors (high sodium, high protein and low potassium), alcohol intake and smoking were all associated with higher serum copeptin levels^[29]. However, it is noteworthy that, in contrast to the Groningen study, alcohol suppresses the release of vasopressin from the pituitary gland^[30,31]. Similarly, smoking is well known to stimulate the release of AVP in the blood plasma. In rabbits, an injection of 0.5 mg/kg of nicotine increased AVP concentrations by nearly 40 times^[32]. The relative importance of each of these factors in influencing copeptin levels, and how they should be considered prior to collecting blood for copeptin in individuals, has not been standardized and further studies are required.

BASAL SERUM COPEPTIN IS NOT DIAGNOSTIC OF ADPKD AND IS STRONGLY CORRELATED WITH RENAL FUNCTION

Several investigators have raised the hypothesis that serum AVP, and therefore copeptin, could be mildly

elevated in ADPKD patients compared to the general healthy population^[33]. For example, in a small study of 30 patients, the difference in mean serum copeptin was 8.92 pmol/L [inter-quartile range (IQR): 0.66-21.86] in ADPKD patients (eGFR 100 ± 23 mL/min/1.73 m²) compared to 6.08 pmol (IQR 0.92-10.79) in healthy individuals (eGFR 104 ± 12 mL/min/1.73 m²) ($P = 0.22$). This mild elevation is most likely due to subclinical volume depletion due to increased urinary losses as a result of impaired urinary concentrating ability and nephrogenic diabetes insipidus, as following water deprivation for 14 h, the difference in mean serum copeptin between ADPKD compared to healthy patients become statistically significant (ADPKD: 17.01 pmol/L; IQR 7.94-17.78 vs healthy: 7.75 pmol, IQR 3.81-8.80; $P = 0.04$)^[33]. However, based on published studies, there is little evidence to support that these findings are specific or diagnostic of ADPKD. In particular, a recent study showed that: (1) Mean levels of copeptin in ADPKD patients were comparable to patients with other types of CKD, such as IgA nephropathy (ADPKD: 26.6 pmol vs IgA nephropathy: 20.7 pmol/L; $P = 0.84$)^[34,35], and (2) the levels were more strongly correlated with the serum creatinine rather than the specific cause of CKD^[35].

IS SERUM COPEPTIN A PROGNOSTIC BIOMARKER OF RENAL OUTCOMES IN ADPKD?

With this background, the remainder of this article will evaluate the specific utility of copeptin as a biomarker in ADPKD. The National Institutes of Health Biomarker Consortium defines a "biomarker" as a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions^[36]. More specifically, the two sub-groups that are relevant to the discussion of copeptin and ADPKD are a "prognostic biomarker" (defined as biomarker that identifies the likelihood of a clinical event, recurrence or progression), and a "predictive biomarker" (defined as a biomarker that identifies those who are likely to respond to a treatment than those that are negative for a biomarker). Furthermore, Park and Ahn^[37] outlined that the ideal biomarker in ADPKD should fulfil three characteristics: (1) It should correlate with the clinical severity of ADPKD; (2) it should detect patients at high-risk of progression; and (3) short-term changes should predict a clinical endpoint. In addition, validation is the process of assessing the biomarker and its measurement performance characteristics, and determining the range of conditions under which it provides reproducible and accurate data. The assessment of whether serum copeptin fulfils the criteria and validation in ADPKD is limited by the paucity of data, as only 26 articles were identified by a PubMed search using the terms "copeptin" and "ADPKD" (with at least

6 being review articles). Furthermore, many of these studies consist of small sample sizes. Despite this, the available data was analysed to answer two questions.

Are serum and urinary copeptin levels correlated with markers of disease severity?

Several cross-sectional studies show that serum copeptin is positively correlated with TKV and negatively correlated with eGFR. Furthermore, longitudinal studies show that higher copeptin levels had significantly higher TKV and urine osmolality, evidently shown by a study where TKV increased by 71% as copeptin levels increased by 23%^[38,39]. Furthermore, a recent study also showed that serum copeptin predicted changes in fibromuscular dilatation in patients with ADPKD, an indicator of cardiovascular disease. To date, only one cohort has evaluated the role of urinary copeptin to creatinine ratio, which reported moderate correlations with ht-TKV ($r = 0.383$, $P = 0.008$) and eGFR ($r = -0.304$, $P = 0.036$) in 50 Japanese patients with ADPKD^[40].

Are there any confounding factors that influence the interpretation of serum and urinary copeptin in ADPKD?

Several studies show that copeptin has a strong relationship with eGFR. Corradi *et al.*^[35] recently demonstrated that glomerular filtration affects copeptin to a greater extent rather than its correlation to AVP. The authors of a previous study indicated that after the removal of a kidney, the copeptin levels relatively remained stable, however, only GFR had declined by 40%^[33,34]. A greater number of nephrons in the body would indicate a relatively higher AVP activity, and hence, a proportional increase in copeptin. The latter, however, opposes this theory, suggesting that perhaps copeptin is only a filtration marker rather than a disease severity marker for ADPKD. Furthermore, it is not known whether eGFR also confounds the level of urinary copeptin^[40].

IS SERUM COPEPTIN A PREDICTIVE BIOMARKER OF TREATMENT RESPONSE TO VASOPRESSIN RECEPTOR ANTAGONISTS OR PRESCRIBED FLUID INTAKE IN ADPKD?

Several authors have suggested that higher baseline levels of copeptin could be used as a method to select patients for AVP blocking therapies, such as tolvaptan or prescribed fluid intake^[12]. While this is an attractive hypothesis, it has yet to be formally tested and validated. In this regard, it would certainly be possible to perform a post-hoc analysis of the large randomized controlled trials involving tolvaptan to answer this question. Similarly, an ongoing randomized controlled trial of prescribed fluid intake will evaluate the long-term changes in serum copeptin and its effect on the progression of TKV^[41].

CONCLUSION

There is strong interest in the role of copeptin as a molecular biomarker in ADPKD. While aligned with the pathogenesis of ADPKD, copeptin seems attractive for this purpose, but many questions remain. The most important question is whether measuring serum copeptin adds extra value over the standard clinical management tools (such as the PRO-PKD score, eGFR, TKV) to predict renal prognosis^[42]? If so, does this predict whether patients with elevated copeptin are more likely to respond to therapies that suppress AVP (either or both pharmacological or life-style factors, such as fluid intake)? If these fundamental questions can be answered, other issues can be addressed, such as: What level of copeptin will be effective in attenuating renal cyst growth? How often should copeptin be measured? Should it be evaluated in all patients who present for the first time? What are the confounding factors that might influence interpretation of the data? Does copeptin itself have a direct pathological role in ADPKD? What is the value of measuring urinary copeptin, and how does serum copeptin compare with other markers of the AVP axis, such as urinary cAMP excretion?

Clearly, well designed prospective studies and health economic data will assist in answering these questions and evaluating the role of copeptin in the management of patients with ADPKD. Until this evidence is available, it will be difficult to influence policy-makers and regulatory bodies to utilize this test in the routine clinical care of patients with ADPKD.

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Diabetic muscle infarction in end-stage renal disease: A scoping review on epidemiology, diagnosis and treatment

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Abstract

Diabetic muscle infarction (DMI) refers to spontaneous ischemic necrosis of skeletal muscle among people with diabetes mellitus, unrelated to arterial occlusion. People with DMI may have coexisting end-stage renal disease (ESRD) but little is known about its epidemiology and clinical outcomes in this setting. This scoping review seeks to investigate the characteristics, clinical features, diagnostic evaluation, management and outcomes of DMI among people with ESRD. Electronic database (PubMed/MEDLINE, CINAHL, SCOPUS and EMBASE) searches were conducted for ("diabetic muscle infarction" or "diabetic myonecrosis") and ("chronic kidney disease" or "renal impairment" or "dialysis" or "renal replacement therapy" or "kidney transplant") from January 1980 to June 2017. Relevant cases from reviewed bibliographies in reports retrieved were also included. Data were extracted in a standardized form. A total of 24 publications with 41 patients who have ESRD were included. The mean age at the time of presentation with DMI was 44.2 years. Type 2 diabetes was present in 53.7% of patients while type 1 in 41.5%. In this cohort, 60.1% were receiving hemodialysis, 21% on peritoneal dialysis and 12.2% had kidney transplantation. The proximal lower limb musculature was the most commonly affected site. Muscle pain and swelling were the most frequent manifestation on presentation. Magnetic resonance imaging (MRI) provided the most specific findings for DMI. Laboratory investigation findings are usually non-specific. Non-surgical therapy is usually used in the management of DMI. Short-term prognosis of DMI is good but recurrence occurred in 43.9%. DMI is an uncommon complication in patients with diabetes mellitus, including those affected by ESRD. In comparison with unselected patients with DMI, the characteristics and outcomes of those with ESRD are generally similar. DMI may also occur in

kidney transplant recipients, including pancreas-kidney transplantation. MRI is the most useful diagnostic investigation. Non-surgical treatment involving analgesia, optimization of glycemic control and initial bed rest can help to improve recovery rate. However, recurrence of DMI is relatively frequent.

Key words: Diabetic muscle infarction; Dialysis; End-stage renal disease; Kidney transplant; Renal replacement therapy

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Core tip: Diabetic muscle infarction (DMI) is an uncommon complication in patients with end-stage renal disease, including kidney transplant recipients. Early recognition of DMI is vital to initiation of prompt treatment. Magnetic resonance imaging is the investigation of choice for diagnosing DMI. Non-surgical treatment involving analgesia, optimization of glycemic control and initial bed rest appears to improve recovery rate. However, recurrence of DMI is relatively common.

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INTRODUCTION

Diabetic muscle infarction (DMI) refers to spontaneous ischemic necrosis of skeletal muscle among people with diabetes mellitus, unrelated to atheroembolism or occlusion of major arteries. DMI is also referred to as spontaneous diabetic myonecrosis. Angervall and Sterner initially described DMI in 1965 as "tumoriform focal muscular degeneration"^[1]. Although diabetes mellitus is a relatively common condition, DMI is a comparatively infrequent complication.

Diabetic nephropathy or other forms of chronic kidney disease are commonly seen in patients with DMI, affecting as many as 71%^[2]. Of the diabetes-related microvascular complications, diabetic nephropathy is the most common one to be present among patients with DMI. Therefore, a proportion of DMI occurs in patients with end-stage renal disease (ESRD). However, little is known about the manifestation, diagnosis, management and outcomes of DMI in patients with ESRD.

This scoping review seeks to answer several questions about DMI regarding patient characteristics, clinical features, diagnostic evaluation, management and outcomes when this condition occurs in people with ESRD.

SEARCH STRATEGY AND STUDY IDENTIFICATION

The literature search was performed in July 2017 in four electronic databases. We searched MEDLINE/PubMed, CINAHL, SCOPUS and EMBASE with key words: ("Diabetic muscle infarction" OR "Diabetic myonecrosis"), AND ("Chronic kidney disease" OR "Renal impairment" OR "Dialysis" OR "Renal replacement therapy" OR "Renal transplant"). The search was done on publications between January 1980 and June 2017. Searches were limited to English language publications. Relevant references from articles identified from the search were also reviewed for comprehensive identification.

SELECTION OF STUDIES

This scoping review included cohort studies, case series and case reports with DMI in the setting of ESRD. Inclusion criteria include patients with ESRD requiring renal replacement therapy (RRT), clinical presentation of cases were adequately described, sufficient data on investigations, treatment and clinical outcome. The authors excluded studies that had not sufficiently eliminated trauma, inflammatory myositis, infection, neoplasm and deep vein thrombosis as possible aetiologies.

The selection process consisted of three stages. In the first stage, two reviewers (KK and TY) independently screened articles based on the title. In the case of doubt or disagreement, the articles were included in the abstract review stage. In the second stage, the abstracts of all articles are selected from the initial stage were reviewed and assessed by two reviewers (KK and TY). Any disagreement was resolved by discussion between the two reviewers. In the final stage, the remaining articles were fully reviewed using pre-determined inclusion criteria and assessed by two independent reviewers (KK and TY). Any disagreement between reviewers was solved by the two reviewers.

DATA EXTRACTION

A standardized template was used to extract data from the included studies using the following heading: general information such as title of article, main author and publication year, patient or cohort characteristics, type of diabetes mellitus, type of RRT (hemodialysis, peritoneal dialysis and kidney transplant), microvascular complications (retinopathy and peripheral neuropathy), macrovascular complications (coronary artery disease, ischaemic strokes and peripheral arterial disease) and pattern of muscle involvement. Laboratory and radiological investigation findings during initial evaluation or during recurrence were also obtained. Clinical outcomes to be considered in this review include time

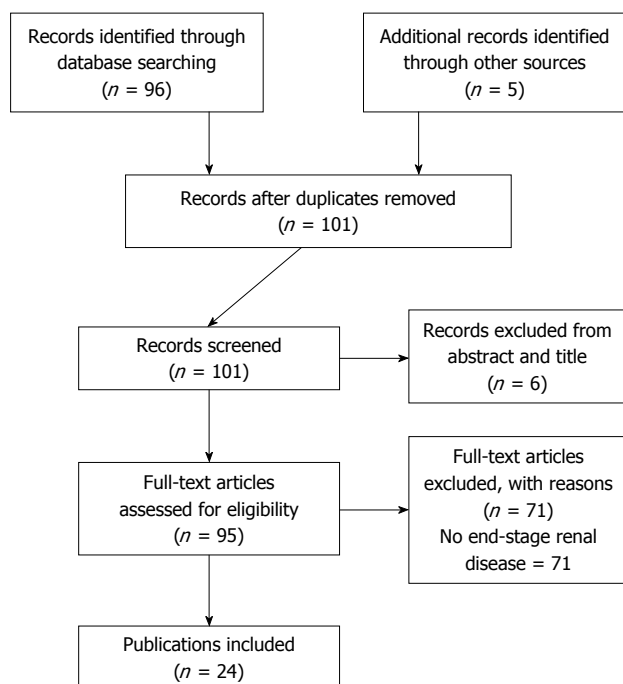


Figure 1 Flow diagram of the review and selection of publications.

to recovery from DMI, recurrence rate and death during the follow-up period.

We identified 101 articles from our initial search. Six were excluded because these were published in non-English languages (Figure 1). Twenty-four publications containing 41 cases with DMI in the setting of ESRD were eligible to be included in this review^[3-26].

PATIENT CHARACTERISTICS

Of the 41 patients with DMI in the setting of ESRD, 22 occurred in women (53.7%). The mean age of presentation of all cases was 44.2 years (range: 19.0-67.0 years). Of these, 17 (41.5%) had type 1 diabetes, 22 (53.7%) had type 2 diabetes and 2 (4.9%) had cystic fibrosis related diabetes (Table 1). One report did not provide information about the type of diabetes that the patient had. The two patients with cystic fibrosis also had lung transplantation. The mean duration of diabetes mellitus at the time of DMI diagnosis was 17.3 (range: 10.0-30.0) years for type 1 diabetes and 15.7 (range: 3.0-24.0) years for type 2 diabetes. Glycohemoglobin (HbA_{1c}) values at the time of DMI diagnosis were reported in 18 cases and the average value was 7.2% (range: 5.0%-12.4%). Eleven out of 18 (61.1%) had HbA_{1c} above 7.0%.

All patients in this cohort had diabetic nephropathy. The RRT modalities included hemodialysis (25 patients; 59%), peritoneal dialysis (9; 22%), combined kidney-pancreas transplantation (4; 16%), kidney transplantation (1; 3%). For eight patients in whom information was provided, the mean duration of receiving dialysis was 2.1 years (range: 2 mo to 6 years). Twenty-four patients had concurrent retinopathy (58.5%) and 23

had peripheral neuropathy (56.1%). In terms of macrovascular diseases, six were reported to have coronary artery disease and three had peripheral arterial disease.

CLINICAL FEATURES

The most frequently affected muscle groups were in the lower limbs (36; 87.8%), in comparison with the upper limbs which were reported only in five cases^[11,22]. In the lower limb, DMI more commonly affected the proximal leg (24/36; 66.7% of those with lower limb involvement) than distal leg, *i.e.*, below knee (6/36; 16.7%). Six patients (16.7%) had both proximal and distal leg muscles involved. Most had unilateral (80.5%) involvement on initial presentation, while eight cases had bilateral involvement. Sixteen (39.0%) involved multiple muscle groups on initial presentation.

The most common clinical presentation of DMI was abrupt onset of pain in the affected muscle group (100%), accompanied by local swelling (97.6%). Fever was reported in six patients (14.6%). In the current analysis, compartment syndrome has been reported in one case^[23].

INVESTIGATIONS

Results of laboratory investigations are usually non-specific for DMI. White cell count (WCC) values were reported in 35 cases but only 31.4% were elevated (Table 2). One patient was found to be leucopenic^[15]. Inflammatory markers are commonly increased in DMI. C-reactive protein (CRP) was reported in 11 cases and was elevated in nine (81.8%) (Table 2). The mean CRP in these cases was 153.6 mg/L (range: 5.0-361.0 mg/L). Erythrocyte sedimentation rate (ESR) in nine cases and was increased in eight (88.9%) (Table 2). The mean ESR was 82.9 mm/h (range: 3.0-137.0 mm/h).

Creatine kinase (CK) values were reported in 34 cases but was elevated in 50.0% (considered as greater than 150.0 IU/L for females or 250.0 IU/L for males) (Table 2). When measured on initial presentation, the mean absolute CK was 292.9 IU/L (range: 23.0-1066.0 IU/L).

Magnetic resonance imaging (MRI) was performed in most patients (35/41; 85.4%). The common abnormalities observed on MRI is muscle enlargement (33/35; 94.2%) and muscle oedema with hyperintense T2 signal (30/35; 85.7%) (Table 2). Other findings include subcutaneous edema (17/35; 48.6%).

Ultrasound was performed in 28 (68.3%) patients but all were done to exclude deep vein thrombosis. Subcutaneous or muscle edema on ultrasound was reported in six cases (21.4%). Computed tomography (CT) was performed less frequently among cases included in this review (12/41; 29.3%).

Muscle biopsy was performed in 16 cases (39.0%). Biopsies usually demonstrate muscle necrosis (100%) and inflammatory cell infiltration (87.5%) (Table 2). In some cases, muscle fibre regeneration (43.8%) was

Table 1 Characteristics of patients with diabetic muscle infarction in the setting of end-stage kidney disease and a cohort from Horton *et al*'s systematic review

	Current review (<i>n</i> = 41)	Findings from Horton <i>et al</i> ²¹ (<i>n</i> = 126)
Mean age (range), yr	44.2 (19.0-67.0)	44.6 (20.0-67.0)
Female/male, <i>n</i> (%)	22 (53.7)/19 (46.3)	68 (54.0)/58 (46.0)
Type of diabetes		
Type 1, <i>n</i> (%)	17 (41.5)	54/108 (50.0)
Type 2, <i>n</i> (%)	22 (53.7)	45/108 (41.7)
Cystic-fibrosis-related, <i>n</i> (%)	2 (4.9)	2/108 (1.9)
Concurrent diabetes-related complications		
Retinopathy, <i>n</i> (%)	24 (58.5)	83 (65.8)
Neuropathy, <i>n</i> (%)	22 (56.1)	-
Coronary artery disease, <i>n</i> (%)	6 (14.6)	-
Peripheral arterial disease, <i>n</i> (%)	3 (7.3)	-
Type of renal replacement therapy		
Hemodialysis, <i>n</i> (%)	25 (60.1)	-
Peritoneal dialysis, <i>n</i> (%)	9 (21.9)	-
Pancreas-kidney transplantation, <i>n</i> (%)	4 (9.8)	-
Kidney transplantation only, <i>n</i> (%)	1 (2.4)	-
Pattern of muscle involvement		
Lower limbs	36 (66.7)	-
Proximal lower limbs (above knee)	24 (58.5)	90 (71.2)
Distal lower limbs (below knee)	6 (14.6)	19 (15.3)
Both proximal and distal lower limbs	6 (14.6)	-
Upper limbs	5 (12.2)	7 (5.4)
Unilateral limb	33 (80.5)	-

Table 2 Investigation results in patients with diabetic muscle infarction in the setting of end-stage renal disease and a cohort from Horton *et al*'s systematic review

	Present review		Findings from Horton <i>et al</i> ²¹
	Number of patients who had the investigation	<i>n</i> (%)	<i>n/n</i> (%)
Leucocytosis (WCC > 11.0 × 10 ⁹ cells/L)	35	11 (31.4)	48/112 (42.5)
Leucopenia (WCC < 4.0 × 10 ⁹ cells/L)	35	1 (2.9)	-
Elevated CRP (> 10 mg/L)	11	9 (81.8)	27/30 (90.0)
Elevated ESR (> 20 mm/h)	8	9 (88.9)	50/60 (83.3)
Elevated creatine kinase (> 150 IU/L for females; > 250 IU/L for males)	34	17 (50.0)	31/98 (31.6)
HbA _{1c} > 7.0%, <i>n</i> (%)	18	11 (61.1)	-
MRI findings		35 (85.4)	
Muscle enlargement	35	33 (94.2)	-
Muscle edema	35	30 (85.7)	76.8
Subcutaneous edema	35	17 (43.6)	-
Muscle biopsy findings		16 (39.0)	
Muscle necrosis	16	16 (100)	-
Inflammatory cell infiltration	16	14 (87.5)	-
Muscle fibre regeneration	16	7 (43.8)	-

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MRI: Magnetic resonance imaging; WCC: White cell count.

also present.

MANAGEMENT

Treatment details were provided in 36 cases. Most patients (31/36; 86%) were managed with analgesia. Four patients received aspirin therapy. There was no clear description in most cases as to whether patients rested in bed or received physiotherapy. Five patients (13.8%) required surgical intervention, which involved debridement of the affected muscle.

In a small number of patients, intensification of glycaemic control (four patients) and dialysis (one patient)

were reported. Seven patients received other forms of treatment which included antibiotics, prednisolone and erythropoietin therapy. However, the effectiveness of these treatments could not be ascertained in this review due to the limited numbers.

Outcomes

As the management approaches to DMI vary considerably in between patients, the efficacy of each treatment modality or the comparisons of outcomes could not be evaluated in this small sample size. In 15 patients, the time interval between diagnosis and resolution of the initial presentation of DMI was 1.4 mo

(range: 2 wk to 4 mo).

Recurrent muscle infarctions were reported in 43.9% of cases. None of the pancreas-kidney transplant recipients experienced any recurrence of DMI. Of those with recurrence of DMI, the mean time interval between the initial episode and the first recurrence was 5.3 mo (range: one week to 18 mo). Most of the recurrences in this case series occurred in a different muscle group to the initial episode (9/11; 81.8%).

In the cases reviewed, seven patients died during the follow-up period after developing DMI. Five of these patients were receiving haemodialysis and two were on peritoneal dialysis. No death was reported among kidney transplant recipients with DMI.

DISCUSSION

DMI is a rare disorder encountered in patients with longstanding diabetes mellitus and end-organ complications. Among patients with ESRD, the manifestation of DMI, investigation findings, management approach and rate of recurrence are similar to the other patients without ESRD who develop DMI. However, this study was not designed to estimate the incidence of DMI among patients with ESRD.

In a review by Trujillo-Santos *et al.*^[27] of 166 episodes of DMI in 115 patients, the mean age at the time of presentation was 42.6 years. The mean duration between diagnosis of diabetes mellitus and first episode of DMI was 14.4 years. In the present review, those with DMI in the setting of ESRD also have a similar age at the time of presentation and duration of diagnosis with diabetes mellitus. As this was a review of case report and series, it is not possible to determine if there is any difference in incidence of DMI between type 1 and type 2 diabetes. Similarly, any difference in incidence between patients who receive hemodialysis and peritoneal dialysis cannot be established in this review. Nonetheless, this review indicates that DMI can occur in patients after kidney transplantations including combined pancreas and kidney transplantations. Unsurprisingly, most patients have other concurrent diabetes-related microvascular complications such as retinopathy and peripheral neuropathy. In relation to patient characteristics, the current cohort of patients with ESRD and DMI was relatively similar to an unselected group of patients with DMI^[2].

There is a propensity for DMI to occur among patients with longstanding diabetes mellitus whose glycaemic control has deteriorated over time. More than 60% of ESRD patients who develop DMI have HbA_{1c} of greater than 7.0%, which indicated inadequate glycaemic control. DMI has been reported in a number of cases with poor glycaemic control^[28]. The pathophysiology for DMI is still unknown but several hypotheses have been suggested. Atherosclerotic changes, diabetes-related microangiopathy, vasculitis with associated thrombosis, and ischemia-reperfusion injury have been postulated as possible mechanism for DMI^[29]. The thromboembolic mechanism is thought to involve endothelial damage

resulting in tissue ischemia which leads to muscle injury and ischaemic necrosis. Reperfusion of ischaemic muscles lead to increase in oxygen radicals and reduced nitric oxide, which in turn releases inflammatory mediators. Alterations in the coagulation-fibrinolysis system resulting in damage of vascular endothelium and hypercoagulability have also been suggested as part of the pathophysiology of DMI^[30].

The diagnosis of DMI remains challenging and can lead to underdiagnosis^[31]. At present, the diagnosis of DMI involves the combination of clinical assessment, MRI and muscle biopsy with atypical presentations. DMI is characterized by localized muscular pain, swelling and tenderness and there is a more frequent involvement of the lower limb musculature, especially the thigh. Rare cases of upper limb muscle involvement have been reported^[11,22]. The reason for this predilection for lower limb muscles is uncertain.

Although MRI findings are not pathognomonic for DMI, this modality is still the most sensitive and specific for diagnosis of this condition^[2]. Characteristic features on MRI include muscle enlargement, oedema within affected muscles, subcutaneous and interfascial oedema^[32]. On MRI examination, the differential diagnoses include intramuscular abscess, inflammatory myositis and necrotising fasciitis^[27]. Sometimes it can be difficult to distinguish these entities and muscle biopsy may be required. Other imaging modalities such as ultrasound or CT scans may assist in excluding other disorders but may not enable the correct diagnosis of DMI. In patients with ESRD, calciphylaxis or calcific uremic arteriopathy (CUA) also needs to be considered in the differential diagnosis. CUA is characterized by vascular and other soft tissue calcification, intimal hypertrophy, and thrombosis of small vessels that results in painful tissue necrosis, including skeletal muscle^[33]. The ischaemic injury in DMI is more confined to the muscle whereas in CUA, cutaneous and other soft tissues can be affected. A histopathological feature of CUA will often reveal extensive calcification, microthrombosis and endovascular fibrosis of small subcutaneous arteries leading to cutaneous ischemia whereas the calcification is not a prominent feature of DMI^[33].

Muscle biopsy can lead to a conclusive diagnosis but this is not currently recommended because of the risk from procedure-related complications^[34]. It can be used as a diagnostic tool in atypical presentations of DMI. Histopathological changes in DMI can vary depending on the timing of biopsy. In general, DMI presents as a pale nonhemorrhagic muscle. Initially, light microscopy would usually show muscle necrosis and phagocytosis of necrotic muscle fibres. At a later stage, the necrotic muscles are replaced by fibrous tissue, lymphocyte infiltration and muscle regeneration.

Blood investigations are generally non-specific for DMI. Surprisingly, a rise in CK has only been reported in half of the patients with DMI and ESRD. It is possible that the lack of rise in CK may be related to the delay in some patients seeking attention and measurement is

performed after this marker has peaked. This is relatively consistent with other systematic review of unselected patients with DMI. CRP and ESR were commonly elevated in DMI but these markers were not specific for this condition.

Early recognition of DMI is important for prompt initiation of treatment. Among patients with DMI and ESRD, supportive care consisting of analgesia was the main management approach. Generally, patients with DMI also receive intensive glycaemic control. Some clinicians have recommended avoiding physical therapy during the acute phase of DMI because it can prolong recovery but others have not observed this^[4,35]. Surgical intervention is required only in selected cases but this is not first-line option because of association with a more prolonged recovery^[14]. Other treatment modalities such as glucocorticoid, antibiotics and erythropoietin have been tried but their efficacy in DMI is uncertain.

The short-term prognosis of DMI is good and most patients recover within 6 mo but recurrence is frequent among patients with ESRD. Almost 50% will experience recurrence of DMI, mostly in another muscle group, within 6 mo after the initial episode. In comparison to unselected patients with DMI, the recurrence rate was reported at 29.2%^[2]. It was interesting to observe that no recurrence has been reported among transplant recipients. Further research is needed to confirm this observation. The long-term survival of patients with DMI can be variable. Death within a year by an episode of DMI are often related to other end-organ complications present in these patients.

The present review is limited by the use of case reports or series with the largest one having four patients. Not all patients had the same type of investigations for DMI. There are also limited reports about functional impairment experienced by patients during episodes of DMI. Furthermore, follow-up of patients in the included reports varied considerably.

More research is needed to better understand the pathogenesis of DMI, strategies for effective treatment and prevention of recurrence. More specifically, in the setting of ESRD and RRT, more investigation is needed to ascertain if adequacy of the RRT may influence outcomes. It will also be useful to better understand the natural history of DMI among patients who have had renal transplantation or those who are candidates for transplantation.

CONCLUSION

DMI is an uncommon complication of diabetes mellitus that can also affect patients with ESRD who are receiving dialysis or recipients of kidney transplantation. Clinical findings which supported by MRI examination is currently the best approach to confirm the diagnosis of DMI. Muscle biopsy is not recommended but may be required in atypical presentations. The best management approach for DMI is currently unclear and present practice is still largely based on expert opinion because

of limited evidence. Nonetheless, nonsurgical treatment appears to be a better option than surgical intervention. The short-term prognosis of DMI is good but recurrence is frequent.

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Basic Study

Genetic defects in ciliary genes in autosomal dominant polycystic kidney disease

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Abstract**AIM**

To evaluate the genetic defects of ciliary genes causing the loss of primary cilium in autosomal dominant polycystic kidney disease (ADPKD).

METHODS

We analyzed 191 structural and functional genes of the primary cilium using next-generation sequencing analysis. We analyzed the kidney samples, which were obtained from 7 patients with ADPKD who underwent nephrectomy. Each sample contained polycystic kidney tissue and matched normal kidney tissue.

RESULTS

In our study, we identified genetic defects in the 5 to 15 genes in each ADPKD sample. The most frequently identified defects were found in genes encoding centrosomal proteins (*PCM1*, *ODF2*, *HTT* and *CEP89*) and kinesin family member 19 (*KIF19*), which are important for ciliogenesis. In addition, pathogenic mutations in the *PCM1* and *KIF19* genes were found

in all ADPKD samples. Interestingly, mutations in the genes encoding the intraflagellar transport proteins, which are the basis of animal models of ADPKD, were only rarely detected.

CONCLUSION

The results of our study revealed the actual state of structural ciliary genes in human ADPKD tissues and provided valuable indications for further research.

Key words: Polycystic kidney disease; Primary cilium; Ciliary genes; Next-generation sequencing; Genetic variants

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Core tip: Many studies have confirmed that the loss of primary cilia promotes renal cyst formation in autosomal dominant polycystic kidney disease (ADPKD). However, these studies are based on mouse models by the inactivation of various ciliary genes, and the actual status of these genes in human ADPKD tissues is unknown. In our study, we analyzed genetic defects in ciliary genes in the human polycystic kidney tissues and matched normal kidney tissues by next-generation sequencing. We found that the loss of the primary cilia in the human ADPKD tissues may be predominantly caused by defects of centrosomal proteins and KIF19 protein.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is a multisystem disorder characterized by the formation of cysts in the kidneys and other organs. ADPKD affects more than 12.5 million people worldwide^[1]. Approximately 50% of patients with ADPKD have end-stage renal disease (ESRD) by 60 years of age. Dialysis and kidney transplantation are the only treatment options for patients with ESRD^[2]. The reason for the absence of targeted treatment is insufficient understanding of the molecular mechanism of cystogenesis.

The molecular nature of the disease includes germline mutation of either the *PKD1* (polycystin-1), *PKD2* (polycystin-2) or *GANAB* gene^[3,4]. Although the germline mutation is present in every cell of the body, formation of cysts is limited to a small number of nephrons. This means that the germline mutation is not in itself sufficient to produce cysts; a second somatic event is also required^[5]. More evidence has accumulated in recent years showing that the primary cilium plays an

important role in the development of ADPKD.

The primary cilium is a signaling organelle that extends from the surface of the plasma membrane of most mammalian cells. Assembly of cilia depends on cell cycle progression, because the centrioles regulating the cell cycle are essential components in the formation of the basal body of the cilia^[6]. The maintenance and elongation of cilia is ensured by a process called intraflagellar transport (IFT). In this process, protein complexes known as IFT trains carry cargo along tracks that run along the length of the cilia. Different motor proteins power the IFT trains in different directions. Kinesin moves IFT trains from the base to the tip, while dynein moves them back in the opposite direction^[7].

Many studies have shown that the loss of primary cilia promotes renal cyst formation *in vivo*^[8,9]. However, the epithelial cells of renal cysts are characterized not only by an absence of cilia but also by excessively long cilia^[10-12]. Recent studies have confirmed that kidney cysts occurred following inactivation of polycystins in otherwise intact cilia or following complete removal of cilia by inactivation of IFT proteins. In addition, a relationship was shown between cilia and polycystins that regulates the severity of ADPKD. According this model, the progression of cysts is regulated by the duration of the interval time between the initial loss of polycystins and the subsequent ablation of cilia. These studies identified a new mechanism of cystogenesis based on the evidence that the loss of renal cilia inhibits cyst growth if the cilia are disrupted at the same time as the polycystins^[13,14]. In addition, it was shown that defective primary cilia or the inactivation of ciliary genes induces aberrant signaling pathways associated with proliferation, differentiation and development in various PKD mouse models^[13-16]. The structural deformity or absence of primary cilia is thus a key driving force in the development of ADPKD.

The results of these studies were achieved in mouse models by targeted inactivation of various ciliary genes, especially genes encoding IFT proteins. However, the actual mutation profile of ciliary genes in human ADPKD tissues is unknown. The aim of our study was to identify the mutation state of genes encoding the structural ciliary components in tissues from patients with ADPKD obtained by nephrectomy through targeted next-generation sequencing analysis.

MATERIALS AND METHODS

Sample collection

In our study, we obtained archived FFPE samples of polycystic kidney tissues and matched normal controls from 7 patients with ADPKD (four women and three men) who had undergone radical nephrectomy. Four patients had nephrectomy for the occurrence of complications associated with the enlarged kidney involved the recurrent infection of the urinary tract, arterial hypertension, and chronic pain. Three patients required nephrectomy to provide the space for the

kidney allograft. The FFPE samples were subjected to histopathological examination. The samples containing at least 50% epithelial cysts were considered suitable for genetic analysis. The genetic testing of the *PKD1* and *PKD2* genes had been carried out previously in our laboratory. The mutation in the *PKD1* gene was confirmed for all of the patients. Our study was approved by an ethics committee and informed consent was provided by all patients at the inception of the study.

DNA extraction and sample quality control

DNA was extracted from the FFPE tissues using the commercially available blackPREP FFPE DNA kit (Analytik Jena, Germany) and from peripheral blood using the QIAamp DNA Mini kit (Qiagen, Valencia, California, United States) according to the manufacturer's instructions. The extracted DNA specimens from FFPE were further quantified using the Qubit dsDNA HS assay kit (Life Technologies/Fisher Scientific, United States) and the Agilent NGS FFPE QC Kit according to the manufacturer's instructions.

Design of the gene panel

Candidate genes were selected using a gene list in the SysCilia Gold Standard (SCGC) Version 1 database^[17]. A panel of 191 genes was designed using the web-based tool SureDesign (Agilent Technologies, United States). The regions of interest included coding regions with 10 base pair (bp) upstream and 10 bp downstream for capture of splicing donor and acceptor sites. Overall, we analyzed genes encoding the proteins of basal bodies (31 genes), centrioles (25 genes), centrosomes (22 genes), IFT (24 genes), transition zone (17 genes), axoneme (9 genes), ciliary membrane (8), cilioplasm (5 genes), ciliary proteins located in the nucleus (5 genes), plasma membrane proteins (5 genes), ciliary tip (4 genes), regulatory ciliary proteins in the Trans-Golgi network (3 genes), ciliary root (2 genes) and ciliary proteins with non-specific localization (31 genes).

Library preparation and variant calling

Sequencing libraries were prepared using the Agilent SureSelect^{XT} Custom 0.5 Mb up to 2.9 Mb according to the manufacturer's instructions. The sequencing analyses were performed on the HiSeq 2500 sequencing system (Illumina, United States). Data were analyzed using a software package that was commercially available - NextGENeTM (SoftGenetics, United States). Only variants with a minimum of 50-fold coverage for at least 80% of the targeted bases were included into analysis. Variants were marked as potential errors if they exhibited strong strand bias (< 0.10), low depth of coverage (< 10), low-quality score (< 30) or low average quality (< 2.0). The functional analysis of variants was performed by using Geneticist Assistant software (SoftGenetics, United States). This software used combined computational prediction methods (SIFT, Polyphen2, LRT, MutationTaster, ANNOVAR, FATHMM, CADD and Mutation Assessor) to calculate

the mean pathogenicity score of identified variants. The pathogenic variants detected by NGS were verified by using the Sanger sequencing method. The germline origin of the pathogenic variants was excluded by analysis of DNA extracted from peripheral blood.

RESULTS

Analysis of sequencing data

In our study, we achieved a high quality of sequenced data. The mean total reads generated per sample was approximately 5000000, with more than 98% of reads aligned with the reference genome and more than 80% of reads mapping to targeted regions. In addition, 93% of the targeted regions were covered by more than 30 reads. Overall, 1440 variants were identified in 7 ADPKD samples. These variants represent disease-specific genetic changes without occurrence in matched normal kidney tissues. Based on the results of the functional analysis, 908 variants were classifying as benign. These variants were reported in known databases of somatic mutations and single nucleotide polymorphisms. Of these, 732 variants were classified as clearly benign. The remaining 176 variants were of unknown significance, but with high value of minor allele frequency, on the basis of which they were determined as polymorphisms.

The other 532 identified variants represented novel genetic changes without record in databases. The results of the functional prediction determined 52 variants as clearly pathogenic. For the other 480 variants, benign status was clearly confirmed in all predictive software. Identified pathogenic variants were present in 39 genes encoding the various structural components of the primary cilium. An overview of these genes is shown in Table 1. The most common pathogenic variants affected the proteins of basal bodies (10 genes), centrosomes (7 genes), centrioles (6 genes) and ciliary proteins with non-specific localization (5 genes). The proteins in other parts of the cilium were rarely mutated.

Analysis of disease-related pathogenic variants

The pathogenic variants were further analyzed based on their occurrence in individual ADPKD samples. The mutation profile of each analyzed sample was unique. Each sample had identified pathogenic variants in 5 to 15 genes, which varied from each other. However, the pathogenic variants in 5 genes were present in the vast majority of the ADPKD samples. Of these, 4 included genes encoded the centrosomal protein HTT (Huntingtin), the subdistal appendage of centriole ODF2 (outer dense fiber protein 2), the distal appendage of centriole CEP89 (centrosomal protein of 89 kDa) and a component of centriolar satellite PCM1 (pericentriolar material 1). The most affected gene was *PCM1*, in which pathogenic variants were present in all samples of ADPKD. The pathogenic variants in the *HTT*, *ODF2* and *CEP89* genes were identified in 5 of the 7 ADPKD samples. Another gene whose pathogenic variants affected all of the ADPKD samples was the *KIF19* (Kinesin

Table 1 Summary of genes affected by pathogenic variants and localization of their coding proteins

Localization	Genes affected by pathogenic variants
Basal body	<i>ODF2, AZI1, BBS12, BBS2, C21orf2, FLNA, LZTFL1, OFD1, PDYD7, TRAF3IP1</i>
Centrosome	<i>CEP89, HTT, CEP135, CEP290, MDM1, NINL, TRAPPC9</i>
Centriole	<i>PCM1, PIBF1, CBY1, FBF1, NEK1, SCLT1</i>
Unspecific localization	<i>STX3, PKD1L1, TTLL3, WDR60, CCDC35</i>
Ciliary tip	<i>KIF19, GLIS2</i>
Intraflagellar transport	<i>IFT172, IFT80</i>
Transition zone	<i>NUP37, NUP62</i>
Regulatory proteins	<i>RAB11FIP3, TRIP11</i>
Ciliary membrane	<i>CRB3</i>
Ciliary root	<i>CROCC</i>
Axoneme	<i>TMEM67</i>

Table 2 Description of the most common pathogenic variants identified in autosomal dominant polycystic kidney disease samples

Gene	DNA-level	Protein-level	Exon	Number of samples with mutation
<i>PCM1</i>	c.3423dupC	p.Ser1142Glnfs*7	22	7
<i>KIF19</i>	c.49dupC	p.Arg17Profs*20	2	7
<i>CEP89</i>	c.412_413delAA	p.Lys138glyfs*16	4	5
<i>HTT</i>	c.108_110delGCA	p.Gln2643del	1	5
<i>ODF2</i>	c.1118delT	p.Leu373Tyrfs*80	10	5

Family Member 19) gene. This gene encodes a key regulator of ciliary length located on the very top of the primary cilia in the ciliary tip included in anterograde IFT. In addition, we identified only one type of the pathogenic variant in these 5 genes (Table 2). In most cases, it was a frameshift mutation resulting in a premature stop codon and truncation of protein. According to the results of the predictive software, all detected variants negatively affected the function of the encoded proteins.

Interestingly, the pathogenic variants in genes encoding proteins of retrograde IFT and other structural ciliary genes were detected in only one of the ADPKD samples. The coverage of protein-coding regions and the flanking regions of all analyzed IFT genes showed high values in each of the ADPKD samples.

DISCUSSION

In the present study, we identified genetic changes in the structural ciliary genes in human ADPKD tissues. The most frequently affected genes encoded the centriolar and centrosomal proteins *PCM1*, *ODF2*, *HTT* and *CEP89*, which are essential for ciliogenesis. Recent studies have confirmed that the loss of these proteins specifically blocks ciliogenesis at the step of centriole-to-membrane docking. Undocked centrioles lose the signs of cilia assembly, even when they were previously under the influence of signals that support ciliogenesis^[18,19]. Thus, disruption of the function of these genes may be the cause of cilia loss in the epithelial cells of renal cysts. The most commonly affected gene in this group was *PCM1*, which is also essential for the correct localization of several centrosomal proteins and for anchoring microtubules to the centrosome. It is generally known that centrosome dysfunction is linked to aneuploidy and chromosomal instability^[20]. Many studies have

shown increased incidence of chromosome imbalances and abnormal chromosome segregation in ADPKD tissues^[21,22]. Loss of function of the *PCM1* gene may therefore be a key factor in these processes.

Another pathogenic variant, which was present in all of the analyzed ADPKD samples, was identified in the *KIF19* gene. This gene encodes a member of the kinesin superfamily protein included in anterograde IFT, which is localized to ciliary tips. The results of a recent study have provided evidence that *KIF19* is a key determinant of the optimal length of cilia. The length of cilia was abnormally extended by knockdown *Kif19* in a mouse model^[23]. Many studies have revealed that the change in the length of the primary cilium is an important trigger of various pathological processes in ADPKD^[24,25]. The epithelial cells of renal cysts usually show an absence or shortening of the primary cilium. However, stages of interstitial fibrosis and end-stage renal disease are associated with the elongation of the primary cilia^[26,27]. In our study, we analyzed the mutation profile in the nephrectomized ADPKD tissues withdrawn at the end stage of renal disease. Given that we identified the pathogenic variant of the *KIF19* gene in all analyzed ADPKD tissues, it may represent a significant event in the progression of the disease. However, these claims will require further analysis.

An interesting result of our study was the low frequency of mutations in the genes encoding IFT proteins. Kidney cysts arise in most mouse models following the disruption of cilia by targeted inactivation of genes encoding IFT components such as the heterotrimeric kinesin components *KIF3a* and the IFT proteins *IFT20* and *IFT88*. However, genetic changes in these genes were not present in any analyzed ADPKD sample. We confirmed the presence of the pathogenic variants in only two genes (*IFT172* and *IFT80*) of the total number

of analyzed IFT genes. In addition, the pathogenic variants in these genes were detected in only one ADPKD sample. The results of our study showed that the loss of the primary cilia in the human ADPKD tissues may be predominantly caused by defects of centrosomal proteins and KIF19 protein. However, this claim requires confirmation by functional analysis of the use of animal models. It is also necessary to verify the results by analyzing a larger number of samples.

In our study, we identified the simultaneous occurrence of genetic changes in various ciliary genes. Each ADPKD tissue had pathogenic variants in 5 to 15 genes. The occurrence of multiple structural defects of the primary cilium may be due to several factors. Firstly, we analyzed the tissues at an advanced stage of the disease, in which genetic changes could have been accumulated. However, disturbances of centrosomal proteins may also be the cause of the multiple defects in the ciliary structure. An interesting finding was the presence of only one pathogenic variant in each individual gene. To determine whether they are "hotspot" mutations representing secondary somatic events in the development of the disease will require further analysis.

The results of our study may be limited by the relatively small number of analyzed samples. The reason for this small number is the fact that the majority of ADPKD patients do not require native nephrectomy, and cystic kidneys are not generally biopsied for technical and ethical reasons. However, this is the first study examining the complex mutational status of the structural and functional ciliary genes in human ADPKD tissues.

In conclusion, our study revealed genetic defects of ciliary genes that can lead to loss of the primary cilium in human ADPKD tissues. In addition, we identified unique genetic findings associated with the disease, which may play a significant role in the pathogenesis of the disease. However, other functional analyses are necessary to confirm this hypothesis. The results of our work thus provided valuable indications for the direction of further research in the area of molecular pathogenesis of ADPKD.

ARTICLE HIGHLIGHTS

Research background

The primary cilia and polycystins play an important role in the regulating the severity of autosomal dominant polycystic kidney disease (ADPKD). While the loss of cilia or polycystins alone results in the development and progression of renal cysts, renal cilia involution reduces the progression of cyst growth induced by the inactivation of polycystins. The epithelial cells of renal cysts usually show various structural deformities of the primary cilium involve an absence, shortening or elongation. These structural changes can be caused by genetic defects of ciliary proteins. Mutation profile of ciliary genes in human ADPKD tissues is unknown. Revealing a genetic basis for ciliogenesis defects may identify causative factors of disease progression and the potential molecular targets for the development of new therapies of ADPKD.

Research motivation

Genetic defects of various ciliary genes whose inactivation leads to the development and progression of ADPKD have been identified in mouse models.

However, recent studies have confirmed that the animal models of ADPKD incompletely mimic the human disease. Therefore, it is important to detect genetic abnormalities that can affect ciliogenesis directly in ADPKD human tissues.

Research objectives

The main objectives of this study is to identify the genetic defects of ciliary genes causing the loss of primary cilium in ADPKD human tissues. The results of our study are important indicators for directing further analysis.

Research methods

In our study, we analyzed 191 structural and functional ciliary genes using next-generation sequencing analysis. The tissue samples used in this study were obtained from 7 patients with ADPKD who underwent nephrectomy. Each sample contained polycystic kidney tissue and matched normal kidney tissue. All analyzed samples were formalin-fixed and paraffin-embedded. The germline origin of the identified variants was excluded by analysis of DNA extracted from peripheral blood.

Research results

We identified unique of mutation profile in each of analyzed ADPKD samples, which was characterized by the presence of pathogenic variants in 5 to 15 ciliary genes. The most frequently identified defects were found in genes encoding centrosomal proteins and kinesin family member 19, which are important for ciliogenesis. In addition, pathogenic variants in the *PCM1* and *KIF19* genes were found in all ADPKD samples.

Research conclusions

Our study had found that the human ADPKD tissues are characterized by the presence of several genetically altered ciliary proteins that plays an important role in ciliogenesis. The structural and functional disturbance of the primary cilium can be induced by mutations of these proteins. An interesting finding of our study was that the mutations in genes encoding the proteins of intraflagellar transport (IFT) were rarely mutated. These genes are considered candidate genes related to ADPKD in mouse models. Centrosomal proteins and kinesin family member 19 are the most commonly mutated ciliary proteins in renal epithelial cells derived from human ADPKD cysts. Consistent with finding of recent studies, we can confirm that animal models not completely mimic the human disease. Mouse models induce polycystic kidney disease by genetic inactivation of one ciliary gene especially genes encoding IFT proteins. However, the genes encoding the proteins of IFT are rarely mutated in the human renal cystic cells. This study offered new insight into comprehensive mutation profile of ciliary genes in human ADPKD tissues. The results of our study suggested that the loss of the primary cilia in the human ADPKD tissues may be predominantly caused by defects of centrosomal proteins and kinesin family member 19. The defects of centrosomal proteins may be also the cause of chromosome imbalances, which are often present in human ADPKD tissues. The genetic defects of the *KIF19* gene may be cause of the primary cilium elongation, which is a characteristic feature of the end-stage renal disease. This is the first study used of archived formalin-fixed and paraffin embedded tissues (FFPE) of ADPKD in order to determine mutation profile of ciliary genes by next-generation sequencing methods. An interesting finding was the presence of only one somatic pathogenic variant in each individual ciliary gene. To determine whether they are "hotspot" mutations representing secondary somatic events in the development of the disease will require further analysis. Somatic mutations in genes encoding centrosomal proteins and KIF19 were present in all analyzed ADPKD samples. These mutations were present exclusively in polycystic kidney tissues and did not occur in matched control so we can assume their effect on cystogenesis. If our hypotheses will be confirmed by further studies, the identified ciliary proteins may represent potential molecular targets for the development of new treatments.

Research perspectives

Mutation profile of ciliary genes can be analyzed directly from archived FFPE tissues of ADPKD by NGS. The first step, it is necessary to verify the results on a larger number of samples and matched tissues controls. Further research should be focused on the functional analysis of identified genetic variants. Consequently, it will be necessary to determine whether the inactivation of

these genes will lead to a change in the structure of renal cilia and affect the development or progression of ADPKD.

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REVIEW

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Antineutrophil cytoplasmic antibody associated vasculitides with renal involvement: Open challenges in the remission induction therapy

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Abstract

Renal involvement with rapidly progressive glomerulonephritis is a common manifestation of antineutrophil cytoplasmic antibody (ANCA) associated vasculitides, which is characterized by end-stage renal disease and high mortality rates in untreated and/or late referral patients. The long-term renal survival has improved dramatically since the addition of cyclophosphamide (CYC) and recently of rituximab (RTX) in association with corticosteroids in the remission induction therapeutic regimens. However, renal prognosis remains unfavorable for many patients and the mortality rate is still significantly high. In this review, we analyze the open challenges to be addressed to optimize the induction remission therapy, principally in patients with advanced kidney failure. This concern the first-line therapy (CYC or RTX) based on different parameters (estimated glomerular filtration rate at baseline, new or relapsed disease, ANCA specificity, tissue injury, safety), the role of plasma exchange and the role of new therapies. Indeed, we discuss future perspectives in induction remission therapy by reporting recent advances in new targeted therapies with particular reference to avacopan, an orally administered selective C5a receptor inhibitor.

Key words: Rapidly progressive glomerulonephritis; Remission induction therapy; Antineutrophil cytoplasmic antibody associated vasculitides; Cyclophosphamide; Rituximab; Corticosteroids; Plasma exchange; Avacopan

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Core tip: Antineutrophil cytoplasmic antibody (ANCA) associated vasculitides with renal involvement, presents as Rapidly Progressive Glomerulonephritis are organ-threatening and potentially life-threatening diseases.

Although remission induction immunosuppressive regimens overall have been very successful in the treatment of these conditions, many questions remain unanswered. The still open challenges and questions concern: (1) The choice of the first-line therapy (cyclophosphamide versus rituximab) based on renal function at baseline, new versus relapsed disease, ANCA specificity, tissue injury and safety; (2) the role of plasma exchange in combination with steroid and non steroid agents; and (3) the advent of novel target therapies and strategies.

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INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) represent a heterogeneous group of autoimmune systemic necrotizing vasculitides that affect predominantly small vessels, with few or no immune deposits, and the appearance of circulating ANCA with specificity toward proteinase-3 (PR3) or myeloperoxidase (MPO). AAVs include granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA; previously known as Churg-Strauss syndrome) and organ-limited AAV, such as renal-limited vasculitis (RLV)^[1].

These autoimmune disorders can potentially affect any organ, but the kidney is often involved. Renal involvement ranges between 71% and 88% among patients with GPA and MPA^[2], whereas in EGPA it occurs only in up to 25% of cases^[3]. EGPA belongs to the spectrum of AAV, but is treated as a separate entity in most clinical trials because it exhibits different pathogenetic mechanisms, genetic associations and clinical manifestations. In particular, severe renal involvement is an uncommon finding in EGPA, and ANCA positivity is observed with much lower frequency than in GPA and MPA^[4]. Therefore, in this review, we will focus exclusively on GPA and MPA, the two clinical conditions with major renal involvement.

The pathologic term Pauci-immune Necrotizing Crescentic Glomerulonephritis (PiNCGN) is commonly used, along with the clinical term Rapidly Progressive Glomerulonephritis (RPGN), which refers to a condition characterized by a nephritic syndrome rapidly progressing to end-stage renal disease (ESRD). Therefore, all patients with proven active ANCA-associated glomerulonephritis require prompt immunosuppressive therapy.

Prior to the introduction of cyclophosphamide (CYC)-based regimens in the late 1970s, the 2-year survival rates were approximately 20%^[5]. Standard immunosuppression

with CYC and gradually tapered corticosteroids (CCS) for remission induction therapy have dramatically improved the prognosis of patients with generalized or severe AAV, with remission rates usually exceeding 90% and 5-year survival rates as high as 80%^[5]. However, this treatment is associated with significant toxicity, including enhanced risk of infection, myelosuppression, infertility, malignancy and cardiovascular disease^[6]. The possibility of partially reducing CYC toxicity by employing intravenous pulse regimens instead of daily oral CYC for remission induction therapy was assessed in the CYCLOPS trial^[7] and recently in the CORTAGE trial^[8]; the pulsed regimen minimized exposure and cumulative toxicity of the drug while maintaining a high efficacy of treatment (Table 1). However, long-term follow-up of patients in the CYCLOPS trial showed that a reduced dose of CYC was associated with a higher risk of relapse, primarily in patients with anti-PR3 ANCA^[9].

Consequently, there has been a growing impetus to look for a new, less toxic and more specific treatment for patients with generalized and severe disease. Two randomized controlled trials (RAVE and RITUXVAS), found that Rituximab (RTX), a B cell-depleting agent, is as effective as CYC for induction of remission in patients with newly diagnosed GPA and MPA^[10,11] (Table 1). The RAVE trial also demonstrated the superiority of RTX versus CYC in patients with relapsing disease^[10]. Nevertheless, in both trials, the short-term adverse event rate after RTX treatment was not lower compared to CYC.

Despite this advancement and the enrichment of our therapeutic armamentarium, the management of remission induction in patients with AAV and renal involvement continues to challenge nephrologists, as renal prognosis is still unfavorable and a significant proportion of patients (20%-25%) develop ESRD within a few years after diagnosis^[12].

In this review, we report and discuss the remaining open challenges and questions in the management of remission induction in AAVs with renal involvement. For this purpose, we have explicitly taken into consideration current randomized controlled trials as they represent the most potent scientific tool for evaluating medical treatments and the basis of current International guidelines for the treatment of AAVs.

The topics covered by the review are the following: (1) should all patients with AAV and renal involvement be primarily treated with RTX? (2) should there be differences in the therapeutic approach between patients with newly diagnosed AAV and those with relapsing disease? And if so, what is the relevance of the antigenic specificity of ANCA in guiding therapeutic choice? (3) should all patients with advanced renal involvement be treated with adjunctive plasma exchange (PLEX) sessions, as suggested by short-term results^[13]? Additionally, we present recent advances in novel targeted therapies and treatment strategies which may further help to modify the disease course, thereby

Table 1 Randomized controlled trials for induction of remission in antineutrophil cytoplasmic antibody associated vasculitides with renal involvement and cyclophosphamide-sparing regimens

Name of the Trial (number of patients)	Inclusion criteria	Treatment groups (drug dose)	Primary end points	Outcome
CYCLOPS ^[7] (149)	New diagnosis of GPA, MPA, or relapse with renal involvement, creatinine 150–500 $\mu\text{mol/L}$ (1.7–5.66 mg/dL)	Intravenous pulse CYC (15 mg/kg) <i>vs</i> Daily oral CYC (2 mg/kg)	Remission, Time to relapse	Pulse CYC not inferior to oral CYC Less leucopenia and trend towards more relapses with pulse CYC
CORTAGE ^[8] (104)	New diagnosis of MPA, GPA, EGPA, PAN and age > 65 yr	Rapid CCS tapering and reduced-dose intravenous pulse CYC (500 mg) <i>vs</i> Standard intravenous pulse CYC (500 mg/m^2)	Severe adverse events	Less severe adverse events with reduced immunosuppression, no difference in remission and relapse rates
RAVE ^[10] (197)	New or relapsing GPA or MPA creatinine $\leq$ 353.6 $\mu\text{mol/L}$ (4 mg/dL)	RTX (4 $\times$ 375 mg/m^2 infusions) <i>vs</i> Daily oral CYC	Complete remission and cessation of CCS at 6 mo	RTX not inferior to oral CYC, RTX better in patients with relapse than after first diagnosis
RITUXVAS ^[11] (44)	New diagnosis of AAV and severe renal involvement	RTX (4 $\times$ 375 mg/m^2 infusions) plus two intravenous pulses of CYC <i>vs</i> intravenous pulse CYC only	Sustained remission	RTX not inferior to pulse CYC

AAV: Antineutrophil cytoplasmic antibody associated vasculitides; CYC: Cyclophosphamide; RTX: Rituximab; CCS: Corticosteroids; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; PAN: Polyarteritis nodosa.

leading to increased renal outcomes and patient survival.

SHOULD ALL PATIENTS WITH AAV AND RENAL INVOLVEMENT BE PRIMARILY TREATED WITH RTX?

Rituximab, a chimeric monoclonal anti-CD20 antibody that induces depletion of all B-lineage cells with the exception of plasma cells and pre-B cells, which do not express surface CD20, was initially used in open label-trials among patients with refractory or relapsing GPA and MPA^[14–18]. The rationale for choosing RTX was based on the primary role performed by B cells in the pathogenesis of the disease and the pathogenicity of ANCA^[19]. The results showed that clinical remission was achieved in approximately 90% of cases within 6 mo^[14–18]. However, these preliminary studies did not include patients with severe renal involvement.

These data established the foundation for the design of two randomized controlled trials of RTX as first-line therapy in patients with severe GPA and MPA. In 2010, the results of RAVE and RITUXVAS heralded a new era in the management of the disease by demonstrating that RTX plus CCS is not inferior to CYC plus CCS for the induction of remission^[11,12]. However, renal function outcomes remain unclear, especially in patients with advanced renal failure at diagnosis, posing an ongoing challenge to the nephrologists who have to decide on the choice of induction therapy.

What the results of current studies are tell us about renal outcomes?

The RAVE trial enrolled 197 patients, of whose approximately half had significant renal disease defined by the presence of at least one of the following findings at baseline: (1) Active, biopsy-proven, pauci-immune glomerulonephritis; (2) red blood cell casts on urine

microscopy; and (3) increase in serum creatinine > 30% or decrease in creatinine clearance > 25%. Although in patients with significant renal disease, the baseline mean estimated glomerular filtration rate (e-GFR) was worse in the RTX group, a post hoc analysis of the trial showed that RTX was as effective as oral CYC in this subgroup^[20]. The proportion of patients who reached clinical remission at 6 mo were not significantly different between the two treatment groups and there was no difference in the proportion of patients with sustained remission at 18 mo^[20]. The latter finding is significant because in order to achieve remission at 3–6 mo, a maintenance regimen with azathioprine (AZA) was administered only to patients in the CYC group, whereas those in the RTX group received no further therapy^[10,20]. Mean e-GFR also increased similarly in both groups when patients were stratified by baseline e-GFR, even among those with e-GFR < 30 mL/min per 1.73 m^2 ^[20]. These data supported the use of RTX in patients with major renal involvement. However, patients with advanced renal failure (serum creatinine > 4 mg/dL) were excluded from RAVE because the clinical evidence was not sufficient to suggest their inclusion in an investigational treatment study at the launch of the trial^[10]. Therefore, the authors concluded that additional studies were required to fully understand the applicability of RTX among this subset of patients since its effectiveness in advanced renal failure had not been investigated in the RAVE trial^[20].

In contrast with the RAVE trial, RITUXVAS enrolled 44 patients newly diagnosed with GPA and MPA with severe renal disease (median e-GFR of 20 mL/min per 1.73 m^2), including also patients requiring dialysis at trial entry. The participants were randomized, in a 3:1 ratio to receive either RTX plus CCS without further maintenance treatment or intravenous CYC for 3–6 mo plus CCS followed by AZA in the maintenance phase. Patients in the RTX group also received two concomitant pulses of intravenous CYC and, for those

with progressive disease within the first 6 mo, a third dose of intravenous CYC was allowed. Furthermore, about a quarter of the patients in both groups received plasma exchange therapy before enrolment^[11]. At 12 and 24 mo, there was no difference in the proportion of sustained remission and ESRD between the RTX and CYC groups^[11,21].

Mansfield *et al.*^[22] investigated in a single centre prospective cohort study (CycLow-Vas) the long-term efficacy of another RTX-based CYC-sparing regimen for renal AAV. The protocol involved the use of RTX as a CYC sparing agent, enabling a cumulative dose of no > 3.5 g of CYC per patient. Twenty-three patients with severe renal involvement (median e-GFR of 24 mL/min per 1.73 m²) were treated. At 6 mo, all patients had achieved complete clinical remission and significant improvement in their renal function^[22]. Median e-GFR increased from 24 mL/min at presentation to 33 mL/min at 1 mo and 42 mL/min at 6 mo. However, in this study, as well as in the RITUXVAS trial it is very difficult to discern the specific contribution of CYC in the RTX-treated patients.

Basing on these data, and in the absence of knowledge regarding RTX as a sole remission induction agent in patients with severe renal involvement, two years after the publication of the RAVE and RITUXVAS trials the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommended the use of RTX plus CCS as an alternative initial treatment only in patients without severe renal disease or in whom CYC is contraindicated^[23] (Table 2).

Recently, two retrospective multi-center studies evaluated the efficacy of RTX plus CCS without concomitant CYC in patients with severe renal involvement (e-GFR < 20 mL/min per 1.73 m²)^[24,25]. Shah *et al.*^[24] evaluated 14 patients with a median e-GFR at diagnosis of 12 mL/min per 1.73 m² with 7 of them requiring dialysis at presentation. All patients achieved remission with a median time to remission of 55 d, and 5 of the 7 patients requiring dialysis recovered renal function and discontinued dialysis by 6-mo follow-up. Geetha *et al.*^[25] evaluated 37 patients with a median e-GFR at diagnosis of 13 mL/min per 1.73m² and 15 were dialysis dependent at presentation. Twelve patients received RTX and CCS and twenty five patients received CYC, RTX and CCS. Thirty two of 33 patients with a minimum follow up of 6 mo achieved disease remission at 6 mo and 10 of 15 patients requiring dialysis recovered renal function. There were no differences in outcome when groups were stratified according to use of concomitant CYC and no significant difference in the percentage of dialysis-dependent patients who achieved renal recovery between the two groups. However, these studies have limitations due to their retrospective design and small sample size. Further prospective randomized trials are needed to confirm these findings in this subset of patients.

In 2016, the 2009 EULAR recommendations for the management of ANCA-associated vasculitis were updated

by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA)^[26]. For remission induction of new-onset or major relapse of organ-threatening or life-threatening GPA and MPA, treatment with a combination of CCS and either CYC or RTX is now recommended. The grade of recommendation was A for both CYC and RTX, but with a different level of evidence 1A for CYC and 1B for RTX, confirming the need for further evidence in this field (Table 2).

The decision of which immunosuppressive regimen is most appropriate in paediatric patients with AAV and renal involvement is also controversial as current treatment regimens are extrapolated from adult studies and at present, there are very little data to allow the development of a paediatric-specific AAV guideline^[27]. A phase IIa study of intravenous RTX in paediatric participants with severe GPA or MPA is currently ongoing (NCT01750697)^[28] and will provide valuable information in this regard.

What is the impact of tubular lesions on therapeutic choice?

The evaluation of histological parameters along with clinical parameters could also be relevant in understanding the effects of treatment on histopathological processes and outcomes and in determining the choice of treatment. Among patients in the RITUXVAS trial, both B cell and T cell-mediated tubulointerstitial lesions were present in renal biopsies before treatment with RTX. However, only tubular intraepithelial T cells were predictive of impaired renal function during follow-up. However, the analysis of the immunostained sections from patients in the control arm who were treated with CYC, an immunosuppressive agent also directed towards T-cells, did not show any evidence that T cell tubulitis was related to renal outcome^[29]. The latter analysis was likely underpowered due to the small size of the control arm, which included only 10 biopsies, but it raised the question of whether T cell tubulitis represents a negative predictor for all treatments or whether its predictive significance is limited to RTX as a result of under-treatment of T cell-mediated lesions by B cell-depleting agents. Unfortunately, for practical and ethical reasons, it was not possible to perform repeat protocol renal biopsies and assess this question in patients who participated in the RITUXVAS trial^[29]. Recently, Geetha *et al.*^[30] conducted a similar study using renal biopsies from patients who participated in the RAVE trial. In contrast to the results of the RITUXVAS study, this study showed that interstitial B- and T-cell infiltrates had no significant impact on long-term prognosis, regardless of the immunosuppression regimen used (RTX or CYC)^[30].

Interestingly, a study of repeat protocol renal biopsies in patients treated with CYC showed a significant decrease in the number of B cells, whereas the number of T cells did not decrease to the same extent^[31]. There are currently no data on repeat renal biopsies after treatment with RTX; thus, the impact of this agent in the

Table 2 Current guidelines in the remission induction therapy for antineutrophil cytoplasmic antibody associated vasculitides with severe renal involvementKDIGO recommendations^[23]

Initial treatment of pauci-immune focal and segmental necrotizing GN with or without systemic vasculitis, and with or without circulating ANCA:
We recommend that CYC and CCS be used as initial treatment (1A)

We recommend that RTX and CCS be used as an alternative initial treatment in patients without severe disease or in whom CYC is contraindicated (1B)

We recommend the addition of PLEX for patients requiring dialysis or with rapidly increasing sCr (1C)

Treatment of relapse

We recommend treating patients with severe relapse of ANCA vasculitis (life- or organ threatening) according to the same guidelines as for the initial therapy (1C)

EULAR/ERA-EDTA recommendations^[26]

For remission-induction of new-onset organ-threatening or life threatening AAV we recommend treatment with a combination of CCS and either CYC or RTX

CYC: Level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 100%

RTX: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 82%

For a major relapse of organ-threatening or life-threatening disease in AAV we recommend treatment as per new disease with a combination of CCS and either CYC or RTX

CYC: Level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 88%

RTX: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%

PLEX should be considered for patients with AAV and a serum creatinine level of > 500 mmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease. Level of evidence 1B; grade of recommendation B; strength of vote 77%

AAV: Antineutrophil cytoplasmic antibody associated vasculitides; KDIGO: Kidney disease improving global outcomes; EULAR: European league against rheumatism; ERA-EDTA: European renal association-european dialysis and transplant association; GN: Glomerulonephritis; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; CYC: Cyclophosphamide; RTX: Rituximab; CCS: Corticosteroids; PLEX: Plasma exchange.

presence of B and T cell tubulointerstitial lesions remains uncertain. Repeat renal biopsies in future trials would help to clarify the contradictory results of the current studies and identify the extent of B and T cell infiltration that could potentially be a significant clinical factor in determining adequate therapy for individual patients in order to ensure that active lesions are adequately treated.

What is the impact of safety and adverse events on therapeutic choice?

Given that safety is a key concern in the evaluation of immunosuppressive agents, there may be individual clinical situation in which RTX is more appropriate than CYC; these may include patients with a high cumulative dose of CYC due to previous exposure, patients with a history of malignancy, and those who are of childbearing age but do not yet have any offspring. However, RAVE and RITUXVAS did not show any benefit of RTX in terms of the incidence of adverse events, regardless of severity^[10,11,32].

Although efficacious remission induction treatment using RTX in patients with severe infection has been reported^[33], this is not recommended as moderate to severe hypogammaglobulinemia occurs in > 50% of AAV patients treated with RTX, resulting in increased risk of infections that could be even higher in patients with reduced renal function^[34-36]. As highlighted in two small cohorts of patients with AAV, the negative impact of RTX on IgG levels can be exacerbated by higher previous CYC exposure^[37,38]. Late-onset neutropenia following RTX has also been described in both GPA and MPA and is associated with a high incidence of infections^[39]. Uncommon but serious adverse events after RTX treatment include hepatitis B (HBV) reactivation, which is largely preventable with antiviral prophylaxis, and

progressive multifocal leukoencephalopathy (PML) caused by reactivation of the human JC polyomavirus^[40-42]. Nevertheless, we must emphasize that PML occurs in the context of a severe cellular immunosuppression and is not specifically associated with any immunosuppressive agent^[43]. In fact, PML has also been reported in patients with GPA treated with CYC^[44]. Moreover, beyond the infectious risk after RTX treatment, RAVE and RITUXVAS raised concerns about a possible higher incidence of malignancy in patients treated with RTX^[10,11,20]. A retrospective study of 323 patients with AAV recently compared the incidence of malignancy between RTX and CYC^[45]. During a mean follow-up of 5.6 years, patients treated with RTX did not show an increased risk compared with the general population. In contrast, patients treated with CYC had a 4.61-fold higher risk of developing malignancies than those treated with RTX. Longer follow-up studies are now required to validate these data.

SHOULD THERE BE DIFFERENCES IN THE THERAPEUTIC APPROACH BETWEEN PATIENTS WITH NEWLY DIAGNOSED AAV AND THOSE WITH DISEASE RELAPSE? IF SO, WHAT IS THE IMPORTANCE OF THE ANTIGENIC SPECIFICITY OF ANCA IN GUIDING THERAPEUTIC CHOICE?

The therapeutic approach to relapses in patients with GPA or MPA and renal involvement remains a challenge and depends on the degree of severity and whether

or not the patient is still undergoing treatment with a maintenance immunosuppressive regimen at the time of relapse.

Treatment of mild renal relapse

Patients with mild, non-organ-threatening relapse (e.g., recurrent red blood cell casts on urine microscopy without concomitant increase in serum creatinine) who are still undergoing maintenance therapy can initially be treated by increasing the dose of CCS and of the immunosuppressive agent used for maintenance therapy, especially if the relapse occurs during a reduction in the dose of maintenance therapy^[26,46]. Mild, non-organ-threatening relapses that arise after discontinuation of maintenance therapy can be treated with the resumption of the prior maintenance therapy. In the latter case, the maintenance therapy should be continued for a more extended period than planned before the relapse^[26]. If the nephrologist is uncertain that the relapse is mild, a kidney biopsy should be performed to clarify whether repeat-induction therapy is warranted. In patients with multiple mild relapses, B cell depletion with RTX must be considered as an alternative approach^[46].

Treatment of severe renal relapse

Severe relapses should be treated with the resumption of induction therapy using a CYC-based or RTX-based regimen as for a new case^[26]. In patients who relapse after a successfully achieving remission with a CYC-based regimen, RTX is preferred because the cumulative dose of CYC is associated with significant toxicity, particularly in patients with frequent relapses^[26,47]. RTX is also the therapy of choice for patients who relapse after previously achieving remission with RTX-based therapy, patients who had difficulty tolerating CYC or those who had a contraindication to CYC during initial induction therapy^[26,47]. The best data in patients with relapsing GPA and MPA come from the RAVE trial. The rate of remission induction in patients with relapse was higher with RTX at 6 and 12 mo, but not at 18 mo^[10,32]. RTX and CYC followed by AZA achieved similar remission rates at 18 mo, although patients in the RTX group who achieved a complete remission by 6 mo received no additional immunosuppression for more than one year^[32]. However, CYC-based therapy should be considered for patients whose relapse is characterized by advanced renal failure, as it is for patients with newly diagnosed AAV, for the abovementioned reasons (Table 2).

What is the impact of the antigenic specificity of ANCA on therapeutic choice?

To date, there is growing evidence that ANCA specificity is superior to clinical diagnosis in defining homogeneous groups of patients, as PR3-ANCA and MPO-ANCA are associated with different genetic backgrounds and epidemiologic patterns^[48]. MPO-ANCAs are present in > 80% of patients with isolated PiNCGN, whereas

patients with PR3-ANCAs have more extra-renal organ manifestations^[49,50]. In the RAVE trial, renal involvement was more common in patients with MPO-ANCAs than in those with PR3-ANCAs (79% vs 59%). Additionally, based on the international working group of renal pathologists (IWGRP) classification system for ANCA-associated glomerulonephritis^[51,52], patients with MPO-ANCAs have a more severe histological phenotype^[53,54]. For instance, in the study by Quintana *et al.*^[53], MPO-ANCAs were associated with a higher frequency of mixed and sclerotic pathology, characterized by more advanced fibrotic changes in the interstitium and worse renal function at 1 and 2 years. These data are in agreement with those observed in most cohorts, which show that patients with MPO-ANCAs have poorer renal outcomes than those with PR3-ANCAs^[49,55-58]. However, numerous studies have shown that relapses are much more frequent in patients with PR3-ANCA seropositivity^[2,49,59-62].

In the RAVE trial, at the 6 mo time point, significantly more patients became PR3-ANCA-negative after RTX therapy than after CYC/AZA therapy (50% vs 17%), whereas comparable proportions of patients receiving either therapy became MPO-ANCA-negative^[10]. Most importantly, a post hoc analysis of the RAVE trial showed similar rates of complete remission at 6 mo in both treatment groups among the subgroup of patients with MPO-ANCA seropositivity, whereas RTX was significantly more effective than CYC/AZA in the subgroup of patients with PR3-ANCAs (65% vs 48%)^[63]. Moreover, among patients with PR3-ANCAs who had relapsing disease at baseline, the risk of disease relapse in RTX-treated patients was inferior not only at 6 mo, but also at 12 and 18 mo, despite the fact that patients randomized to RTX had not received a maintenance regimen^[63]. However, in another post hoc analysis of patients with renal involvement enrolled in the RAVE trial, no variations in remission rates or improvements in eGFR at 18 mo were observed when the analysis was stratified by ANCA type, AAV diagnosis (GPA vs MPA), or new diagnosis versus relapsing disease at entry^[20].

In conclusion, the demonstrated superiority of RTX compared to CYC in patients with PR3-ANCAs and in patients with relapsing disease has not yet been confirmed in long-term follow-up in patients with renal involvement^[20]. Further clinical trials are needed to evaluate this question in well-defined homogenous patient populations according to ANCA specificity.

SHOULD ALL PATIENTS WITH ADVANCED RENAL INVOLVEMENT BE TREATED WITH ADJUNCTIVE PLASMA EXCHANGE SESSIONS, AS SUGGESTED BY SHORT-TERM RESULTS?

The rationale for PLEX in AAV is that removal of ANCAs and other plasma constituents involved in the

pathogenesis of the disease, such as protein produced by activated lymphocytes and macrophages, cytokines, complement components, clotting factors, and adhesion molecules, could reduce further tissue damage and promote reversal of the pathologic process^[64,65].

The effect of PLEX in addition to standard immunosuppressive therapy in patients with AAV and renal involvement, was evaluated in an initial randomized trial that demonstrated the efficacy of PLEX in the subgroup of patients with serum creatinine of at least 500 mmol/L (5.8 mg/dL) or on dialysis at diagnosis, but not in the group with a creatinine lower than 500 mmol/L^[66]. In 2007, the methylprednisolone vs plasma Exchange (MEPEX) trial, the largest randomized trial in patients with a severe renal disease (serum creatinine > 500 mmol/L) was published^[13]. All 137 enrolled patients were treated with CYC plus oral CCS and were randomly assigned to receive either seven PLEX sessions or three pulses of 1000 mg of methylprednisolone. At 3 mo, the proportion of patients who were alive and independent of dialysis was significantly higher in the PLEX group compared to the methylprednisolone group (69% vs 49%). Additionally, PLEX was associated with a 24% reduction in the risk of progression to ESRD at 12 mo, although the overall rates of survival and adverse events were similar between both groups after 1 year of follow-up^[13].

A subsequent meta-analysis of 387 patients from nine trials, including the MEPEX trial, showed a 20% relative risk (RR) reduction in the composite outcome of death or ESRD requiring dialysis after the addition of PLEX to standard immunosuppressive therapy^[67]. However, the authors of the meta-analysis concluded that, although this result was statistically significant, too few patients had been randomly assigned and sensitivity analyses were not sufficiently robust to reliably conclude that PLEX results in at least a moderate decrease in the composite end point of ESRD or death^[67].

Moreover, although these short-term results obtained with PLEX are encouraging, the long-term benefits remain unclear. In fact, long-term follow up of the MEPEX trial showed an attenuated benefit of PLEX with no significant reduction of progression to ESRD at four years, and equivalent mortality in both groups (51%)^[68]. Currently, the most recent EULAR/ERA-EDTA recommendations for the management of AAV suggest that PLEX should be considered for patients with AAV and a serum creatinine level of > 500 µmol/L in the setting of new or relapsing disease. The level of evidence is 1B and the grade of recommendation is B^[26] (Table 2).

In conclusion, PLEX continues to be a promising therapy, but further trials are required before widespread use for patients with renal vasculitis can be implemented. The ongoing PEXIVAS trial [Plasma Exchange and Glucocorticoids for Treatment of Anti-Neutrophil Cytoplasm Antibody (ANCA) - Associated Vasculitis; ClinicalTrials.gov Identifier: NCT00987389]

should help to further clarify the value of PLEX in these patients^[69].

NOVEL TARGETED AGENTS AND FUTURE PERSPECTIVES IN THE INDUCTION REMISSION THERAPY FOR AAV WITH RENAL INVOLVEMENT

The greatest challenge in the management of AAV is the development of new agents and innovative strategies, which are urgently needed to improve patients' prognosis and reduce the co-morbidities associated with current regimens. Future potential therapies, including molecules that block signaling pathways crucial in the pathogenesis of AAV and the development of PiNCGN, are currently being investigated in preclinical studies and early clinical trials, with promising results.

As previously mentioned, to date, high-dose CCS remain an integral part of induction remission therapy for AAV, in combination with an immunosuppressive agent (CYC) or a biological agent (RTX). Even though CCS rapidly control inflammation and prevent further renal damage, the increased susceptibility to infections and other potential co-morbidities such as diabetes mellitus, cardiovascular events, osteoporosis, cataracts and gastrointestinal complications^[70], have prompted researchers to reduce or replace their use.

Currently, several ongoing trials are assessing different strategies to minimize the use of CCS for remission induction. The above-mentioned multinational PEXIVAS trial (NCT00987389)^[69] and the LoVAS (Low-dose Glucocorticoid Vasculitis Induction) trial (NCT02198248)^[71] could provide valuable information on this crucial question (Table 3).

However, the most promising advancement for remission induction therapy is avacopan (CCX168), an orally administered selective C5a receptor inhibitor (Table 4). The efficacy of avacopan was first tested in an ANCA-associated glomerulonephritis mouse model induced by injection of MPO IgG^[72]. The recently completed CLEAR study, a phase 2, randomized, double-blind, placebo-controlled trial, met its primary endpoint, indicating that avacopan can replace high-dose CCS efficiently and safely in patients with newly diagnosed or relapsing AAV^[73] (Table 3). The 67 enrolled patients were randomized to receive placebo plus prednisone starting at 60 mg daily (control group), avacopan (30 mg, twice daily) plus reduced-dose prednisone (20 mg daily), or avacopan (30 mg, twice daily) without prednisone. The early efficacy of avacopan was substantiated by a rapid improvement in albuminuria, which was statistically significantly superior to that of the control group. Moreover, renal inflammation improved rapidly and to a higher degree in the avacopan groups compared with the control group, as demonstrated by the greater reduction of urinary MCP-1 (Monocyte Chemoattractant Protein-1) levels,

Table 3 Trials for induction of remission in antineutrophil cytoplasmic antibody associated vasculitides with renal involvement and corticosteroids-sparing regimens

Name of the Trial (number of patients)	Inclusion criteria	Treatment groups (drug dose)	Primary end points	Outcome
LoVAS ^[71] (140)	New clinical diagnosis of MPA or GPA, Age > 20 yr, eGFR > 15 mL/min	Low-dose CCS (0.5 mg/kg per day tapered and off within 6 mo) plus RTX <i>vs</i> High-dose CCS (1.0 mg/kg per day tapered to 10 mg/d within 6 mo) plus RTX	Proportion of the patients achieving remission at 6 mo (BVAS = 0 and CCS < 10 mg)	Ongoing trial (NCT02198248)
PEXIVAS ^[69] (704)	New or previous clinical diagnosis of MPA or GPA, Age > 15 yr, eGFR < 50 mL/min	without PLEX: normal versus reduced CCS <i>vs</i> with PLEX: normal versus reduced CCS (reduced dose regimen provides approximately 55% of the standard dose regimen over the first 6 mo)	All-cause mortality and ESRD at 2 yr	Ongoing trial (NCT00987389)
CLEAR ^[73] (67)	New or previous clinical diagnosis of MPA or GPA, Age > 18 yr, eGFR > 20 mL/min	Placebo plus 60 mg prednisone <i>vs</i> Avacopan (30 mg x 2/d) plus 20 mg prednisone <i>vs</i> Avacopan (30 mg x 2/d) without prednisone	Safety of Avacopan in subjects with AAV over the 12-wk treatment period	Avacopan can replace high-dose CCS efficiently and safely in patients with newly diagnosed or relapsing AAV
ADVOCATE ^[75] (300)		Avacopan in combination with RTX or CYC/AZA <i>vs</i> Prednisone in combination with RTX or CYC/AZA	The proportion of patients achieving disease remission at 26 wk	Ongoing trial (NCT02994927)

AAV: Antineutrophil cytoplasmic antibody associated vasculitides; GPA: Granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; CYC: Cyclophosphamide; AZA: Azathioprine; RTX: Rituximab; CCS: Corticosteroids; PLEX: Plasma exchange; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; BVAS: Birmingham vasculitis activity score.

a renal inflammation marker, in the avacopan groups. The most important finding from the CLEAR trial with regard to renal outcomes is that e-GFR and hematuria improved similarly in all three groups over the 12-wk treatment period, indicating that improvement in renal function in patients receiving avacopan did not require high-dose CCS. Another phase 2 trial, the CLASSIC trial (NCT02222155) investigated the addition of two different doses of avacopan or placebo to standard-dose CCS with CYC or RTX. No safety concerns were described in the avacopan treatment groups, and a trend towards a dose-dependent improvement in clinical response was shown^[74]. ADVOCATE (NCT02994927), a phase 3 trial, is now enrolling patients and will assess the safety and effectiveness of avacopan as an alternative to prednisone in inducing and maintaining remission in patients with AAV^[75] (Table 3).

Other new potential therapeutic agents in the induction remission therapy for AAV with major renal involvement include the following (Table 4).

Bortezomib: A proteasome inhibitor, was found to be more efficacious than CYC + CCS in decreasing the number of MPO-specific plasma cells and anti-MPO titers, thereby preventing the development of necrotizing crescentic glomerulonephritis in a mouse model of MPO AAV^[76]. Currently, there is only a single case report of a patient with AAV refractory to conventional treatment who achieved a prolonged remission of kidney disease after a single cycle of Bortezomib (four subcutaneous injections of 1.3 mg/m² at weekly intervals). At four years of follow-up, kidney function remained stable

without any maintenance treatment^[77]. More studies are now required to determine the efficacy and safety of this agent in the treatment of AAV patients.

Fostamatinib: A selective spleen tyrosine kinase (SYK) inhibitor that blocks B cell activation has been shown to attenuate autoantibody production and reverse autoimmune crescentic glomerulonephritis in a rodent model of anti-glomerular basement membrane disease^[78]. Additionally, in a rodent model of MPO AAV, SYK inhibition with fostamatinib has been an effective treatment for crescentic glomerulonephritis and lung hemorrhage^[79]. Immunohistochemical analysis confirmed SYK expression in human ANCA-associated glomerulonephritis, and SYK expression correlated with histological disease severity.

Given these encouraging results, clinical studies investigating the effect of SYK –targeted treatment in ANCA-associated glomerulonephritis are now warranted.

Anakinra: A recombinant nonglycosylated human interleukin-1 receptor antagonist (IL-1Ra) used in the treatment of rheumatoid arthritis, reduced the severity of necrotizing crescentic glomerulonephritis in a mouse model of MPO AAV^[80] and could be a potential therapeutic agent.

Gusperimus: An analogue of spargualin that inhibits the proliferation and activation of T cells, B cells, monocytes and dendritic cells and reduces the production of IFN- γ , IL-6 and IL-10^[81] has been shown to improve mortality and reduce proteinuria in a murine model of ANCA-

Table 4 New agents investigated in preclinical models and clinical trials in humans for antineutrophil cytoplasmic antibody associated vasculitides with renal involvement

Agent	Therapeutic target	Preclinical models	Human trials
Avacopan	Complement C5a receptor inhibitor	Mice ^[72]	CLEAR, a phase II trial, Status: Completed ^[73] CLASSIC, a phase II trial, Status: Completed ^[74] ADVOCATE, a phase III trial, Status: Recruiting (NCT02994927) ^[75]
Bortezomib	Proteasome inhibitor	Mice ^[76]	Not available
Fostamatinib	Spleen tyrosine kinase (Syk) inhibitor	Mice ^[79]	Not available
Anakinra	Interleukin-1 receptor antagonist (IL-1Ra)	Mice ^[80]	Not available
Gusperimus	NF-κB translocalization inhibition in leucocytes IFNγ, IL-6, IL-10 production reduction	Mice ^[82]	Phase II trials ^[83-85] Status: Completed
Alemtuzumab	Anti-CD52 humanized antibody inducing T-cell and macrophages depletion	Not available	Phase II trial ^[86] Status: Completed

associated crescentic nephritis^[82]. Three multicenter open-label studies have demonstrated the effectiveness of this agent in the treatment of refractory GPA and relapsing GPA^[83-85]. However, gusperimus should not be used in AAV due to serious adverse events and frequent neutropenia.

Alemtuzumab: An anti-CD52 monoclonal antibody that induces profound macrophages and T-cell depletion has also been shown to be effective in inducing remission in patients with relapsing or refractory AAV, but the increased frequency of relapse and severe adverse events limit its use^[86].

CONCLUSION

In recent years RTX has enriched our armamentarium for remission induction treatment for severe organ- or life-threatening AAV. However, data from randomized controlled trials on the efficacy of RTX in patients with advanced kidney failure without concomitant CYC are lacking. Additionally, despite the reported superiority of RTX in patients with relapsing disease and those with PR3-ANCA seropositivity, no differences in remission rates or increases in e-GFR are evident when the analysis is stratified by ANCA type or by new diagnosis versus relapsing disease in patients with major renal involvement^[20]. These data are contradictory and could create confusion for nephrologists who must decide on which immunosuppressive therapy is most appropriate for their patients. For that reason, new clinical trials in well-defined homogeneous patient populations, selected according to their ANCA specificity and renal function, are needed. Until then, CYC should remain the first-line treatment in the induction of remission for patients with severe renal involvement. Nevertheless, RTX may be considered as first-line treatment rather than CYC in young patients without offspring, patients with a history of malignancy and those who have received a high cumulative dose of CYC due to previous exposure as a result of relapsing disease.

Similarly, more data are needed to clearly define the utility of PLEX in the treatment of AAV with severe

renal involvement. The results of the PEXIVAS study are expected to elucidate this question^[69].

Finally, the continuous enrichment of our knowledge on the pathogenetic mechanisms of this disease may be translated into new therapeutic strategies based on novel biological drugs. Soon there may be therapeutic regimens with low doses of CCS or without CCS, thanks to the use of avacopan, a selective C5a receptor inhibitor that has proven to be an excellent glucocorticoid-sparing agent.

Other agents still under evaluation, with promising preclinical studies, are also expected to contribute to further improvement of renal outcomes and patient survival.

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Retrospective Study

Role of narrow band ultra violet radiation as an add-on therapy in peritoneal dialysis patients with refractory uremic pruritus

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Abstract

AIM

To assess the role of narrow band ultraviolet B (UVB) as a treatment option in peritoneal dialysis patients with refractory uremic pruritus.

METHODS

In this retrospective study, 29 adult patients with end stage renal failure on peritoneal dialysis, and who had refractory uremic pruritus, were given narrow band UVB radiation as an add-on therapy to standard care for a duration of 12 wk. The response to the pruritus was assessed both weekly and at the end of the study period using a visual analogue score (VAS).

RESULTS

The average VAS score at the end of the study was 3.14 ± 1.59 , which was significant compared to the baseline value of 7.75 ± 1.02 ($P < 0.05$). Improvements in symptoms were noted in 19 out of 21 (90.4%) patients. However, relapse occurred in six out of the 19 patients who responded. The dropout rate was high during the study period (33.3%).

CONCLUSION

Narrow band UVB is effective as an add-on therapy in peritoneal dialysis patients with refractory uremic pruritus. However, the present regime is cumbersome and patient compliance is poor.

Key words: Narrow band ultraviolet radiation; Uremic

pruritus; Peritoneal dialysis; Visual analogue score; Retrospective study

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Core tip: Uremic pruritus is a very distressing condition commonly seen in patients with advanced renal failure. Patients respond poorly to the currently available treatment regime. Narrow band ultraviolet (NUV-B) radiation is a treatment option in patients with refractory symptoms. In this study, we selected patients on peritoneal dialysis who had refractory pruritic symptoms, and used NUV-B as an add-on therapy to the standard medical care for a period of 12 wk. We found that using NUV-B improved symptoms in more than 90% of patients. However, the present regime used is not patient-friendly and compliance is poor.

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INTRODUCTION

Uremic pruritus is a very common and troublesome complication seen in patients with advanced chronic kidney disease^[1-4]. The pathophysiology is complex, and many factors have been identified, including skin dryness^[5,6], hyperparathyroidism^[7,8], calcium phosphate deposition^[9,10], imbalances between mu and kappa opioid receptors^[11,12] and systemic inflammation. Anemia, inadequate dialysis, elevated serum magnesium and aluminum levels, and hepatitis C infection are also believed to have some contributing effects. However, the causes remain unexplained in many cases. There are strong associations of uremic pruritus with depressive symptoms and poor sleep quality. The pruritus is sometimes severe and refractory to treatment. Narrow band ultraviolet B (NB-UVB) phototherapy is one therapeutic option in these difficult cases. NB-UVB decreases the proinflammatory cytokine levels and induces mast cell apoptosis. In this study, we aim to investigate the role of NB-UVB as an add-on therapy to the standard treatment that is used in treating severe uremic pruritus in peritoneal dialysis patients.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Dermatology at the Jawaharlal Nehru Institute of Medical Sciences Imphal, a tertiary referral center in northeastern India. Adult end-stage renal disease patients on peritoneal dialysis with refractory uremic

pruritus were included in the study. The patients were recruited from the nephrology units of three hospitals in Imphal from September 2011 to September 2017. The selected patients were referred to the Dermatology Department at the Jawaharlal Nehru Institute of Medical Sciences Imphal for NB-UVB therapy.

Inclusion criteria

In order to be eligible for inclusion in this study, patients had to be older than 18 years of age, have end-stage renal disease, be on peritoneal dialysis as their treatment modality, and have refractory uremic pruritus.

From September 2011 until September 2017, 29 patients satisfied the criteria. Uremic pruritus was defined as pruritus developing in patients with chronic kidney disease in the absence of other systemic, dermatological disorder or psychological factors. Refractory uremic pruritus was defined as uremic pruritus not that was not responsive to any of the two agents known to relieve the symptoms over a 4 wk period. These agents included topical emollients, topical capsaicin, antihistamines, pregabalin, gabapentin and tricyclic antidepressants.

Exclusion criteria

Patients with a prior history of photosensitivity, and other prior dermatological diseases that can cause pruritus, were excluded from this study.

Protocol: The patients were administered NB-UVB therapy every other day, three times per week for a total of 12 wk. They were started at a dose of 270 mJ/cm², and then increased by 15% at each visit. If patients had asymptomatic erythema after the session, then treatment was continued at the same dose. The dose was reduced by 15% if the patient developed erythema with minimal pain/itchiness. If the patient developed painful erythema or bullous lesions, treatment was restarted at one-third of the dosage. Phototherapy was administered using "Derma India, Chennai Lightning cubicles PUVA", which is equipped with 24 UVA lamps that emit a radiation spectrum of 320-400 nm with a maximum of 366 nm, and 24 UVB lamps that emit a radiation spectrum of 290-320 nm with a maximum of 300 nm.

The patients were allowed to continue with their previous medications/agents for uremic pruritus during the study period. A peritoneal adequacy test was performed in all patients upon entry into the study. Serum calcium, phosphate, intact parathyroid hormone, iron and hemoglobin profiles were evaluated in all patients.

A visual analogue scale (VAS) (0 = no pruritus; 10 = most severe pruritus) was used to identify the intensity of itch. VAS was measured at baseline and then weekly until the end of the 12th week. After completion of the treatment protocol, VAS was then measured monthly during the follow-up period.

Table 1 Baseline characteristics of the patients

Age (yr)	56.17 ± 15.65
Sex (male/female)	18/11
Hemoglobin (g/L)	9.99 ± 0.99
Corrected calcium (mg/dL)	8.92 ± 1.1025
Phosphate (mg/dL)	4.46 ± 1.35
Intact parathyroid hormone (pg/mL)	132.28 ± 176.63
Mean Kt/V	1.77 ± 0.11
No. of patients with weekly Kt/V > 1.7	19
Skin phototype	IV-20, V-9
Other agents used for pruritus	
Topical emollient	
Topical capsaicin	
Oral anti histaminics: Fexofenadine	
Pregabalin	
Gabapentin	
Amitriptylline	

The outcomes were grouped into the following: (1) Complete responders: defined as a VAS score of zero at the end of the study period; (2) Partial responders: defined as a VAS score between one to five at the end of treatment, and with a final VAS score less than the value at baseline; and (3) Non-responders: a VAS score greater than five at the end of the treatment period.

Relapse was defined as a VAS score greater than five after previously showing a complete or partial response.

After the completion of the treatment protocol, patients were followed-up on a monthly basis for another 6 mo. During the follow-up period, patients were assessed for relapse of the pruritus. VAS scores were recorded during these visits. A feedback form was also provided to the patient. This form allowed them to rate their experience with the treatment protocol and provide suggestions to improve their adherence.

Statistical analysis

Statistical analysis was performed using the SPSS 16 software. Continuous data were described as the mean ± SD, and categorical data by frequency and percentage. Paired *t*-tests were used to compare the mean VAS scores at baseline with those at the end of the study. A two-sided *P* score of < 0.05 was considered significant.

RESULTS

A total of 29 patients took part in this study. Seven patients dropped out during the treatment period. One patient died during this period. Baseline characteristics of the patients are shown in Table 1.

The mean age of the patients was 56 ± 15 years. The mean duration on peritoneal dialysis of these patients at the time of study was 10 ± 8 mo. The average baseline VAS for pruritus was 7.75 ± 1.02. At the end of the treatment period, the average VAS score was 3.14 ± 1.59, which was a significant drop from the baseline score (*P* < 0.05). Twenty-one patients

completed the study, and 19 of them (90.4%) showed improvements in pruritus severity. Complete resolution of pruritus was noted in three patients (14.2%). Two patients (9.5%) continued to have persistent pruritus, with VAS scores greater than five (Table 2).

Follow-up data were available for 14 patients. The mean VAS score at the end of the follow-up period was 4.14 ± 2.85. Six patients relapsed with pruritus, with VAS scores greater than five. The mean time to relapse was approximately 4.2 ± 2.99 mo.

No significant adverse effects attributable to NB-UVB were identified.

DISCUSSION

Uremic Pruritus is a fairly common entity in patients with advanced renal failure, including patients on hemodialysis as well as peritoneal dialysis. In a recent study in Chinese patients, the prevalence of uremic pruritus in patients on peritoneal dialysis was approximately 62.5%^[13].

The usual protocol followed in managing patient with uremic pruritus includes optimization of the dialysis dosage, optimizing treatment of hyperparathyroidism, hyperphosphatemia and anemia. Initially, patients are usually managed with emollients and topical analgesics for symptomatic measures. Many of these patients eventually require systemic medications, such as anti-histamines, pregabalin, gabapentin, and anti-depressants. Hemoperfusion has been used in combination with hemodialysis for hyperparathyroidism and pruritus in hemodialysis patients^[14]. A small population of patients continue to have persistent symptoms in spite of all these measures. Phototherapy may be tried as a treatment modality in these cases.

In a small open pilot study, Ada *et al* reported a satisfactory response to NB-UVB in patients with uremic pruritus^[15]. The randomized clinical study by Ko *et al*^[16] showed significant improvement in the pruritus intensity, however the beneficial effect was marginal when compared to the control group that received long-wave UVA radiation.

In our study, we noted that NB-UVB phototherapy was helpful as an add-on therapy in relieving symptoms of uremic pruritus in patients on peritoneal dialysis. A previous randomized controlled trial by Ko *et al*^[16] failed to show any substantial benefit compared to broadband UVA phototherapy. This lack of benefit was due to improvement in pruritus intensity in the control arm, which they attributed to the placebo effect. However, the population studied in that trial differs from that of our study. In our study, we included only patients with end-stage renal disease who were on peritoneal dialysis. Conversely, the study by Ko *et al*^[16] used a mixed population of patients, including those with chronic kidney disease on conservative treatment. Only three patients in that study were on peritoneal dialysis. Another important difference from that study is the duration of the treatment period. Per our protocol, the total duration

Table 2 The baseline and weekly visual analogue assessment scores for pruritus

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Mean VAS score	7.75 ± 1.02	7.55 ± 1.02	7.48 ± 0.82	7.03 ± 0.68	6.37 ± 0.49	5.66 ± 0.55	5.53 ± 0.64	5.20 ± 0.70	4.87 ± 0.74	4.60 ± 0.72	3.04 ± 1.32	3.42 ± 1.63	3.14 ± 1.59
No. of patients	29	29	29	29	27	27	26	25	24	23	22	21	21

VAS: Visual analogue score.

of therapy was 12 wk compared to the six week time-span used in the randomized trial. The extended duration of our treatment is based on our preliminary experience with such patients, where we noted a more significant improvement in symptoms when they received a more prolonged course of treatment.

The pathophysiology involved in uremic pruritus is very complex and multifactorial. Multiple hypotheses have been proposed, including the potential involvement of anemia, xerosis, hyperparathyroidism, hyperphosphatemia, inadequate dialysis, imbalance of opioid receptors, and inflammation. Some of the factors that contribute to pruritus in non-dialysis patients may not be applicable in patients who are already on peritoneal dialysis. The response of uremic pruritus to phototherapy may differ in the peritoneal dialysis population when compared to patients on hemodialysis. The beneficial effects of NB-UVB is believed to be attributable to the induction of mast cell apoptosis and the reduction in proinflammatory cytokine levels^[17].

In our study, the mean hemoglobin levels (9.99 ± 0.9) are very near the target set by KDIGO^[18]. The serum phosphate levels (mean value 4.44 mg/dL) and intact parathyroid levels (mean value 132.28 pg/mL) were also reasonable for patients on dialysis. Nineteen out of the 21 patients who completed the study had adequate small solute clearance (weekly $\text{kt/v} > 1.7$), suggesting that factors other than inadequate dialysis played a significant role in the pathogenesis of uremic pruritus in our patients.

We noted that using NB-UVB as an add-on therapy was effective in our patients. The mean VAS score improved from a baseline score of 7.75 ± 1.02 to 3.14 ± 1.59 by the end of therapy. Complete resolution of pruritus was noted in three patients (14.2%). In two patients (9.5%), no significant improvements were noted. Six of the patients who showed an improvement in pruritus ultimately relapsed (31.5%).

The beneficial effects of the phototherapy session set in by the 3rd week, and the effect became more pronounced after the end of the 7th week. The mean VAS score at the end of six weeks was 5.53 ± 0.64 , which means that many of these patients would have been classified as non-responders if they had received the 6 wk protocol, as in the previous randomized trial. The mean VAS score at the end of the 6 mo follow-up was 4.14 ± 2.85 , which was significantly lower than the baseline VAS score ($P < 0.001$).

Our study is limited by its retrospective nature. Although the population studied here is uniform, it is also small. We noted that it was difficult for the patients to strictly abide by the three times per wk for 12 wk UVB protocol. Upon reviewing the feedback forms, we realized that our patients found the treatment regime to be cumbersome, and many were not willing to enroll in a repeat course of such treatment sessions in the future. This was in spite of the short duration of each session, usually lasting less than two to 3 min. Many of the patients found the frequent visits to the hospital to be very inconvenient. Transportation was also a big hindrance, as many of these patients cannot drive and thus arranging logistical support to bring them to the hospital three times a wk for 12 wk becomes an issue. It is noted that the duration of the overall treatment protocol was longer compared with previous studies. As such, one might consider a slightly shorter duration of NB-UVB treatment (e.g., twice per week for eight to 10 wk, or three times per week for 8 wk).

Many questions still remained unanswered at the end of this study. The treatment, even if effective, does not offer long-term protection. Relapse occurred in nearly a third of the patients. The optimal treatment duration and frequencies of the session are not known. As such, we need to come up with a large well-designed randomized controlled trial comparing different treatment regimes in order to come up with the most effective yet acceptable regime.

In conclusion, using NB-UVB as an add-on therapy to standard agents in refractory uremic pruritus on peritoneal dialysis is effective in reducing the intensity of itching. However, there is a chance of relapse after discontinuation of the phototherapy. The 12 wk treatment regime used in this study is cumbersome and patient acceptance is poor.

ARTICLE HIGHLIGHTS

Research background

Uremic pruritus is a common and troublesome entity in patients on peritoneal dialysis. The presence of pruritus affects both sleep quality and overall lifestyle, which can lead to depressive symptoms and mood disorders. In patients with difficult-to-treat pruritus, narrow band ultraviolet B (NB-UVB) can be tried as a treatment option. There is only one randomized controlled trial that has compared the role of NB-UVB in uremic pruritus. There is very limited data regarding the use of NB-UVB in the peritoneal dialysis population. There is therefore an urgent need to identify the effectiveness of such a treatment modality in the peritoneal dialysis population.

Research motivation

With the limited data available, there is no clear-cut consensus regarding the role of NB-UVB in peritoneal dialysis patients who have severe pruritus. The most effective and optimal duration of treatment is also not clear. A previous randomized trial had used a course of three times a week for 6 wk. However, that study mixed in a population of chronic kidney disease patients and also included patients on hemodialysis, peritoneal dialysis, as well as patients who were treated conservatively and had not been initiated on dialysis. There were only three patients in this study who were on peritoneal dialysis, so the results therefore cannot be extrapolated to the peritoneal dialysis population. In this study, we selected a homogenous population of patients with end-stage renal disease who were on peritoneal dialysis with severe uremic pruritus, and used NB-UVB as an add-on therapy to the standard treatment.

Research objectives

The purpose of our study was to assess the effectiveness of NB-UVB as an add-on therapy to standard treatment in peritoneal dialysis patients with refractory uremic pruritus. We included a follow-up 6 mo post-treatment completion to assess for relapse. Patients were also given a feedback form to highlight their experience with the treatment protocol and solicit their suggestions to improve the quality of treatment.

Research methods

This is a retrospective study where peritoneal dialysis patients with refractory uremic pruritus were put on a 12 wk course of NB-UVB, in addition to their standard treatment. We used visual analogue scale (VAS) to record the intensity of pruritus, which was measured during each visit. After the completion of their treatment protocol, patients were followed-up on a monthly basis for six months, and their VAS scores were measured during these visits. The patient feedback forms were also collected during these follow-up visits.

Research results

In this study, we noted that the mean VAS score improved from a baseline of 7.75 ± 1.02 to 3.14 ± 1.59 by the end of treatment. Nineteen out of the 21 patients who completed the study had improvement in symptoms. In three patients (14.2%), complete resolution of pruritus was noted. Two patients (9.5%) continued to have persistent pruritus, with VAS scores greater than five. Six (31.5%) of those patients who showed improvement in pruritus ultimately relapsed. The mean VAS score at the end of the 6 mo follow-up was 4.14 ± 2.85 , which was significantly lower than the baseline VAS score ($P < 0.001$).

Research conclusion

In this study, we found that NB-UVB therapy is effective as an add-on therapy in difficult-to-treat patients with uremic pruritus in the peritoneal dialysis population. In our study, we used a 12 wk treatment protocol that showed effective results. We noted that the response at 6 wk was suboptimal, and many of our patients would have been classified as non-responders if our treatment was confined to 6 wk period. However, patient compliance was poor, and the frequent visits to the hospital for treatment became an issue when we used the 12 wk regime. We therefore need to come up with an effective treatment regime that will also be acceptable to patients.

Research perspectives

Future studies should try alternative treatment regimes, such as two times per wk for 10 wk, or three times per wk for 8 wk.

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Case of human immunodeficiency virus infection presenting as a tip variant of focal segmental glomerulosclerosis: A case report and review of the literature

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Abstract

The incidence of the collapsing variant of focal segmental glomerulosclerosis (FSGS) as a human immunodeficiency virus (HIV)-associated nephropathy has reduced since the introduction of antiretroviral therapy (ART). However, the incidence of other variants of FSGS, except for the collapsing variant, is increasing, and its therapeutic strategies remain uncertain. A 60-year-old HIV infected man in remission with ART was admitted for progressive renal insufficiency and nephrotic-ranged proteinuria. Renal biopsy revealed a tip variant of FSGS and his clinical manifestations resolved with corticosteroid therapy. HIV infected patients might develop non-collapsing FSGS, including tip variant of FSGS and corticosteroid therapy might be effective for them. A renal biopsy might be essential to determine the renal histology and to decide on corticosteroid therapy.

Key words: Focal segmental glomerulosclerosis; Tip variant; Antiretroviral therapy; Corticosteroid therapy;

Human immunodeficiency virus

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Core tip: Collapsing variant of focal segmental glomerulosclerosis (FSGS) is the most common kidney disease in human immunodeficiency virus (HIV) infected patients. However, the incidence has reduced since the introduction of antiretroviral therapy (ART). Although the incidence of other variants of FSGS, except for the collapsing variant, is increasing, the tip variant of FSGS has been rarely reported. Therefore, we report an HIV infected patient under remission with ART, who presented with a rare tip variant of FSGS, which resolved with corticosteroid therapy. We suggest a renal biopsy might be essential to determine the renal histology and to decide on corticosteroid therapy.

Goto D, Ohashi N, Takeda A, Fujigaki Y, Shimizu A, Yasuda H, Ohishi K. Case of human immunodeficiency virus infection presenting as a tip variant of focal segmental glomerulosclerosis: A case report and review of the literature. *World J Nephrol* 2018; 7(4): 90-95 Available from: URL: <http://www.wjnet.com/2220-6124/full/v7/i4/90.htm> DOI: <http://dx.doi.org/10.5527/wjn.v7.i4.90>

INTRODUCTION

Human immunodeficiency virus (HIV) infection as a cause of various kidney diseases is well known. The collapsing variant of focal segmental glomerulosclerosis (FSGS), as an HIV-associated nephropathy (HIVAN), is one of the most frequently occurring kidney diseases^[1]. HIVAN was first reported by Rao *et al*^[2] in 1984. It is characterized by tubular abnormalities that include cellular degeneration and necrosis as well as cystic dilatation and interstitial changes that are edematous and often infiltrated by lymphocytes, in addition to the collapsing variant of FSGS^[2].

Antiretroviral therapy (ART) is effective for preserving renal function and reversing HIVAN^[3]. It is reported that the use of ART slows the progression to renal replacement therapy in patients with HIVAN^[4]. However, ART has no beneficial effect on the renal function in patients with lesions other than HIVAN, including the tip variant of FSGS^[4]. HIV-immune-complex kidney disease (HIVICK), thrombotic microangiopathy, and nephrotoxicity caused by ART are the other types of renal damage associated with HIV infection^[3]. Although the occurrence of other variants of FSGS, except the collapsing variant, is increasing^[5], the tip variant of FSGS is still a rare kidney disease in HIV infected patients^[6]. We report here, a rare case of HIV associated nephrotic syndrome caused by the tip variant of FSGS, which was resolved with corticosteroid therapy.

CASE REPORT

A 60-year-old HIV positive Asian male was treated with ART (abacavir, atazanavir, and lamivudine) since the early 2000s. He had been HIV RNA negative since September 2010. There were no urinary abnormalities and his serum creatinine (sCr) level was within normal limits (sCr 0.72 mg/dL) in June 2015. However, he developed edema of the lower limbs beginning in the middle of June 2015 and gained 6 kg in two weeks. No symptoms of heart failure were found during the clinical course. His sCr level increased to 1.0 mg/dL. Atazanavir was changed to dolutegravir at the beginning of July 2015, due to suspicion of atazanavir-induced nephropathy. However, his sCr further increased to 1.99 mg/dL. Hypoalbuminemia (0.8 g/dL) and massive proteinuria (16.96 g/gCr) were observed in late July 2015 at which time he was admitted to our institute.

He had no other significant past history except for the HIV infection. He was on abacavir, lamivudine, and dolutegravir as ART, and furosemide to reduce the edema of the lower limbs. Physical examination on admission was as follows: Height 166 cm, weight 86.2 kg, body mass index (BMI) 31.3 kg/m², body temperature 36.3 °C, blood pressure 114/89 mmHg, and regular pulse rate 101 beats/min. Extremities had remarkable pitting edema. Laboratory investigations were shown in Table 1.

A renal biopsy was performed in late July 2015. The light microscopic findings revealed that 34 out of 35 glomeruli showed minor glomerular abnormalities without glomerular hyperfiltration. In addition, changes of the glomerular capillaries, such as spike formation and bubbling appearance, or glomerular nodular lesions were not found. However, one glomerulus showed epithelial hypercellularity at the tubular pole, where a confluence of the tubular cells at the tubular outlet was observed. No collapse of the glomerular tuft was seen. Although diffuse tubular atrophy and interstitial fibrosis were seen, infiltration of inflammatory cells was sparse and microcystic tubular dilatation associated with HIVAN was absent (Figure 1). Immunofluorescent microscopic examination showed the absence of immunoglobulins and complements (data not shown). Electron microscopy revealed a wide range of foot process effacement. No thickness of glomerular basement membrane was observed. Moreover, no tubulo-reticular inclusions in the glomerular endothelium were found and electron-dense deposits (EDDs) were absent (Figure 2). A diagnosis of tip variant of FSGS was made.

Following renal biopsy, corticosteroid therapy (prednisolone 50 mg/d) and angiotensin II receptor blocker (ARB) were administered to reduce the proteinuria. Three weeks later, proteinuria was absent and the levels of sCr and urinary β 2-microglobulin decreased from 1.99 mg/dL to 0.99 mg/dL, and 65500 μ g/L to 346 μ g/L, respectively. Thereafter, the dose of prednisolone was tapered and there was no recurrence of proteinuria.

Table 1 Laboratory data at the time of administration

Hematology		Blood chemistry		Immunology		Urinalysis	
WBC	7720/ μ L	Na	133 mEq/L	CRP	0.27 mg/dL	Protein	11.28 g/24 h
CD4	549/ μ L	K	4.1 mEq/L	IgG	426 mg/dL	Sugar	3+
RBC	567×10^3 / μ L	Cl	106 mEq/L	IgA	293 mg/dL	Occult blood	3+
Hb	18.9 g/dL	Ca	7.2 mg/dL	IgM	83 mg/dL	Urinary RBC	5-9/HPF
Hct	53.20%	Pi	2.6 mg/dL	CH50	48.7 U/mL	β 2MG	65500 g/L
Plt	42.5×10^3 / μ L	BUN	20.1 mg/dL	C3	159 mg/dL	NAG	173.2 IU/L
		sCr	1.99 mg/dL	C4	42 mg/dL	Crystal	(-)
		UA	4.4 mg/dL	ANA	40 $\times$		
		LDH	243 IU/L	MPO-ANCA	< 1.0 U/mL		
		AST	23 IU/L	PR3-ANCA	< 1.0 U/mL		
		ALT	20 IU/L	anti-GBM Ab	< 2.0 U/mL		
		TP	3.9 g/dL				
		Alb	0.8 g/dL				
		LDL-cho	418 mg/dL				
		BS	121 mg/dL				
		HIV RNA	(-)				
		HBS Ag	(-)				
		HCV Ab	(-)				

CD: Cluster of differentiation; BUN: Blood urea nitrogen; sCr: Serum creatinine; UA: Uric acid; LDH: Lactate dehydrogenase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDL-cho: Low-density lipoprotein cholesterol; HIV: Human immunodeficiency virus; HBS Ag: Hepatitis B virus surface antigen; HCV Ab: Hepatitis C virus antibody; CRP: C-reactive protein; CH50: Total complement activity; ANA: Anti-nuclear antibody; MPO-ANCA: Myeloperoxidase-antineutrophil cytoplasmic antibody; PR3-ANCA: Proteinase 3-antineutrophil cytoplasmic antibody; Anti-GBM ab: Anti-glomerular basement membrane antibody; HPF: High power field; β 2MG: β 2 microglobulin; NAG: N-acetylglucosaminidase.

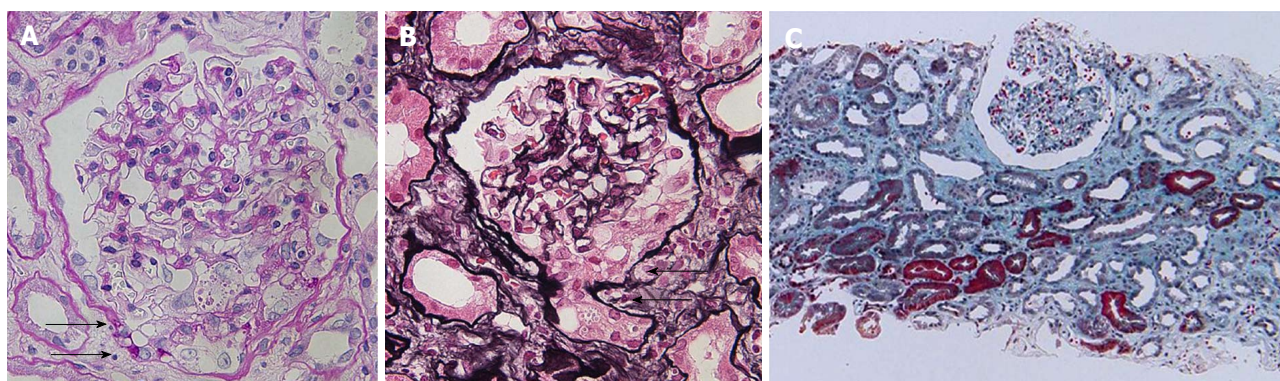


Figure 1 The results of light microscopy. A and B: The glomerulus shows epithelial hypercellularity at the tubular pole, where a confluence of the tubular cells at the tubular outlet is observed (arrows). No collapse of the glomerular tufts associated with human immunodeficiency virus-associated nephropathy (HIVAN) is seen (A: Periodic acid-Schiff stain: Original magnification 400 $\times$; B: Periodic acid-methenamine-silver-HE stain: Original magnification 400 $\times$); C: Diffuse tubular atrophy and interstitial fibrosis are seen. However, infiltration of the inflammatory cells is sparse and microcystic tubular dilatation associated with HIVAN is absent (Masson's trichrome stain: Original magnification 100 $\times$).

(Figure 3).

DISCUSSION

An HIV infected patient in remission with ART, was diagnosed with the tip variant of FSGS. Steroid treatment corrected the renal dysfunction and nephrotic-ranged proteinuria.

Although it is generally considered that HIV infection of the renal cells and HIV viral proteins play an important role in the occurrence and the progression of HIVAN^[3], HIV RNA was negative in this case. It is known that HIV patients may develop non-collapsing FSGS, even when HIV mRNA levels are negative. Lescure *et al.*^[5] reported that FSGS was the primary diagnosis in 21 of the 32

patients (65% of total, HIVAN: 6 patients, non-collapsing FSGS: 15 patients) who underwent a renal biopsy from 2004 to 2007 when ART was the standard therapy for HIVAN. In addition, non-collapsing FSGS accounted for 15 of 26 patients (58%) who underwent renal biopsy for causes other than HIVAN^[5]. The high incidence of non-collapsing FSGS in this study may be due to 66% of the included patients identified their race as black. It is known that patients of African descent are susceptible to genetic mutations of APOL1, which is associated with the development of FSGS^[7]. Though the incidence of biopsy-proven idiopathic FSGS was reported to be 49% in black patients^[8]. Thus, the prevalence of non-collapsing FSGS in patients with HIV infection seemed to be higher compared to that in black patients without HIV infection.



Figure 2 The results of electron microscopy. Electron microscopy reveals a wide range of foot process effacement (arrows). No tubulo-reticular inclusions in the glomerular endothelium are seen and electron-dense deposits are absent (original magnification: 3000 ×).

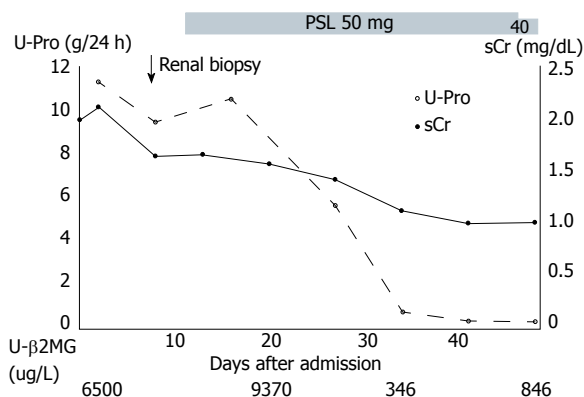


Figure 3 Clinical course after admission. The solid line with closed circles indicates serum creatinine (sCr) levels, and the dashed line with open circles indicates daily urinary protein (U-Pro) excretion levels. PSL: Prednisolone, U-β2MG; Urinary β2-microglobulin.

Moreover, the patients with HIV infection might be susceptible not only to HIVAN but also to another variant of FSGS.

The tip variant of FSGS is a rare kidney disease in HIV infected patients. Meehan *et al* reported that only one of twenty-six patients developed a tip variant in a cohort of 46 HIV positive patients^[6]. Howie and Breer defined the term glomerular tip lesion (GTL) as hypercellularity at the tubular pole in nephrotic patients for the first time^[9]. Since GTLs are observed in some glomerular disorders such as membranous nephropathy, IgA nephropathy, or diabetic nephropathy, it is possible that GTLs are interpreted as nonspecific renal pathological findings^[10]. However, since the rate of chronic kidney diseases and end-stage renal failure is higher in patients with GTLs compared to patients with minimal change nephrotic syndrome, GTLs are considered as a variant of FSGS^[11]. However, the tip variant of FSGS exhibits unique characteristics among idiopathic FSGS. Several reports mention that the levels of interstitial fibrosis, global sclerosis, and glomeruli with segmental lesions

were lower in the tip variant of FSGS and the rate of complete remission of the nephrotic syndrome is higher than that in not otherwise specified (NOS) variants of FSGS^[11]. It is difficult to deny that GTLs were completely caused by other diseases. However, in this case no significant findings except for segmental lesions in one glomerulus were found in the light microscopic findings. The absence of immunoglobulins and complements by immunofluorescent microscopic examination and the absence of the thickening of the glomerular basement membrane and EDDs by electron microscopic examination excluded that the GTLs were caused by other diseases and confirmed the diagnosis of the tip variant of FSGS.

Because this patient was remarkably obese (BMI: 31.3 kg/m²), obesity-associated FSGS was suspected as a differential diagnosis. However, this patient's clinical features were considerably different than those of obesity-associated FSGS based on the following evidence: (1) Although obesity was not improved, urinary protein levels were dramatically decreased by steroid treatment; and (2) Praga *et al*^[12] reported that the levels of proteinuria in obesity-associated FSGS are lower and that the incidences of hypoalbuminemia and edema are less frequent than in patients with idiopathic FSGS. In addition, they indicated that glomerular hyperfiltration is more frequently found in renal biopsy specimens of patients with obesity-associated FSGS than in renal biopsy specimens of patients with idiopathic FSGS. Therefore, this case was unlikely to be of obesity-associated FSGS.

It could not be completely denied that this was a case of a patient with HIV infection and the tip variant of FSGS. However, Lescure *et al*^[5] indicated that HIVAN decreased from 75% in 1995-2000 to 29% in 2004-2007 because of the introduction of ART, and that FSGS other than HIVAN conversely increased from 11.1% in 1995-2000 to 46.9% in the 2004-2007. The incidence of FSGS with HIV infection in both periods is much higher (86.1% in 1995-2000 and 75.9% in 2004-2007) than that of black patients without HIV infection (49%)^[8]. Those results indicated that HIV infection is associated with the FSGS pathogenesis with or without the presence of HIV RNA. Additionally, immunodeficiency and dysregulation of immunoglobulin synthetic responses and T-cell function, which can lead to pathogenesis of kidney diseases, are increased in HIV infected patients^[13]. It is likely that the corticosteroid therapy corrected the dysregulation of the immune system caused by the HIV infection in this tip variant of FSGS. However, the pathogenesis of FSGS without HIV RNA in HIV infected patients who were effectively treated with ART should be clarified.

At first, atazanavir-induced progressive renal insufficiency and nephrotic-ranged proteinuria were suspected. However, these did not improve after the discontinuation of atazanavir. Moreover, to the best of our knowledge, atazanavir-induced tip variant of FSGS has yet to be reported in literature. Therefore, we believe that atazanavir did not cause the massive progressive renal

insufficiency and nephrotic-ranged proteinuria.

In this case, the level of urinary β 2MG was markedly elevated at the time of admission and rapidly decreased with corticosteroid therapy. Exposure to tenofovir, indinavir, and atazanavir has been reportedly associated with a higher incidence of chronic kidney disease^[14]. Atazanavir is known to cause crystalluria and urolithiasis^[15]. In this case, the patient began receiving dolutegravir after it was suspected that the atazanavir was inducing nephropathy. Fujigaki *et al*^[16] reported proximal tubular injuries in adults with minimal change nephrotic syndrome, which was probably due to massive proteinuria. As previously described, early discontinuation of atazanavir, as well as early remission of massive proteinuria, may improve the tubulointerstitial damage and rapidly decrease urinary β 2MG excretion levels, as seen in this case.

In conclusion, this was a rare case of a patient in remission from HIV who presented with the tip variant of FSGS. Since the tip variant of FSGS can occur in HIV patients in remission with ART, a renal biopsy might be essential to determine the renal histology, and to decide on corticosteroid therapy. Further research with a larger sample size of patients is necessary to understand the mechanisms and efficacy of corticosteroid therapy for the tip variant of FSGS in HIV-infected patients.

ARTICLE HIGHLIGHTS

Case characteristics

We reported a human immunodeficiency virus (HIV) infected patient in remission with antiretroviral therapy (ART), who presented with a rare tip variant of focal segmental glomerulosclerosis (FSGS), which resolved with corticosteroid therapy.

Clinical diagnosis

We diagnosed the patient as a case of HIV infection presenting as a tip variant of FSGS.

Differential diagnosis

HIV-associated nephropathy (HIVAN) or other causes of FSGS have to be differentiated because therapeutic strategies (ART or steroids) are different.

Laboratory diagnosis

Whether HIV RNA levels are positive or negative are important.

Pathological diagnosis

Tip variant of FSGS is needed to diagnose that more than one glomerulus show epithelial hypercellularity at the tubular pole, where a confluence of the tubular cells at the tubular outlet is observed in renal biopsy specimen.

Treatment

Steroid therapy is considered to administer to other causes of FSGS except for HIVAN including the tip variant.

Related reports

Lescure *et al* is important for the readers to understand the changes of HIV-associated kidney glomerular diseases with time and ART.

Term explanation

Tip variant is one of the diagnoses in the Columbia classification of FSGS and is

explained as follows: More than one glomerulus shows epithelial hypercellularity at the tubular pole, where a confluence of the tubular cells at the tubular outlet is observed in renal biopsy.

Experiences and lessons

When renal damage is caused in HIV-infected patients, a renal biopsy may be essential to determine the renal histology and to decide on corticosteroid therapy.

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ORIGINAL ARTICLE

Basic Study

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Basic Study

A small molecule fibrokinase inhibitor in a model of fibropolycystic hepatorenal disease

Prani Paka, Brian Huang, Bin Duan, Jing-Song Li, Ping Zhou, Latha Paka, Michael A Yamin, Scott L Friedman, Itzhak D Goldberg, Prakash Narayan

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Abstract

AIM

To evaluate the novel platelet-derived growth factor receptor and vascular endothelial growth factor receptor dual kinase inhibitor ANG3070 in a polycystic kidney

disease-congenital hepatic fibrosis model.

METHODS

At 6 wk of age, PCK rats were randomized to vehicle or ANG3070 for 4 wk. At 10 wk, 24 h urine and left kidneys were collected and rats were continued on treatment for 4 wk. At 14 wk, 24 h urine was collected, rats were sacrificed, and liver and right kidneys were collected for histological evaluation. For Western blot studies, PCK rats were treated with vehicle or ANG3070 for 7 d and sacrificed approximately 30 min after the last treatments.

RESULTS

Compared to the wild-type cohort, the PCK kidney (Vehicle cohort) exhibited a marked increase in kidney and liver mass, hepato-renal cystic volume, hepato-renal fibrosis and hepato-renal injury biomarkers. Intervention with ANG3070 in PCK rats decreased kidney weight, reduced renal cystic volume and reduced total kidney hydroxyproline, indicating significantly reduced renal interstitial fibrosis compared to the PCK-Vehicle cohort. ANG3070 treatment also mitigated several markers of kidney injury, including urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, cystatin C and interleukin-18 levels. In addition, this treatment attenuated key indices of renal dysfunction, including proteinuria, albuminuria and serum blood urea nitrogen and creatinine, and significantly improved renal function compared to the PCK-Vehicle cohort. ANG3070 treatment also significantly decreased liver enlargement, hepatic lesions, and liver fibrosis, and mitigated liver dysfunction compared to the PCK-Vehicle cohort.

CONCLUSION

These results suggest that ANG3070 has the potential to slow disease, and may serve as a bridge toward hepato-renal transplantation in patients with fibropolycystic disease.

Key words: Congenital hepatic fibrosis; Cyst; Fibrosis; Autosomal recessive polycystic kidney disease; Kidney; Liver; Therapy

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Core tip: In autosomal recessive polycystic kidney disease (ARPKD)-congenital hepatic fibrosis (CHF), a genetically acquired and congenital disease, approximately 20-30% of affected patients succumb within the first 1-2 mo of life, with pulmonary insufficiency secondary to renal enlargement as the primary cause of death. For children, nephrectomy and dialysis or kidney liver transplant is often warranted by approximately ten years of age. Other than transplantation, there is no cure for ARPKD-CHF. We report that platelet-derived growth factor and vascular endothelial growth factor are the intermediaries between the cystic and fibrotic components of progressive fibropolycystic disease and ANG3070, a novel dual kinase inhibitor therapy that may serve as an interesting bridge

toward hepato-renal transplantation in patients with ARPKD-CHF.

Paka P, Huang B, Duan B, Li JS, Zhou P, Paka L, Yamin MA, Friedman SL, Goldberg ID, Narayan P. A small molecule fibrokinase inhibitor in a model of fibropolycystic hepatorenal disease. *World J Nephrol* 2018; 7(5): 96-107 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v7/i5/96.htm> DOI: <http://dx.doi.org/10.5527/wjn.v7.i5.96>

INTRODUCTION

The highly aggressive fibropolycystic disease, autosomal recessive polycystic kidney disease (ARPKD) - congenital hepatic fibrosis (CHF), is characterized by the formation and expansion of fluid-filled cysts in the kidneys, enlargement of the kidneys and progressive fibrosis of both the kidney and the liver^[1,2]. Caroli's disease, which manifests as cystic dilatation of the intrahepatic ducts, often accompanies ARPKD-CHF^[3]. Afflicted children that survive past two years of age more often than not require renal and/or hepatic transplantation by age ten. The need for transplantation is driven as much by progressive organ dysfunction as by significant enlargement of the diseased organ(s) accompanied by severe pain^[4].

Aberrant signaling by tyrosine kinases, including platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) and their receptors (R), PDGFR and VEGFR/KDR, respectively, has been implicated in the formation and expansion of renal cysts. A PDGF-driven ciliopathy and/or overexpression of PDGF in the cyst lining and adjacent tubules are thought to, in part, drive renal cystic disease^[5-7]. Cowley *et al*^[8] posited that elevated and abnormal c-myc proto-oncogene expression drives ARPKD; c-myc expression is controlled by PDGF^[9].

VEGF-driven angiogenesis is also thought to contribute to the growth of renal cysts, and inhibition of VEGFR/KDR signaling is associated with decreased tubule cell proliferation, decreased cystogenesis, and blunted renal enlargement^[10,11]. Nevertheless, the role of VEGF in fibropolycystic disease is more controversial, with at least two reports suggesting that this growth factor might be associated with disease mitigation^[12]. Aside from their roles in renal cyst formation and expansion, it is being recognized in ARPKD-CHF that aberrant PDGF and VEGF signaling are also associated with extracellular matrix deposition in the liver and kidney^[13-15].

The PCK rat model is a well-established and well-characterized model that resembles human polycystic kidney and liver disease^[16]. In the present study, we employed the PCK rat model to evaluate the therapeutic effects of ANG3070 on hepato-renal fibropolycystic disease. ANG3070 is an orally bioavailable, highly water-soluble, small molecule PDGFR and VEGFR/KDR inhibitor that binds

its target receptors with nanomolar affinity but exhibits limited interaction with other receptor tyrosine kinases as described by Panicker *et al*^[17] and Narayan *et al*^[18].

MATERIALS AND METHODS

Animal model

All studies relating to animals were approved by the Angion Biomedica animal use and care committee. Four week old male PCK/CrljCrl-Pkhd1^{pck}/Crl rats and age-matched male Sprague-Dawley (wild-type) rats were purchased from Charles River Labs (Wilmington, MA) and acclimatized for a week with a standard laboratory diet and water *ad libitum* at Angion prior to starting experiments. The PCK rat model includes ARPKD and autosomal dominant polycystic kidney disease (ADPKD). Many of the biochemical and morphological changes using these PCK rat models closely resemble human hepato-renal fibro polycystic disease^[16]. We will use the best-characterized PCK rat model to establish therapeutic efficacy and the time window of our novel dual kinase inhibitor, ANG3070. PCK rats exhibit renal pathology starting from 4 wk of age with continuous progression of hepato-renal fibropolycystic disease with aging^[16,17].

Sample size

Upon consultation with a biostatistician and based on formal power analysis, we expect a 30%-50% reduction in hepato-renal injury and pathology with ANG3070 treatment vs vehicle cohort, with a 30% standard deviation in each group and 80% power required to observe $P < 0.05$. Ten to 14 PCK rats were required for each group.

The total rats used in three separate experiments = approximately 18 wild type SD rats and 68 PCK rats. Some animals (PCK, $n = 2$; wild-type, $n = 4$) were sacrificed at 6 wk of age to confirm disease pathology. The PCK rats were then randomized to vehicle (water, $n = 14$) or ANG3070 (25 mg/kg, PO, BID; $n = 14$). Drug dose and dosing schedule was based on data (not shown) from previous studies in models of chronic kidney disease. At 10 wk of age (*i.e.*, after 4 wk of drug treatment), 24 h urine was collected, animals were anesthetized with isoflurane (2%), a midline incision was made and the left kidney was removed for analysis. Animals were then returned to their cages and allowed to recover. At 14 wk of age (*i.e.*, after 8 wk of drug dosing), 24 h urine was collected, animals were anesthetized, and the right kidney and liver were removed. For Western blot studies, 10 wk old male PCK rats were treated with vehicle or ANG3070 (25 mg/kg, PO, BID) for 7 d and sacrificed approximately 30 min after the last vehicle/drug administration. Kidneys were collected and stored in formalin and liquid N₂.

Cystic index

Cystic index (*i.e.*, the percentage of renal parenchyma occupied by cysts) was quantified using two independent blinded observers in hematoxylin and eosin (H and E)

- stained kidney sections using digital planimetry (NIS Elements Viewer) as described previously^[18]. The data from the two observers were averaged for each kidney.

Tissue and biomarker analysis

Body weight, kidney and liver masses were determined. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN) and serum creatinine (SCr) were measured by Northwell laboratory (New Hyde Park, NY). Proteinuria was measured using a modified Bradford and Lowry Bio-Rad protein assay and expressed as mg/24 h urine. Microalbuminuria (Abcam ELISA) was expressed as $\mu\text{g}/24 \text{ h}$ urine. Levels of neutrophil gelatinase-associated lipocalin (NGAL) (BioPorto Diagnostics, <http://www.bioparto.com>), cystatin C (R and D Systems, <http://www.rndsystems.com>), interleukin-18 (IL-18) (Biomedical Assay, <http://www.biotechist.com>) and kidney injury molecule-1 (KIM-1) (BioTrend, <http://www.biotrend.com>) were determined in urine samples using an enzyme-linked immunosorbent assay. Kidney and liver hydroxyproline, markers of tissue fibrosis, were measured from tissue homogenates^[19] and expressed as $\mu\text{g}/\text{kidney}$ or $\mu\text{g}/\text{liver}$.

Histopathology and immunohistochemistry

Formalin-fixed kidney and liver sections from PCK and/or wild-type rats were stained with Masson's trichrome or Picrosirius red to visualize collagen deposition in these tissues. The presence of multiple large and small cysts in the kidney and highly dilated irregular-shaped ducts in the liver, characteristic of this model of fibropolycystic kidney and liver disease, made it difficult to quantify fibrosis using histochemical stains. These stains therefore acted instead as a visual aid for the presence and location of matrix deposition in this model. Kidneys were also stained with anti-phospho PDGFR antibody (Antibody #3161, Cell Signaling) conjugated to horseradish peroxidase to visualize the presence and location of the activated receptor in this model of renal disease.

Western blot analysis

As described by Takikita-Suzuki *et al*^[20], the frozen kidney tissue was homogenized on ice in buffer containing Tris-HCl (20 mmol/L; pH 7.5), ethylenediamine tetraacetic acid (1 mmol/L), NaCl (140 mmol/L), Nonidet P-40 (1%), aprotinin (50 $\mu\text{g}/\text{mL}$), NaF (50 mmol/L), sodium orthovanadate (1 mmol/L) and phenylmethyl sulfonyl fluoride (1 mmol/L). Homogenized tissue was centrifuged for 30 min at 15000 rpm at 4 °C. Supernatant was collected and protein concentrations were measured using the method of Bradford. After 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis, the protein was transferred to a nylon membrane (Amersham Pharmacia Biotech, Buckinghamshire, England, United Kingdom). Blocking was performed for 2 h in phosphate-buffered saline (PBS) solution containing 5% (w/v) skim milk,

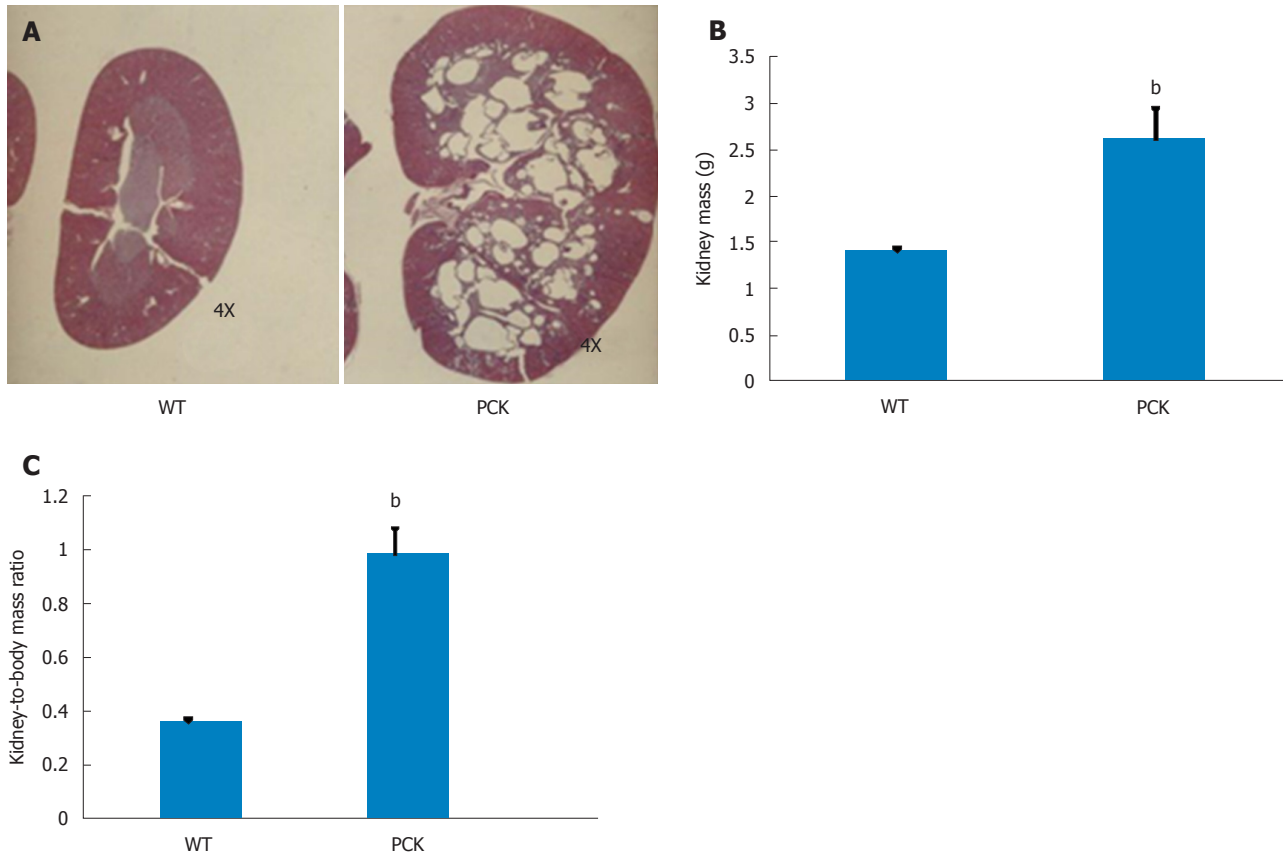


Figure 1 Renal characteristics in the PCK rat. A: Renal sagittal sections from 6 wk old wild-type (WT, Sprague-Dawley) and PCK rats showing an enlarged renal parenchyma and the medulla almost completely occupied with numerous cysts in the latter; B, C: At this time point, both kidney mass (B) and kidney-to-body mass ratio (C) were greater in the PCK rat (^b $P < 0.01$, vs WT).

followed with incubation with anti- α smooth muscle actin (α -SMA; Abcam) or anti-pPDGFR β (Antibody #3161, Cell Signaling) antibodies, followed by an appropriate HRP-conjugated secondary antibody (Cell Signaling). Proteins were detected using an enhanced chemiluminescence kit (Amersham/GE Healthcare, United Kingdom). Densitometric analysis for pPDGFR β was performed with normalization to GAPDH.

Statistical analysis

Data are presented as mean $\pm$ SD. Between-group effects were analyzed by one-way analysis of variance followed by Tukey's *post-hoc* test. A P -value < 0.05 is considered significant.

RESULTS

ANG3070 slows progressive kidney pathophysiology

Four-week treatment study: By approximately 6 wk of age, kidneys from PCK rats were enlarged and filled with numerous cysts (Figure 1). Both renal mass and renal-to-body mass ratio in PCK rats were significantly greater compared to the wild-type, age-matched cohort (Figure 1). By 10 wk of age, PCK rats (treated with vehicle, *i.e.*, 0.5 mL water, PO, BID) exhibited significant renomegaly compared to the wild-type cohort.

Intervention with ANG3070 from weeks 6-10 was associated with a reduction in renal mass, renal-to-body mass ratio and renal cystic index (Figure 2). Compared to kidneys from wild-type animals, kidneys from PCK rats exhibited increased fibrosis, evidenced by increased tissue hydroxyproline content with ANG3070 treatment of the PCK rat associated with a reduction in renal hydroxyproline content (Figure 2). In addition to its effects on renal morphology, ANG3070 therapy was associated with the mitigation of kidney injury demonstrated by a reduction in 24-h urine NGAL and urine KIM-1 and amelioration of renal dysfunction, evidenced by reduced proteinuria and reduced albuminuria (Figure 2).

Eight-week treatment study: The effects of 8 wk of ANG3070 treatment were obvious in both kidneys and livers harvested from 14 wk old animals. At this time, the average kidney mass in the PCK rat (vehicle cohort) was several fold that of its wild-type counterpart and cystic index was approximately 30%. Nevertheless, a reduction in renal mass, renal-to-body mass ratio and cystic index was observed with drug treatment. At 14 wk of age, in addition to severe renal cyst formation, kidneys from PCK rats exhibited interstitial fibrosis evidenced by trichrome staining. The dominating presence of large cysts made analysis of the trichrome-stained area impractical, and

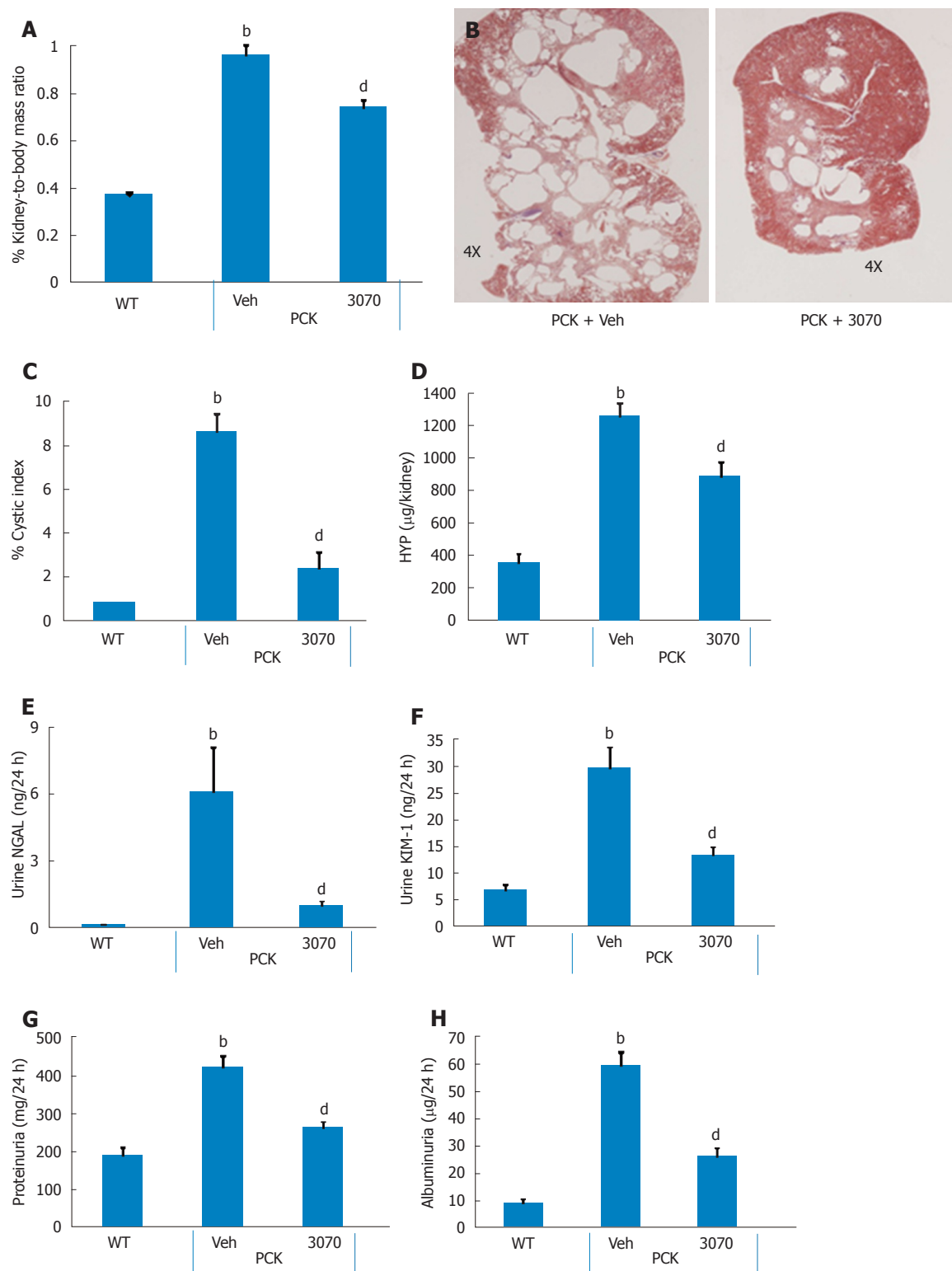


Figure 2 ANG3070 therapy attenuates renal mass, cystic index, renal injury, fibrosis and renal dysfunction. A, C: By approximately 10 wk of age, PCK rats [vehicle (Veh) cohort] had significantly larger renal mass and renal-to-body mass ratio (A) and increased cystic index (C) compared to the age-matched WT cohort ($^bP < 0.01$); B: Representative hematoxylin and eosin (HE)-stained renal sagittal sections (B) from PCK + Veh and a PCK + ANG3070 rats demonstrating cystic distribution across the renal parenchyma. Treatment of PCK rats with ANG3070 from weeks six to ten was associated with reduced kidney mass and kidney-to-body mass ratio (A) ($^dP < 0.01$, vs PCK + Veh); C: Treatment with ANG3070 reduced renal cystic index ($^dP < 0.01$, vs PCK + Veh); D: Total kidney hydroxyproline (a marker of collagen) content was increased at week ten in the PCK (Veh) rat, treatment with ANG3070 was associated with a reduction in this marker of kidney fibrosis ($^bP < 0.01$, vs WT; $^dP < 0.01$, vs PCK + Veh); E, F: Compared to the WT cohort, PCK (Veh) rats exhibited renal injury evidenced by increased urine neutrophil gelatinase-associated lipocalin (NGAL) (E) and urine kidney injury molecule-1 (KIM-1) (F) ($^bP < 0.01$, vs WT). Treatment with ANG3070 was associated with a reduction in these urinary markers (E and F) of renal injury; G, H: Renal dysfunction, evidenced by elevated proteinuria (G) and albuminuria (H) was reduced with ANG3070 treatment ($^dP < 0.01$, vs PCK + Veh). HYP: Collagen marker.

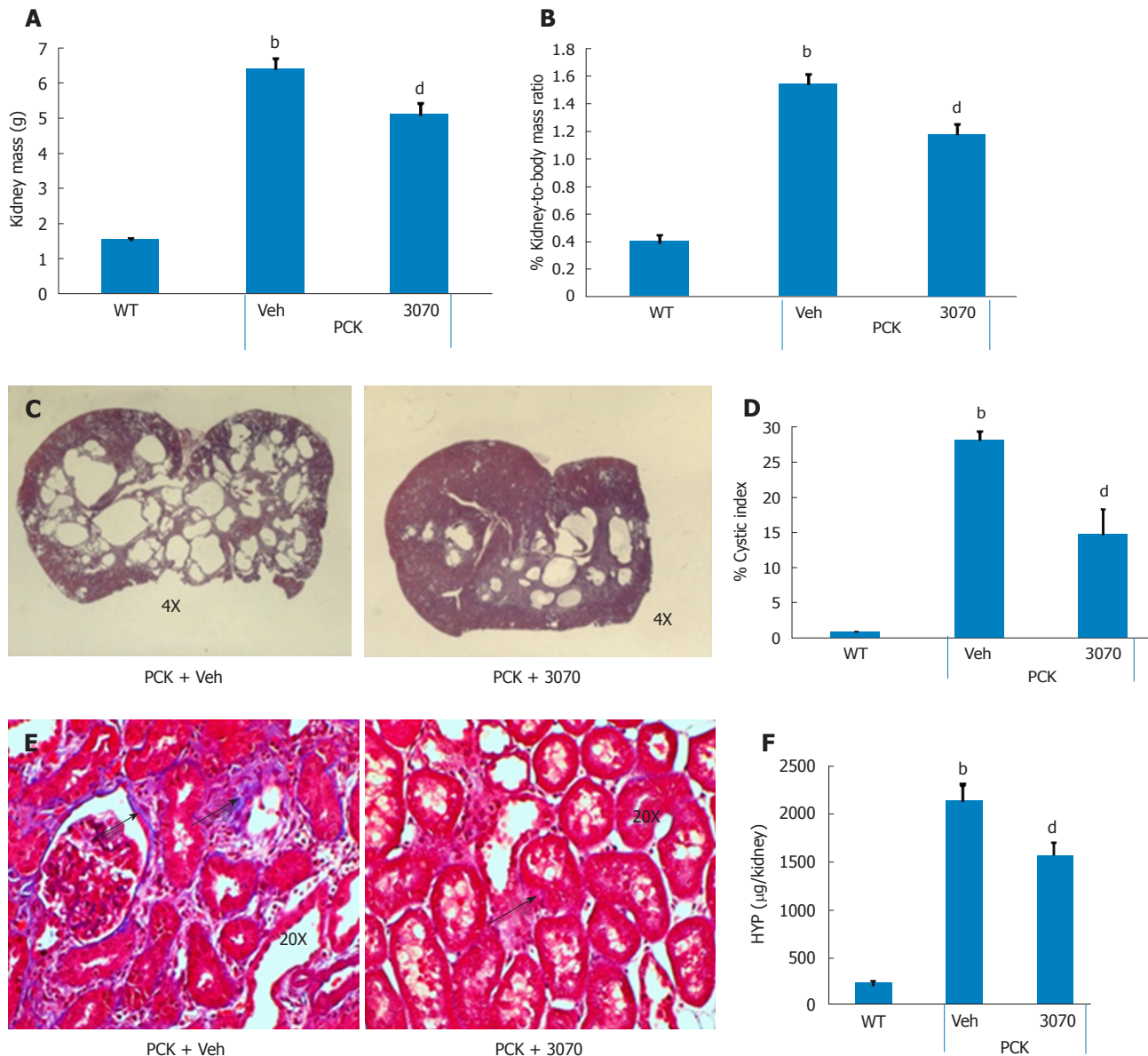


Figure 3 ANG3070 attenuates renal pathology and fibrosis in the PCK rat. A, B and D: By week 14, kidney mass (A), kidney-to-body mass ratio (B) and renal cystic index (D) were several-fold higher in PCK [vehicle (Veh)] rats compared to the WT cohort (^a $P < 0.01$, vs WT). ANG3070 therapy from weeks 6-14, mitigated renomegaly (A and B); C: Representative H and E-stained renal transverse sections from PCK + Veh and a PCK + ANG3070 rats demonstrating cystic distribution across the renal parenchyma at week 14; D: Treatment with ANG3070 reduced renal cystic index (^d $P < 0.01$, vs PCK + veh); E: Representative Masson's trichrome stained renal sections from PCK rats showing scarring within the renal interstitium (arrows) of PCK rats; F: Total kidney hydroxyproline (HYP—a marker of collagen) content was increased at week 14 in the PCK (Veh) rat (^b $P < 0.01$, vs WT). Treatment with ANG3070 was associated with a reduction in HYP, marker of kidney fibrosis (^d $P < 0.01$, vs PCK + Veh).

the extent of renal extracellular matrix deposition was therefore estimated biochemically in renal homogenates. Compared to the wild-type cohort, the PCK kidney (vehicle cohort) exhibited a marked increase in hydroxyproline content. Intervention with ANG3070 reduced renal fibrosis, evidenced by a decrease in total PCK kidney hydroxyproline content (Figure 3). Equally important, treatment with drug reduced renal injury, as evidenced by decreased 24-h urine - NGAL, KIM-1, cystatin C and IL-18 levels and attenuated key indices of renal dysfunction including proteinuria, albuminuria, BUN and SCr (Figure 4).

ANG3070 mitigates liver lesions: In addition to fibropolycystic kidney disease, PCK rats exhibit features of CHF and Caroli's disease, including hepatomegaly and ductal fibrosis with highly dilated intrahepatic ducts. Upon sacrifice (*i.e.*, approximately 14 wk of age), these characteristics of CHF and Caroli's disease were seen in PCK rats. Livers showed dilated intrahepatic ducts which were surrounded by matrix deposition, visible using H and E and Picrosirius red stains (Figure 5). Furthermore, frank hepatomegaly was evident in the PCK (vehicle) cohort. Although there was no increase in ALT (PCK vs wild-type, data not shown), AST was elevated. Treatment with

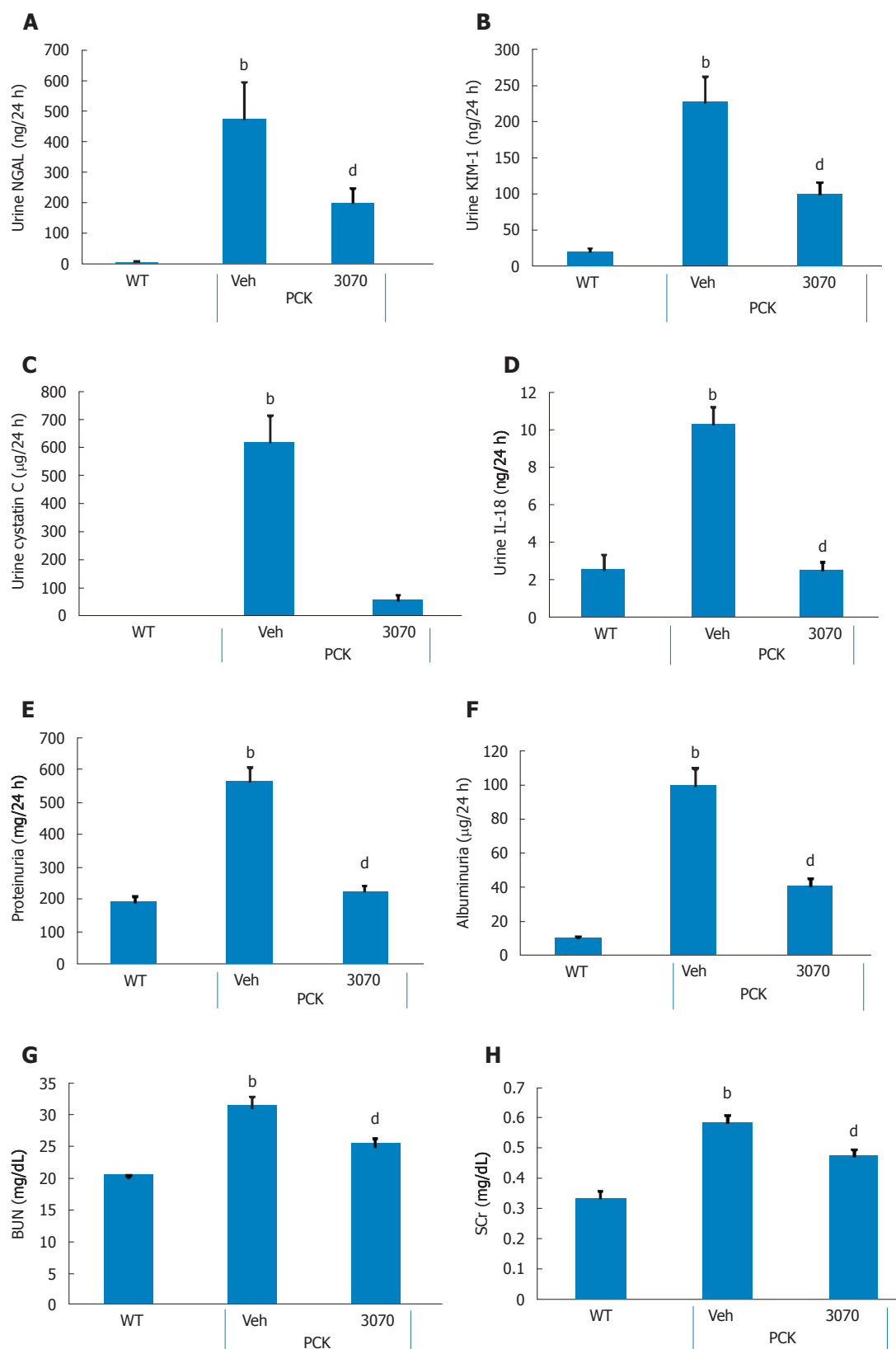


Figure 4 ANG3070 attenuates renal injury biomarkers and renal dysfunction. A-D: Compared to the WT cohort, at 14 wk of age, PCK [vehicle (Veh)] rats exhibited severe renal injury evidenced by increased urine - neutrophil gelatinase-associated lipocalin (NGAL) (A), kidney injury molecule-1 (KIM-1) (B), cystatin C (C) and interleukin-18 (IL-18) (D) (^b $P < 0.01$, vs WT). Treatment with ANG3070 was associated with a reduction in these urinary markers (A-D) of renal injury (^d $P < 0.01$, vs PCK + Veh); E-H: Renal dysfunction, evidenced by elevated proteinuria (E), albuminuria (F), blood urea nitrogen (BUN) (G) and serum creatinine (SCr) (H), was reduced with ANG3070 treatment (^b $P < 0.01$, vs WT; ^d $P < 0.01$, vs PCK + Veh).

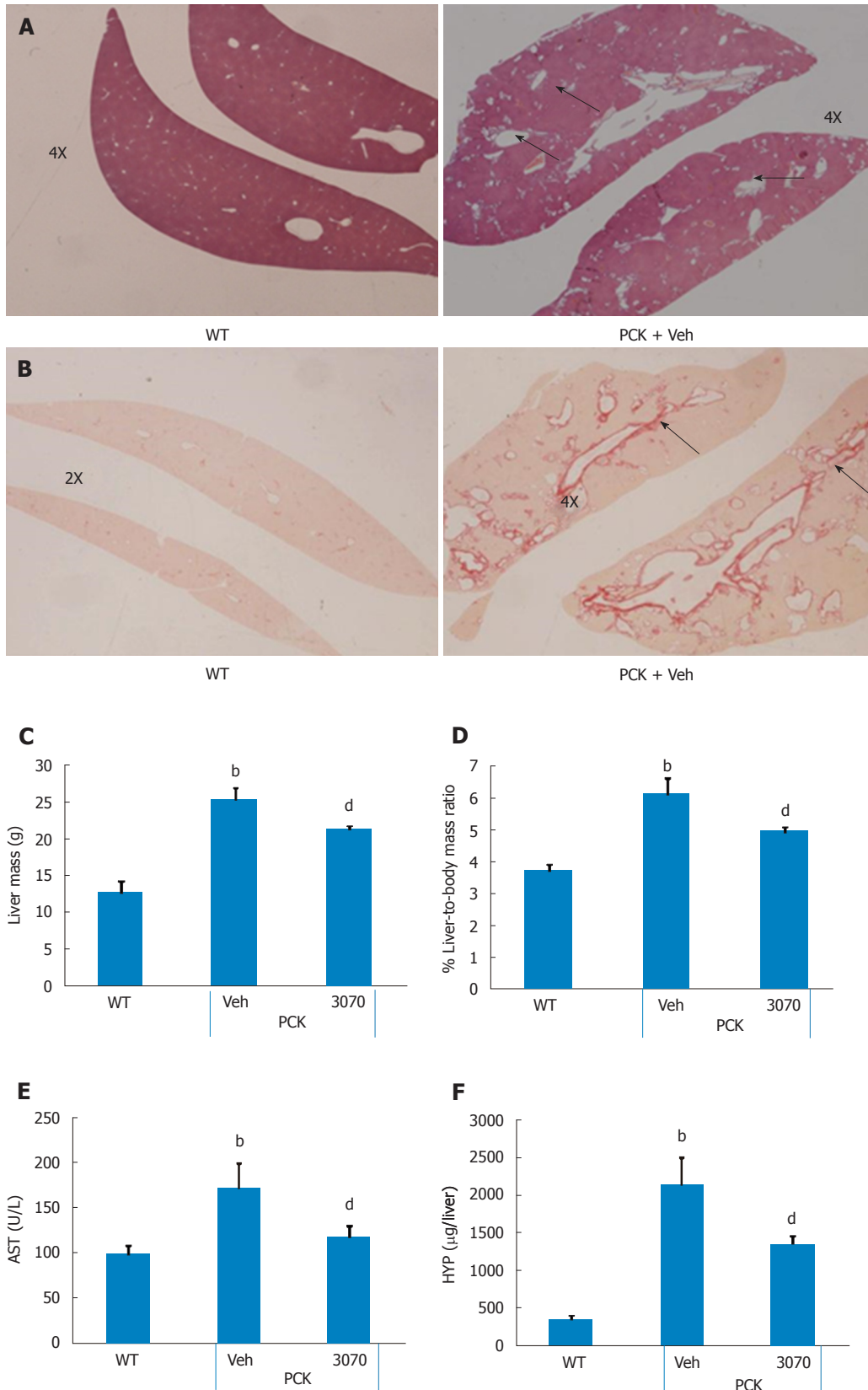


Figure 5 ANG3070 attenuates hepatic lesions, fibrosis and improves liver function in the PCK rat. A: Compared to the WT cohort, multiple, highly dilated bile ducts (arrows) are visible in H and E-stained PCK [vehicle (Veh)] livers by week 14; B: Representative Picrosirius red-stained liver showing ductal fibrosis (arrows) in the PCK (Veh) cohort; C-F: At sacrifice, PCK rats (Veh) exhibited increased liver mass (C), liver-to-body mass ratio (D) and aspartate aminotransferase (AST) (E) compared to the WT cohort. Total liver hydroxyproline content was also increased in the PCK rat (F). Treatment with ANG3070 was associated with a reduction in AST (E), hepatic lesions and fibrosis (HYP: Collagen marker) (A, B, C and F) (^b $P < 0.01$, vs WT; ^d $P < 0.01$, vs PCK + Veh).

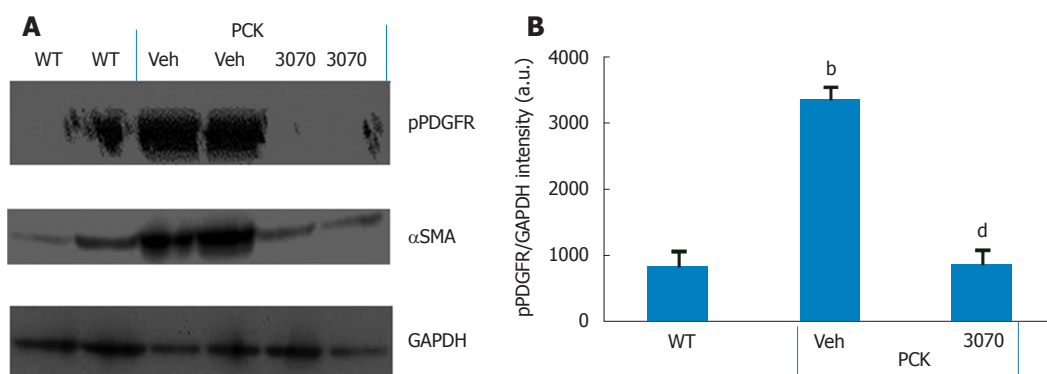


Figure 6 ANG3070 decreases phosphorylated platelet-derived growth factor receptor in the PCK rat kidney. A: Western blot analysis of kidney homogenates showed intense phosphorylated platelet-derived growth factor receptor (pPDGFR) levels in the PCK + vehicle (Veh) cohort compared to the WT and PCK + ANG3070 cohorts. A similar expression profile was seen with the fibrotic marker α smooth muscle actin (α SMA) in these kidneys. GAPDH expression is shown at the bottom; B: pPDGFR in renal homogenates from 10 wk old WT, PCK + Veh and PCK + ANG3070-treated animals was visualized with anti-PDGFR- α antibody and submitted to densitometric analysis with normalization to GAPDH. ANG3070 treatment was associated with a marked reduction in phosphorylated PDGFR levels (^b $P < 0.01$, vs WT; ^d $P < 0.01$, vs PCK + Veh).

ANG3070 reduced liver mass, liver-to-body mass ratio, AST and total liver hydroxyproline content (Figure 5).

ANG3070 pharmacodynamics: It has been reported that the cystic milieu is enriched in growth factors such as PDGF^[20]. The presence of multiple large and extensive cysts made immuno-histochemical quantification of pPDGFR impractical. Therefore, to determine whether the salutary effects of ANG3070 are associated with inhibition of this target, we evaluated the levels of pPDGFR together with the fibrotic marker α -SMA in renal homogenates from wild-type and vehicle- or ANG3070-treated PCK rats. As seen in Figure 6, compared to kidneys from wild-type animals, kidneys from the vehicle-treated PCK animals exhibited increased levels of both pPDGFR and α -SMA. In comparison to the PCK + Veh cohort, kidneys from the PCK + ANG3070 cohort exhibited decreased pPDGFR and α -SMA levels. Densitometric analysis of Western blots of renal homogenates from wild-type vs vehicle-treated PCK rats exhibited increased pPDGFR intensity, an effect that was reduced with ANG3070 treatment (Figure 6).

ANG3070 safety/toxicology profile: ANG3070 was efficacious and no potential toxic effects were observed in several rodent models. As detailed below, to date, there is no evidence of toxicity (liver or renal) in mice or rats dosed repeatedly over several weeks with ANG3070. In hundreds of mice and rats dosed several weeks with 150 mg/kg ANG3070 (PO, QD), there were no excursions in BUN (Veh 73 mg/dL; ANG3070 69 mg/dL) or SCr (veh 0.36 mg/dL; ANG3070 0.35 mg/dL) with ANG3070. In other rats dosed for 3 wk with ANG3070 (25 mg/kg, PO, BID $\times$ 3 wk), no excursions were seen in liver enzymes vs vehicle-dosed rats (ALT - veh: 92 IU; ANG3070: 61 IU; AST - Veh 158 IU; ANG3070 136 IU). There were no adverse events reported in 14 d toxicology studies in rats and dogs at nine-fold higher doses (450

mg/d) (data not shown) than the efficacious dose of ANG3070 (50 mg/d) at which antifibrotic efficacy was observed in fibropolycystic kidney disease-CHF. These studies indicate that ANG3070 was safe and well-tolerated without any potential toxic effects. In PCK rats, treatment of ANG3070 for several weeks did not increase sCR, BUN, AST and ALT. In fact, sCR and AST were reduced with 3070 treatment. Overall ANG3070 was efficacious in decreasing kidney and liver fibrosis with no potential toxic effects in other organs.

DISCUSSION

We herein report that intervention with the orally bioavailable small molecule PAGFR and VEGFR dual kinase inhibitor ANG3070 ameliorates fibropolycystic disease progression in the PCK rat model of ARPKD-CHF. Intervention with this drug mitigated renomegaly, renal injury and renal dysfunction and fibrosis, effects associated with reduced renal PDGFR phosphorylation. Treatment with ANG3070 also reduced hepatic enlargement and fibrosis while improving liver function.

The formation and expansion of fluid-filled cysts drive kidney enlargement, with both an increasing cystic index and progressive extracellular matrix deposition driving functional insufficiency in fibropolycystic ARPKD-CHF^[21,22]. A genetically-acquired and congenital disease, approximately 20-30% of affected patients succumb within the first 1-2 mo of life, with pulmonary insufficiency secondary to renal enlargement as the primary cause of death. For children making it past that stage, nephrectomy and dialysis or kidney transplant is often warranted by approximately ten years of age^[23,24]. Intervention at this age is driven both by renal insufficiency and the need for a reduction in severe flank pain due to highly enlarged kidneys. The hepatic lesion in ARPKD-CHF is CHF resulting from a malformation of the ductal plate secondary biliary strictures and periportal

fibrosis, with the majority of patients also presenting with hepatomegaly^[25,26]. Clinical studies in ARPKD-CHF reveal that a subset of patients progress to hepatocellular carcinoma^[27]. Other than transplantation, there is no cure for ARPKD-CHF.

Mutations in the human *PKHD1* gene or mutations in *PKHD1* orthologs in rats and mice are required for development of ARPKD-CHF. However, experimental studies have identified that epithelial cells drive changes in the renal interstitium, with alterations in the cystic epithelia followed by changes in the interstitial fibroblasts and progressive accumulation of extracellular matrix. This ultimately leads to the development of renal fibrosis within that organ^[28,29]. Furthermore, data from a number of studies suggest that growth factors, including PDGF and VEGF, are the intermediaries between the cystic and fibrotic components of progressive fibropolycystic disease^[5,11]. A study^[5] in the DBA/2FG-*pcy* mouse model of PKD suggests that increased expression of PDGF-A and PDGF-B chains may contribute to the progression of renal cystic lesions. Qin *et al*^[30] reported impaired degradation of PDGFR in renal cells from PKD mice. In the ORPK murine model of PKD, responses to PDGF by fibroblasts, in which ciliary assembly is defective, are abnormal. In fact, Norman *et al*^[31] identified a paracrine, PDGF-mediated regulatory loop between inner medullary collecting duct epithelial cells and medullary fibroblasts, highlighting the importance of tubular epithelial-interstitial fibroblast interactions in PKD. Compared to age-matched normal fibroblasts, PKD fibroblasts demonstrate an enhanced proliferative response to PDGF, synthesize more fibroblast growth factor, and elicit more rapid and persistent tyrosine phosphorylation of intracellular proteins. Consistent with these reports, pPDGFR signaling in our hands appeared to be increased in PCK rats compared to the wild-type cohort. PDGF activation was accompanied by upregulation of the fibrotic marker α SMA and matrix deposition in the renal interstitium. ANG3070 treatment decreased pPDGFR signaling and α SMA expression, indicating a decrease in fibrosis.

In the kidney, VEGF expression is most prominent in glomerular podocytes and in tubular epithelial cells, while VEGF receptors are mainly found on pre-glomerular, glomerular, and peritubular endothelial cells. Raina *et al*^[32] reported that anti-VEGF therapy in the Han: SPRD rat, a model of ADPKD, was associated with an exaggerated cystic response of the proximal tubules and severe kidney injury. Huang *et al*^[33] reported that VEGF therapy in the *Pkd1^{nl/nl}* mouse model of ADPKD was associated with robust benefits across a spectrum of endpoints, with far more modest benefits evident in the *Cys1^{cpk/cpk}* mouse, a model of ARPKD. On the other hand, it has been postulated that VEGF-driven angiogenesis drives cyst cells to grow, and may be responsible for increased vascular permeability and fluid secretion into the cysts. In fact, data from clinical trials

point to a relationship between circulating VEGF and renal structural disease, including total renal volume, cyst volume and cyst number, and are indicative of a potential role for upregulated angiogenesis in early renal cyst progression^[10-13]. Finally, Jiang *et al*^[14] postulated that a pathogenic triumvirate, comprised by hyperproliferation of cyst wall growth, pericystic fibrosis, and inflammation, drives CHF/ARPKD progression.

ANG3070 is a proprietary, highly water-soluble, orally bioavailable potent inhibitor of PDGF and VEGF/KDR, which binds its targets with a K_d of approximately 5 nmol/L. In the PCK rat model of ARPKD-CHF, ANG3070 efficacy was observed across a spectrum of clinically-relevant endpoints, including a decrease in renomegaly, renal cystic index, renal injury markers, renal fibrosis and improvement in kidney function. Importantly, intervention with ANG3070, even after established renal disease at both 10 and 14 wk (a time when renal pathology is fairly advanced in the PCK rat), proved efficacious. Taken together, these data indicate that ANG3070 has therapeutic efficacy and slows a hallmark indicator of disease progression in ARPKD-CHF *via* cystic expansion of the kidney.

Another salient finding of this study was the effect of ANG3070 in mitigating renal injury in this model of ARPKD-CHF. Urinary markers of renal injury, including NGAL, KIM-1, cystatin C and IL-18, were increased in the PCK rat compared to wild-type controls. Previous studies have described the elevation of such markers in models of ARPKD-CHF. In fact, work by Nieto *et al*^[34] indicates that BUN, SCr and 24-h urine IL-18 levels are biomarkers for increasing cystic index and increasing renal mass in the PCK rat. The fact that ANG3070 treatment was associated with a reduction of these biomarkers, including BUN, SCr and urine IL-18, not only suggests that this drug attenuates kidney injury but also suggests that it mitigates cystogenesis and renal expansion.

A pharmacodynamic exercise to confirm the mechanism of action of ANG3070 was undertaken in renal homogenates from the wild-type and PCK cohorts. Consistent with data from the aforementioned studies, PDGFR signaling was enhanced in the PCK rat kidney, evidenced by increased levels of pPDGFR. Administration of ANG3070 to the PCK rat reduced renal phosphorylated PDGFR levels, suggesting that the drug is indeed engaging its target and that the salutary effects of ANG3070 in the kidney are associated with inhibition of PDGFR signaling.

In addition to its effects on the kidney, ANG3070 exhibited activity against the hepatic lesions that accompany this disease. While hepatomegaly, elevated serum AST and increased hepatic collagen content were observed in the PCK rat at 14 wk of age, 8 wk treatment with ANG3070 resulted in significant amelioration of both liver pathology and liver dysfunction. This is an important finding, in that not only can hepatomegaly and hepatic fibrosis necessitate liver transplantation in

ARPKD-CHF patients, but also that a cytokine-driven feedback mechanism might exist between hepatic and renal lesions in this disease. Needless to say, there were some clear limitations to this study. Given the historical challenges associated with demonstrating a pharmacodynamic signature of VEGFR/KDR phosphorylation inhibition, we did not attempt to evaluate this signaling mechanism in the kidney or liver. Finally, the PCK rat is one model of ARPKD-CHF and it remains to be determined whether ANG3070 exerts similar effects in other models of this disease. In summary, intervention with ANG3070 favorably impacted both the renal and hepatic components in the PCK rat model of fibropolycystic disease. These data suggest that ANG3070 has the potential to slow ARPKD-CHF and may serve as a bridge toward hepato-renal transplantation in patients with fibropolycystic disease.

ARTICLE HIGHLIGHTS

Research background

In autosomal recessive polycystic kidney disease (ARPKD)-congenital hepatic fibrosis (CHF), a genetically acquired and congenital disease, mutations in the human *PKHD1* gene or mutations in *PKHD1* orthologs in rats and mice are required for the development of ARPKD-CHF. Nevertheless, experimental studies have identified that epithelial cells drive changes in the renal interstitium, with alterations made to the cystic epithelia followed by changes in the interstitial fibroblasts and progressive accumulation of extracellular matrix. This leads to the development of renal fibrosis within the kidney and/or liver. For children, nephrectomy and dialysis or kidney or liver transplant is often warranted by approximately ten years of age. Other than transplantation, there is no cure for ARPKD-CHF. We report that platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) are the intermediaries between the cystic and fibrotic components of progressive fibropolycystic disease, and that a PDGFR + VEGFR dual inhibitor can be a novel therapeutic approach.

Research motivation

The development of new therapies that prevent the transition from cystogenesis to fibrosis or adenocarcinoma in advanced stages of ARPKD-CHF will have tremendous clinical potential and decrease the number of hepato-renal transplants in patients with ARPKD-CHF.

Research objectives

The main objectives of our studies were to evaluate a novel PDGFR and VEGFR dual kinase inhibitor, ANG3070, in a PKD-CHF model. These studies could lead to a novel therapeutic approach for fibropolycystic kidney disease.

Research methods

Renal pathology was confirmed in PCK rats at 6 wk compared to the age and gender-matched wild type SD rats. At 6 wk of age, PCK rats were then randomized to vehicle or ANG3070 for 4 wk. At 10 wk, 24 h urine and left kidneys were collected and rats were continued on treatments for 4 wk. At 14 wk, 24 h urine was collected, rats were sacrificed, and liver and right kidneys were collected for histological evaluation. For Western blot studies, PCK rats were treated with vehicle or ANG3070 for 7 d and sacrificed approximately 30 min after the last treatments.

Research results

A well-characterized PCK rat model was used to study fibropolycystic kidney disease. Compared to the wild-type cohort, the PCK kidney (Vehicle cohort)

exhibited a marked increase in kidney and liver mass, hepato-renal cystic volume, hepato-renal fibrosis and hepato-renal injury biomarkers. Intervention with ANG3070 in PCK rats decreased kidney weight, reduced renal cystic volume and reduced total kidney hydroxyproline, thus indicating significantly reduced renal interstitial fibrosis compared to the PCK-Vehicle cohort. ANG3070 treatment also mitigated several markers of kidney injury, including urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, Cystatin C and interleukin-18 levels. This treatment also significantly attenuated key indices of renal dysfunction, including proteinuria, albuminuria and serum blood urea nitrogen and creatinine, and improved renal function compared to the PCK-Vehicle cohort. ANG3070 treatment also significantly decreased liver enlargement, hepatic lesions, decreased liver fibrosis and mitigated liver dysfunction compared to the PCK-Vehicle cohort. A dose-response study of ANG3070 needs to be evaluated to establish a minimum dose for maximal therapeutic efficacy in this PCK rat model.

Research conclusions

The development of new therapies that prevent the transition from cystogenesis to fibrosis or adenocarcinoma in advanced stages of ARPKD-CHF will have tremendous clinical potential. Studies indicate that PDGF and VEGF are the intermediaries between the cystic and fibrotic components of progressive fibropolycystic disease. We have identified and synthesized a novel small molecule PDGFR + VEGFR/KDR dual kinase inhibitor, ANG3070, using molecular modeling coupled with rational drug design, medicinal chemistry and structure activity relationship. We have evaluated ANG3070 therapeutic effects in a rat model of ARPKD-CHF and have proven it to be efficacious in mitigating kidney and liver injury biomarkers and decreasing hepatic and renal dysfunction. These studies could lead to the identification of a novel therapeutic approach in slowing fibropolycystic disease and decreasing the number of hepato-renal transplants in patients with ARPKD-CHF. These results suggest that ANG3070 has the potential in slowing disease, and may serve as a bridge toward hepato-renal transplantation in patients with fibropolycystic disease.

Research perspectives

The results of our studies suggest that ANG3070 has the potential therapeutic effect of slowing disease, and may serve as a bridge toward hepato-renal transplantation in patients with the fibropolycystic disease ARPKD-CHF.

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Basic Study

Unique interstitial miRNA signature drives fibrosis in a murine model of autosomal dominant polycystic kidney disease

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Abstract

AIM

To delineate changes in miRNA expression localized to the peri-cystic local microenvironment (PLM) in an orthologous mouse model of autosomal dominant

polycystic kidney disease (ADPKD) (*mcwPkd1^{nl/nl}*).

METHODS

We profiled miRNA expression in the whole kidney and laser captured microdissection (LCM) samples from PLM in *mcwPkd1^{nl/nl}* kidneys with Qiagen miScript 384 HC miRNA PCR arrays. The three time points used are: (1) post-natal (PN) day 21, before the development of trichrome-positive areas; (2) PN28, the earliest sign of trichrome staining; and (3) PN42 following the development of progressive fibrosis. PN21 served as appropriate controls and as the reference time point for comparison of miRNA expression profiles.

RESULTS

LCM samples revealed three temporally upregulated miRNAs [2 to 2.75-fold at PN28 and 2.5 to 4-fold ($P \leq 0.05$) at PN42] and four temporally downregulated miRNAs [2 to 2.75 fold at PN28 and 2.75 to 5-fold ($P \leq 0.05$) at PN42]. Expression of twenty-six miRNAs showed no change until PN42 [six decreased (2.25 to 3.5-fold) ($P \leq 0.05$) and 20 increased (2 to 4-fold) ($P \leq 0.05$)]. Many critical miRNA changes seen in the LCM samples from PLM were not seen in the contralateral whole kidney.

CONCLUSION

Precise sampling with LCM identifies miRNA changes that occur with the initiation and progression of renal interstitial fibrosis (RIF). Identification of the target proteins regulated by these miRNAs will provide new insight into the process of fibrosis and identify unique therapeutic targets to prevent or slow the development and progression of RIF in ADPKD.

Key words: Inflammation; End-stage renal disease; Cysts; Autosomal dominant polycystic kidney disease; miRNA; Renal interstitial fibrosis

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Core tip: An essential and consistent histologic feature of progressive autosomal dominant polycystic kidney disease (ADPKD) is interstitial inflammation and fibrosis. This study investigated miRNA expression in local pericystic areas between cysts that become fibrotic as the disease progresses. This study identifies a critical limitation to whole organ transcriptomic approaches and demonstrates that laser capture microdissection (LCM) provides a means to overcome the dilutional factor of whole organ miRNA analysis. The precision of LCM provides a unique miRNA signature, which identifies novel molecular and therapeutic targets that initiate and drive interstitial fibrosis in ADPKD.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by bilateral fluid-filled tubular cysts and progressive renal interstitial fibrosis (RIF). Renal function remains relatively normal until RIF reaches a tipping point, initiating a rapid decline of function leading to end-stage renal disease (ESRD).

miRNAs play key roles in diverse biological processes including cell division and death, intracellular signaling, cellular metabolism, immunity, and RIF. miRNAs are known to be involved in a variety of common human disorders including RIF^[1,2].

ADPKD is a common life-threatening renal disease that affects an estimated 12 million patients worldwide^[3]. ADPKD is a heterogeneous disease with mutations in *PKD1* (MIM173910) (16p13.3) and *PKD2* (MIM173900) (4q22.1), which are responsible for approximately 80% and 15% cases respectively, with the remaining cases due to mutations at other rare loci^[4].

Although ADPKD is a systemic disorder, it is characterized by the progressive development and growth of bilateral fluid-filled tubular cysts^[5,6]. Renal cyst formation and expansion is followed by the development of RIF that ultimately leads to ESRD. Half of all ADPKD patients develop ESRD and require renal replacement therapy by their fifth decade^[5,7].

Therapies currently in clinical trials focus on increased total kidney volume (TKV) as an indicator of disease severity, with decreased TKV reflecting the success of treatment^[8-10]. However, an essential feature of the disease is interstitial inflammation and fibrosis^[11-13]. Such interstitial changes lead to decreased TKV and strongly correlate with a decline in kidney function.

Renal fibrosis is the key determinant of the progression of all renal disease including ADPKD, irrespective of the original cause, and dictates the eventual outcome^[11,13,14]. As cystic lesions enlarge, they compress both normal renal parenchyma and vascular elements between multiple cysts, creating a peri-cystic local microenvironment (PLM) that becomes fibrotic over time. The decline of renal function and the development of ESRD correlate with the progression of fibrosis in ADPKD^[13,15,16]. Despite this link of ESRD to fibrosis, there is virtually no therapy specifically targeting fibrosis in ADPKD. This unmet clinical need calls for additional studies and a better understanding of the underlying mechanistic changes that lead to renal fibrosis.

Recent published studies have identified an essential role for miRNAs in the pathogenesis of both cyst formation and fibrosis in polycystic kidney disease^[17-21]. miRNAs are short noncoding RNAs that regulate gene expression by reducing the translation of messenger RNAs^[22-24]. miRNAs function in a diverse range of biological processes

and demonstrate spatial and temporal expression patterns^[25]. MicroRNAs have been associated with many basic cellular processes as well as with a wide spectrum of diseases^[1,24,25]. In the kidneys, miRNAs have been associated with renal development, homeostasis, and physiological functions^[24,25]. Aberrant miRNA expression has been observed in mouse models of kidney fibrosis^[18,20,26]. Notably, all previously published analysis has been performed in either whole kidney or cell culture models.

As cysts develop and enlarge, a local interstitial microenvironment is created between enlarging tubular cysts. This PLM is a complex milieu that integrates reciprocal signals from resident interstitial cells, infiltrating immune cells and proliferating cystic epithelial cells from enlarging tubular cysts. A complex interplay of many factors, including those driven by miRNA expression, occurs within the PLM. miRNAs play a role in determining the balance between pro-fibrotic and anti-fibrotic factors and how the dynamics of this balance drive the development of fibrosis^[18,26]. In this study, we delineate changes in miRNA expression localized to the PLM in an orthologous mouse model of ADPKD (*mcwPkd1^(nl/nl)*). This model reliably demonstrates two phases of PKD: (1) the development and progressive enlargement of renal cysts, and (2) the development and progression of RIF, leading to loss of renal function. This model has a stable genetic background and permits both the investigation of pathogenic mechanisms and testing of potential therapeutic interventions. In the current study, we identify a unique PLM miRNA signature that drives fibrosis in this model.

MATERIALS AND METHODS

ADPKD mouse model (*mcwPkd1^(nl/nl)*)

The *mcwPkd1^(nl/nl)* mice were generated as previously described^[27]. Briefly, insertion of a neo-cassette into the *Pkd1* allele (*Pkd1^{nl}*) resulted in a cryptic splice site that allowed approximately 20% expression of a normal *Pkd1* allele in homozygous *Pkd1^(nl/nl)* mice^[27]. In contrast to homozygous *Pkd1* knockout mice, which are embryonically lethal, homozygous *mcwPkd1^(nl/nl)* mice are viable, with bilaterally-enlarged polycystic kidneys by postnatal (PN) day 21, followed by the development and progression of RIF and ESRD between PN120 and PN150.

In the *mcwPkd1^(nl/nl)* mouse, renal cystic lesions begin in utero, and TKV peaks by PN35. The initial appearance of light, wispy trichrome staining occurs in PLM at PN28.

All animal experiments were conducted in accordance with policies of the NIH Guide for the Care and Use of Laboratory Animals and the Institutional Animal Care and Use Committee (IACUC) of the Medical College of Wisconsin. The protocols used in this study were conducted under AUA 4379, which was approved by the Medical College of Wisconsin IACUC committee. The

Animal Welfare Assurance for the Medical College of Wisconsin is A3102-01.

Sample preparation

Characterization of *mcwPkd1^(nl/nl)* identified the time points of interest for this study. Triplicate samples from each of three time points were collected for analysis. These time points include: PN21, before evidence of collagen deposition with trichrome (controls); PN28, where trichrome-positive PLM was first evident; and PN42, when fibrosis was widespread. One kidney was placed directly in 10% formalin and paraffin-embedded (FFPE), and the contralateral kidney was flash frozen for RNA isolation.

Laser capture microdissection (LCM)

Serial 10 μ m sections, at three different depths of the FFPE tissue, were floated onto PEN[®] membrane slides (Zeiss-415190-9081-000). A section from each of the three groups was stained lightly with McLethie's Trichrome stain for fibrosis. This stained section was used to guide LCM of its serial companion section. LCM of PN21 was accomplished by taking areas between multiple cysts due to the absence of trichrome-positive areas. The PN21 pre-fibrotic cystic kidney was used as the appropriate control, because aged-matched wildtype kidney is devoid of adequate interstitial areas for comparative analysis (Figure 1).

RNA extraction

After harvesting 300000 μ m² of PLM, total (miRNA and mRNA) RNA was extracted with Qiagen's miRNeasy FFPE kit (Qiagen #217504) according to the manufacturer's instructions. The isolated total RNA was converted to cDNA using the miScript II RT Kit (Qiagen #218161), according to the manufacturer's instructions, and was subsequently amplified using the miScript PreAMP PCR kit (Qiagen #331452). The amplified cDNA was used for reverse transcription PCR using the miRNome miScript miRNA PCR Array (Qiagen #331222) to assess changes in miRNA expression over time. miRNA profiling of contralateral whole kidney samples was similarly performed as described above.

Quality control

The quality of the samples was assessed by determining the 260/280 ratios and RNA integrity numbers (RIN) using the Agilent 2100 bioanalyzer and RNA 6000 Pico kits, respectively. RNA samples with a 260/280 ratio > 1.6 yielded an RIN between 7 and 9. RINs > 7 passed the internal RNA quality control test of the Qiagen miRNA plates. Samples with a 260/280 ratio > 1.6 were analyzed immediately and had to pass the internal controls of the plates to be included in our analysis. The RIN of the samples was periodically obtained. In all cases where the 260/280 ratio exceeded 1.6, RIN values

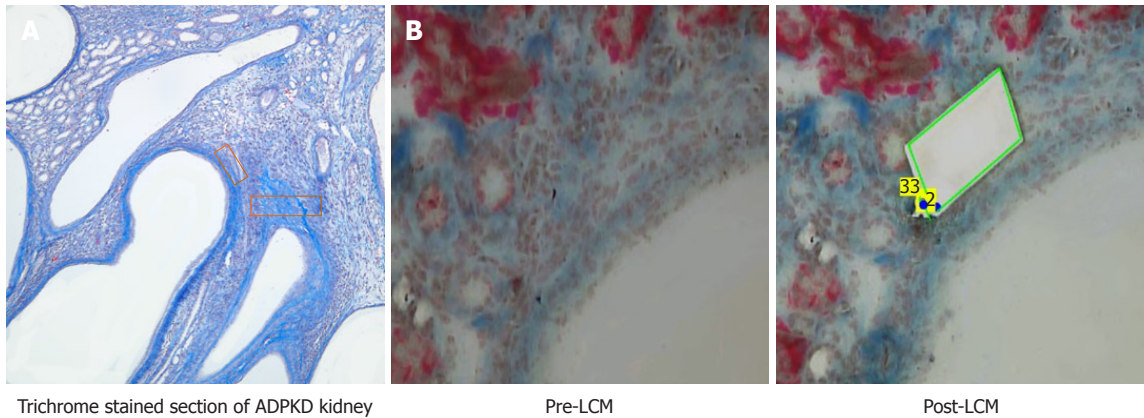


Figure 1 Laser capture microdissection of the peri-cystic local microenvironment. A: Trichrome-stained section of a dominant polycystic kidney diseased (ADPKD) kidney with representative laser capture microdissection (LCM) areas marked by red rectangles; B: Trichrome-stained section of an ADPKD kidney before and after LCM.

exceeding 7.0 were obtained and passed the internal controls of the Qiagen plates.

Trichrome staining

Slides were deparaffinized in xylene, then rehydrated in 95% ETOH. Slides were then stained with McLethie's Trichrome (Newcomer Supply #9177), according to the manufacturer's instructions.

Statistical analysis

A total of three animals were included at each time point (PN21, PN28 and PN42) for both the LCM and whole kidney groups. Data were normalized for miRNA expression to stably-expressed housekeeping genes (*SNORD68* and *SNORD96A*) at each time point. Whole kidney miRNAs from contralateral kidneys were similarly examined at PN21, PN28 and PN42.

Average CT values and the standard deviations for the miRNAs expressed were examined. A sample size of $n = 3$, sufficient for appropriate statistical analysis, was selected. Data was analyzed using the Qiagen® online portal and GraphPad® Instat 3. Data are expressed as a change in expression for a particular miRNA (fold-regulation) at PN28 and PN42 compared to PN21 for both the PLM region and whole kidney. Only changes ± 2 -fold are included in the analysis. $P \leq 0.05$ was considered significant.

TargetScan and miRDB websites were used to determine targets for the miRNAs.

RESULTS

More than 900 miRNAs were examined in the laser captured PLM at the three different time points (PN21, PN28, PN42). miRNA expression in PLM at two different time points (PN28 and PN42) was compared with PN21 in order to: (1) provide a relative change in the expression of miRNAs during the onset of fibrosis; and (2) reflect local micro-environmental changes with

disease progression.

Whole kidney miRNA changes compared with PLM miRNA changes

Whole kidney miRNA expression was compared to the miRNA expression profiles obtained from laser captured PLM samples at PN28 and PN42, with PN21 as a control (Figure 2). The heat maps show major differences in the expression levels of key miRNAs between the whole kidney and PLM areas (Figure 2).

PLM miRNA changes with onset of fibrosis at PN28

The mechanism(s) by which miRNAs represses translation allows us to make certain predictions. An increase in miRNA expression would likely lead to a reduction in the level of the target protein, and a decrease in miRNA expression would yield an increase in the target protein.

In Figure 3A, there are three miRNAs that show temporal increase in expression at PN28 and PN42. miR-667-3p, miR-3074-5p and miR-7b-3p are upregulated 2 to 2.75-fold at PN28, and are further upregulated to 2.5 to 4-fold and reach statistical significance at PN42.

In Figure 3B, a similar comparison made for sequentially downregulating miRNAs shows that a total of four miRNAs that are downregulated at PN28 continue to further decrease expression at PN42. miR-378a-3p, miR-30e-5p, miR-30a-5p and miR-344f-5p are downregulated 2 to 2.75-fold at PN28, and are further reduced 2.75 to 5-fold and reach statistical significance at PN42.

PLM miRNA changes with progressive fibrosis at PN42

Figure 4 show the results of PLM miRNA changes at PN42, which represents a stage of progressive fibrosis.

miRNAs with decreased expression > 2 -fold at PN42 are shown in Figure 4A. miR-484, miR-455-3p, miR-130a-3p, miR-93-5p, miR-106-5p and miR-677-3p are significantly downregulated in the range of 2.25 to 3.5-fold. miR-106-5p showed the largest decrease at 3.5-fold.

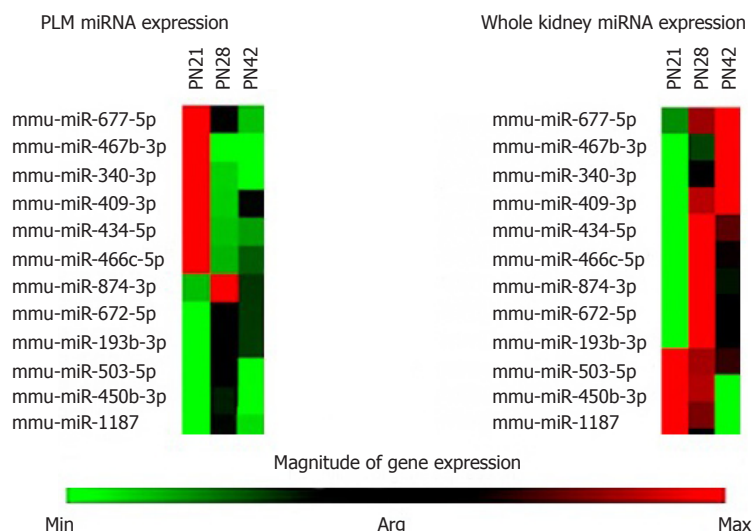


Figure 2 Heat map comparing miRNA expression. Heat map showing comparative expression of a set of miRNAs at three different post-natal (PN) time points (PN21, PN28 and PN42) for peri-cystic local microenvironmental regions and whole kidney samples (green represents downregulated miRNA expression, whereas red represents upregulated miRNA expression).

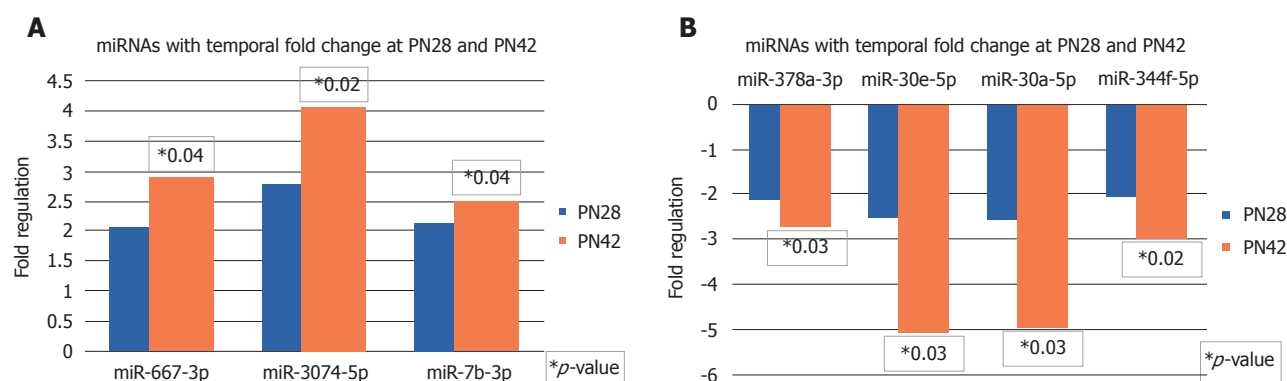


Figure 3 miRNA expression profiles. Expression profiles of a set of miRNAs at PN28 and PN42 that are temporally upregulated (A) and downregulated (B) when compared with PN21 in peri-cystic local microenvironmental regions.

miRNAs with increased expression >2-fold at PN42 are shown in Figure 4B. miR-409-3p, miR-762, miR-298-5p, miR-149-5p, miR-186-5p, miR-125a-3p, miR-331-3p, miR-155-5p, miR-329-3p, miR-186-5p, miR-376c-3p, miR-665-3p, miR-383-5p, miR-107-3p, miR-542-3p, miR-672-5p, miR-32-5p, miR-96-5p, miR-503-5p and miR-466d-3p are significantly upregulated (2 to 4-fold).

DISCUSSION

In ADPKD, despite massive increases in kidney size, loss of renal function and progression to ESRD is largely dependent upon the development of renal fibrosis^[11]. In the *mcwPkd1*^(nln) mouse, we discovered that fibrosis started in discreet areas between multiple cysts at PN28, evidenced by light wispy trichrome-positive staining in sporadic areas between multiple cysts. Similar areas between multiple cysts were evident in PN21 kidneys, but they never showed positive trichrome staining. By PN42, trichrome staining revealed a spread of the fibrosis outward from PLM. This suggested to us that we may

be able to identify critical elements necessary for the initiation and progression of fibrosis by using LCM to capture and analyze changes in PLM areas at the specific time-points noted. PN21 PLM areas provided appropriate controls, as they are devoid of fibrosis. Wild-type tissue was not an appropriate control in this experiment because it has minimal interstitial tissue that can be targeted for LCM. The risk of contaminating the wild-type LCM samples with epithelial tissue is unacceptably high.

Many previous studies have examined miRNA expression in whole kidneys to study progressive renal diseases^[18,21,28-30]. However, a critical limitation to transcriptomic approaches of whole kidney is the kidney's cellular complexity: arrays from whole kidney reflect the averaged= expression of 26 or more different cell types^[31-33]. This limitation is exacerbated in the presence of inflammatory cells in diseased kidneys.

The most striking result of these studies was the difference in miRNA profiles from PLM and whole kidney as shown in cluster heat maps (Figure 2). The expression of miRNAs in PLM is very different when compared to

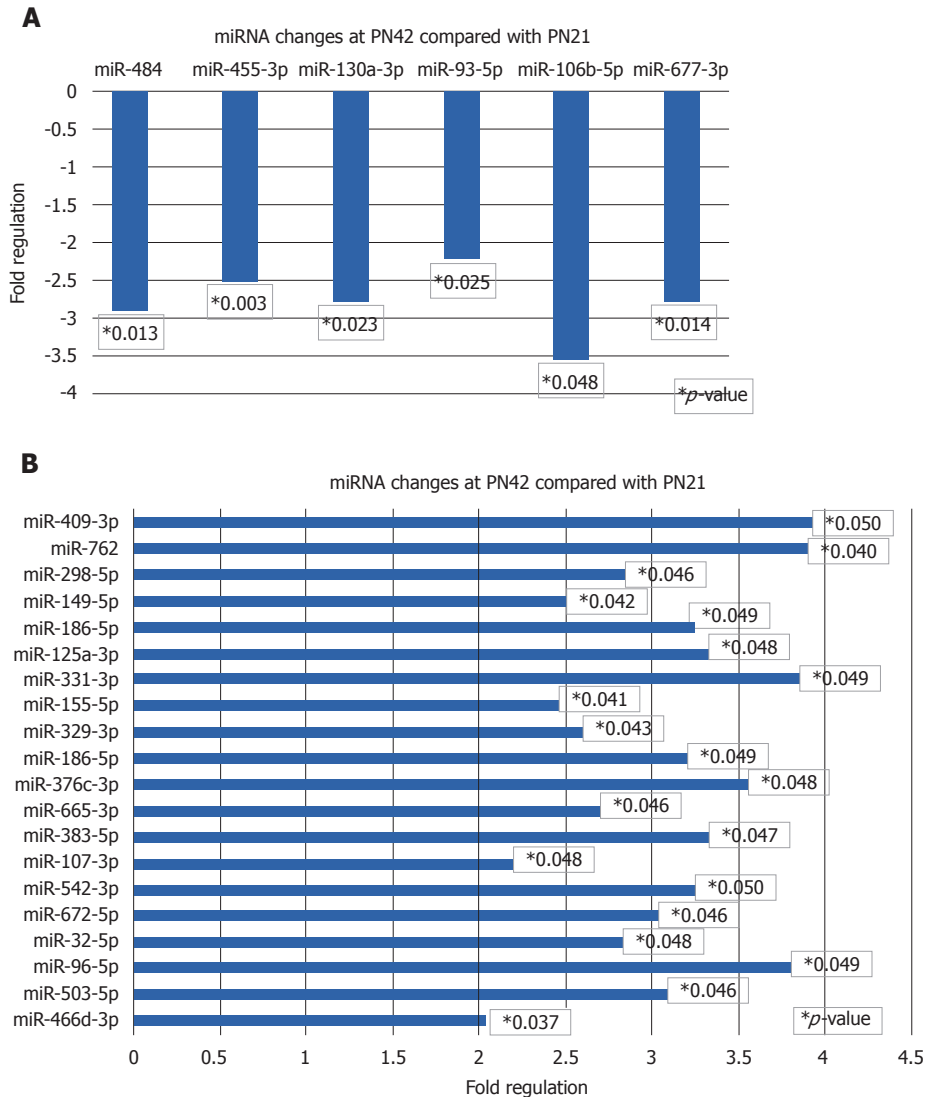


Figure 4 miRNA expression profiles. Expression profiles of a set of miRNAs with significantly decreased (A) and increased (B) expression at PN42 in peri-cystic local microenvironmental regions compared with PN21.

whole kidney expression. These findings likely reflect a dilution of important local changes in miRNAs when whole kidney comparisons are made. The implication of this is clear. Relying on whole kidney analysis may lead one to make errors in interpreting miRNA data.

The key miRNA changes noted in PLM, interestingly, are involved in or have predicted targets that play a role in the pathogenesis of either fibrosis, PKD or are unique. miRNAs with decreased expression at PN28 and PN42 (Figure 3B) have predicted targets (listed in brackets) as follows: miR-30a-5p and miR-30e-5p (Socs6, Timp2, Rock2, Bcl6, Col9a3, Col13a1, Smad1, Irf4) and miR-378a-3p (Mapk). Timp2 inhibits extracellular matrix proteolysis in multiple tissues, thus promoting fibrosis. Rock2, Irf4 and BCL6 have known roles in macrophage polarization, which plays an important role in the process of both inflammation and fibrosis. Mapk is an important mediator in the pathogenesis of PKD^[34]. The expression of these miRNAs sequentially decreases at PN28 and PN42, which correlates with worsening PLM fibrosis.

Moreover, there are six additional interesting miRNAs that have decreased expression in PN42 PLM (Figure 4). These miRNAs with their targets are as follows: miR-484 (Tgfr3, Fgf1), miR-455-3p (HB-EGF), miR-130a-3p (Tgfr2, Tgfr1, Tnf, Wnt1, Ppar), miR-677-5p (Col15a1), miR-106b-5p and miR-93-5p (Fgf4, Vegfa, Stat3, Mapk4, Mapk9, Hif1 α , Ppar α , Col4a3, Col4a4). Tgfr and Tgfr are integral to the processing of fibrosis, but are involved in late stages of progressive fibrosis^[35]. HB-EGF is a member of the EGF family of proteins and is produced by monocytes and macrophages^[36,37]. Recently, high urinary levels of HB-EGF are discovered in the urine of patients with severe PKD^[36-38]. Stat3 plays an important role in the pathogenesis of PKD^[39,40]. Hif1 has roles in angiogenesis, fibrosis, and is closely tied to local hypoxia^[35], which may be the direct result of expanding cystic lesions.

Furthermore, PLM miRNAs with increased expression at PN42 are shown in Figure 4A and their predicted targets are as follows: miR-466d-3p (Smad7), miR-

542-3p (Bmp7), miR-96-5p (β Raf, Nox4), miR-186-5p and miR-329-3p (Usf2) miR-762 (Cx3cl1), miR-155-5p (Socs1, Csf1r), and miR-331-3p (Mmp13). Smad7 inhibits TGF- β signaling by preventing formation of Smad2/Smad4 complexes^[35,41]. BMP7 reduces extracellular matrix formation and hence fibrosis^[35]. With increased expression of miRNAs, the targets Smad 7 and BMP7 are expected to decrease and hence promote fibrosis. Along with these miRNAs, there are many other novel miRNAs that should be considered for further investigation.

Realizing that all forms of fibrosis eventually involve the TGF- β pathway, we anticipated we would see a few unique differences in miRNA profiles at PN28, the initiation point of fibrosis. We were surprised by the degree of difference and the fact that some were maintained at least through PN42, as seen in Figure 3. Some changes may reflect differences in canonical and non-canonical TGF- β signaling cascades. However, the majority of differences are not likely due to different TGF- β pathways but rather due to differences in methodology. Other changes may reflect key differences in methodology utilized in this study.

A dilution effect created by using an organ with 26 different cell types must be considered when examining miRNAs in whole kidney samples. This has huge implications in the pursuit of therapeutic interventions. The heat map in Figure 2 demonstrates that while the identification of miRNAs that change may be the same with both techniques, the direction of change for some miRNAs goes in opposite directions. This could lead to a situation where a therapy based on whole organ analysis could exacerbate the disease. More importantly, LCM-obtained tissue is expected to represent the local pathology of interest that is being studied.

Fibrosis seen in this ADPKD model is initially localized to discrete areas between multiple cysts, which then expand with the progression of disease. The PLM in which fibrosis occurs undergoes multiple molecular and cellular changes with disease progression. The PLM areas isolated by LCM include locally proliferating cells that likely have key roles in the process of fibrosis. The changes preceding early fibrosis in the PLM of ADPKD kidneys act as a trigger factor that then stimulate cells locally to lay down collagenous extracellular matrix, which causes fibrosis. The isolation of these areas with LCM, as well as examining them at various stages before and after the onset of fibrosis, offers unique insight into this dynamic microenvironment.

Further work is required to identify the phenotypes of these cells and their specific roles. A large number of cells in PLM tissue from ADPKD are phenotypically identified as macrophages. Their role in fibrosis has been well studied and reported^[42]. Some or many of these PLM miRNA changes may be directly or indirectly related to macrophage changes that then drive the process of fibrosis. miRNAs are known to modulate macrophage activation and miRNAs are shown to be induced by hypoxia/ischemia. With cyst expansion and compression

of parenchyma between these expanding cysts, local hypoxia and ischemic changes can be expected early in the disease course of ADPKD. Whether such hypoxic/ischemic changes drive the early changes in the cellular make-up of the peri-cystic interstitium and drive PLM miRNA changes remain to be investigated.

In conclusions, this study identifies a unique interstitial miRNA signature that drives fibrosis in the new *mcwPkd1^{nl/nl}* model of ADPKD. Such changes in miRNA profiles in ADPKD PLM obtained by LCM provide unique insight into signaling in local areas where fibrosis begins. These PLM miRNA changes are not seen in whole kidney miRNA analysis. These PLM miRNAs have unique predicted targets, and some have established roles in hypoxia, proliferation, angiogenesis and fibrosis. Many of the LCM miRNAs identified are unique and represent new candidates for further study. This approach identifies novel future molecular and therapeutic targets. Further cell-specific miRNA expression studies will provide valuable information in further identifying potential therapeutic targets of fibrosis in ADPKD.

ARTICLE HIGHLIGHTS

Research background

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic renal condition, with an incidence of 1 in 500 to 1000 individuals. ADPKD affects approximately 750000 people in the United States and 12.5 million people worldwide. Nearly 50% of ADPKD patients will develop kidney failure that requires dialysis or transplantation. To date, clinical trials targeting cyst growth (epithelial proliferation) have been largely ineffective in improving or slowing the decline in renal function, despite reducing epithelial proliferation and total kidney volume (TKV). Tolvaptan, the most promising therapy to date, has an estimated cost of \$744100 per year per quality-adjusted life-year gained compared with standard care.

Research motivation

In ADPKD, as fluid-filled cysts develop and enlarge, a peri-cystic local micro-environment (PLM) is created between the cysts, which become fibrotic over time. TKV decreases with such fibrotic changes and has a strong correlation with loss of renal function. Despite this connection between fibrosis and end-stage renal disease (ESRD), there is no experimental or FDA-approved therapy that specifically targets fibrosis in ADPKD.

Research objectives

To investigate miRNA expression in PLM between cysts that become fibrotic as disease progresses.

Research methods

We employed LCM to analyze the miRNA profile of PLM at PN21, prior to any morphometric sign of fibrosis (trichrome stain), and at two time points of increasing degrees of fibrotic severity at PN28 (initiation) and PN42 (progression). These results were compared to age-matched expression profiles of whole kidney analysis of the miRNA expression profile.

Research results

The most striking result of these studies was the difference in miRNA profiles from PLM and whole kidney, as shown in cluster heat maps. The expression of miRNAs in the PLM was significantly distinct when compared to whole kidney expression.

Research conclusions

Relying on whole kidney analysis may lead one to pursue not only the wrong

miRNA, but may also lead to targeting a miRNA or protein that exacerbates the disease process you are trying to ameliorate. Therefore, published data that relies upon whole kidney transcriptomic analysis should be viewed with careful skepticism. Identification of the molecular and cellular changes in the PLM will lead to new therapeutic targets, with the potential to prevent the initiation or slow the progression of fibrosis.

Research perspectives

This study presents a unique approach to identify novel molecular and therapeutic targets that initiate and drive interstitial fibrosis in ADPKD. The use of therapies targeting fibrosis alone or in combination with therapies targeting epithelial proliferation will dramatically improve the quality of life of ADPKD patients by extending the time to ESRD.

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Oral alkali therapy and the management of metabolic acidosis of chronic kidney disease: A narrative literature review

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is currently no consensus on its management in the Republic of Ireland. Recent trials have suggested that appropriate active management of metabolic acidosis through oral alkali therapy and modified diet can have a deterring impact on CKD progression. The potential benefits of treatment include preservation of bone health and improvement in muscle function; however, present data is limited. This review highlights the current evidence, available primarily from randomised control trials (RCTs) over the last decade, in managing the metabolic acidosis of CKD and outlines ongoing RCTs that are promising. An economic perspective is also briefly discussed to support decision-making.

Key words: Chronic metabolic acidosis; Chronic kidney disease; Oral sodium bicarbonate; Oral alkali therapy; Health economics; Serum bicarbonate

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Core tip: Chronic metabolic acidosis contributes to the progression of chronic kidney disease (CKD). We summarise and analyse current evidence regarding the management of the metabolic acidosis of CKD, as well as the potential benefits and adverse effects. We also offer novel therapeutic guidelines for clinicians, which include the most evidence-based range to maintain serum bicarbonate in the CKD patient population.

Ahmed AR, Lappin D. Oral alkali therapy and the management of metabolic acidosis of chronic kidney disease: A narrative literature review. *World J Nephrol* 2018; 7(6): 117-122 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v7/i6/117.htm> DOI: <http://dx.doi.org/10.5527/wjn.v7.i6.117>

Abstract

Chronic metabolic acidosis is a common complication seen in advanced chronic kidney disease (CKD). There

INTRODUCTION

The prevalence of chronic kidney disease (CKD) in the

Republic of Ireland is estimated to be around 4.5% in the general population, rising to around 11.6% in individuals over 45 years of age^[1]. CKD management has a significant economic impact on the healthcare system, with the cost of care inversely proportional to a decline in renal function. Thus, interventions that can delay the progression of CKD will potentially contribute to an overall decrease in cost. This relation can be seen in economic evaluations of the RENAAL study, which demonstrated that early management of proteinuria in diabetic patients with losartan lead to a decrease in the progression to end-stage kidney disease and long-term health care costs. In fact, one of these studies was conducted in Canada, which has a public health care system relatively similar to Ireland^[2-4].

There are relatively few modifiable factors in CKD management that can slow the progression of renal function decline. The management of hypertension, proteinuria and glycaemic control in patients with diabetes are the primary focuses with regards to delaying CKD progression^[5,6]. In the last decade, however, a renewed interest in the treatment of metabolic acidosis of CKD (MA-CKD) has emerged and has been identified as an independent factor causing CKD progression^[7-9].

MA-CKD is a complication commonly seen in patients with a glomerular filtration rate (GFR) less than 30 mL/min per 1.73 m² (CKD G4-5), and is defined as serum bicarbonate levels that are persistently less than 22 mmol/L^[10,11]. It is associated with a worsening of CKD-mineral and bone disease, muscle wasting, hyperkalaemia, insulin resistance, hyperlipidaemia, and, most importantly, with the progression of CKD and increased mortality^[7,12]. In Ireland, there is currently no consensus on the management of MA-CKD, such as when to initiate oral alkali therapy or introduce a less acidogenic diet. It is therefore important to assess and develop national guidelines on the complications like MA-CKD that can prove cost-effective for the health system and improve the long-term outcome of CKD patients^[13].

MECHANISM OF INJURY

The most commonly proposed mechanism of injury associated with MA-CKD is related to renal ammonium metabolism. As CKD progresses, there is a loss of nephrons that is coupled with compensatory hypertrophy of the remaining nephrons to maintain acid balance. The hypertrophied nephrons increase their capacity to produce ammonia, which activates a complement pathway that leads to renal fibrosis and CKD progression^[9]. Animal models and some observational studies have also demonstrated that a rise in endothelin levels and activation of the intrarenal renin-angiotensin system in response to acidosis may play a role in the pathogenesis of renal fibrosis^[14-16].

ANALYSIS OF EVIDENCE

Animal models using alkali agents to treat metabolic

acidosis have suggested a decline in CKD progression; however, the results were not consistent^[17]. Numerous observational studies in human cohorts have demonstrated beneficial effects of oral alkali therapy on renal function^[8,18,19]. The first randomised control trial (RCT) on this subject was published in 2009^[7]. The trial involved a total of 134 patients with estimated glomerular filtration rate (eGFR) between 15-30 mL/min per 1.73 m² and serum bicarbonate between 16-20 mmol/L. Sixty-two patients were in the intervention group, which involved supplementation with sodium bicarbonate, with the aim of maintaining a serum bicarbonate level of more than 23 mmol/L. Sixty-seven patients were in the control group and did not receive any alkali supplementation over a two-year study period^[7]. One of the primary outcomes shown was a significantly lower decline in creatinine clearance in the treatment group at 1.88 mL/min per 1.73 m² compared to 5.93 mL/min per 1.73 m² in the nontreated group.

Subsequently, an American RCT was published looking at this topic in 120 patients with hypertensive nephropathy who had eGFR between 60-90 mL/min per 1.73 m²^[20]. The patients were divided into three equal groups: A sodium bicarbonate intervention group, a sodium chloride group and a placebo group. All participants had normal baseline venous total carbon dioxide (equivalent to serum bicarbonate) averaging 26 mmol/L, and albuminuria of more than 300 mg/g^[20]. Over five years of follow-up, there was a decrease in the rate of GFR decline of 1.47 mL/min per 1.73 m²/year in the sodium bicarbonate group, compared to 2.05 mL/min per 1.73 m²/year in the sodium chloride group and 2.13 mL/min per 1.73 m²/year in the placebo group. The study demonstrated that even without overt metabolic acidosis, oral alkali therapy contributed significantly to slowing the progression of CKD.

Both of these studies were included in the NICE CKD guidelines, which were updated in 2014, and led the authors to recommend that medical teams should consider oral sodium bicarbonate supplementation in patients with GFR less than 30 mL/min per 1.73 m² and serum bicarbonate levels below 20 mmol/L, a recommendation not previously seen in NICE CKD guidelines^[21,22]. The KDIGO 2012 CKD guidelines also suggested using oral bicarbonate therapy in the CKD patient population, but at a serum bicarbonate value of less than 22 mmol/L. This is a lesser biochemically overt acidosis used to initiate therapy, compared to the 2014 updated NICE CKD guidelines^[23].

A shorter duration RCT (8-12 wk) consisting of 41 patients looked mainly at the effects of oral bicarbonate supplementation on thyroid function in the CKD population (GFR < 35 mL/min per 1.73 m²) with serum bicarbonate levels less than 22 mmol/L^[24]. The aim was to achieve serum bicarbonate > 24 mmol/L in the treatment group^[24]. The results noted not only an improvement in thyroid function, but also a preservation of GFR in the treatment group compared to a decline

Table 1 Summary of evidence

RCT	Participants (n)	Intervention and aim	eGFR (mL/min per 1.73 m ²) baseline	Serum HCO ₃ ⁻ (mmol/L) at baseline	Duration (months)	Rate of Decline of eGFR (mL/min per 1.73 m ²)
De Brito-ashurst <i>et al</i> ^[27]	Total: 134 Intervention: 62	Oral sodium bicarbonate tablets to maintain serum HCO ₃ ⁻ > 23 mmol/L	15-29	16-20	24	HCO ₃ ⁻ group: 1.88 Non treated group: 5.93
Mahajan <i>et al</i> ^[20]	Total: 120 Intervention: 30	Oral sodium bicarbonate tablets	60-89	26	60	HCO ₃ ⁻ group: 1.47 per year Non treated group: 2.05 per year
Goraya <i>et al</i> ^[26]	Total: 71 Intervention: 30	Oral sodium bicarbonate and F and V	15-29	< 22	12	HCO ₃ ⁻ and F and V groups: Preservation of eGFR
Goraya <i>et al</i> ^[27]	Total: 108 Intervention: 72	Oral sodium bicarbonate and F and V	30-59	22-24	36	Non treated group: 13.8 over 3 yr HCO ₃ ⁻ : 5.4 over 3 yr F and V: 5.4 over 3 yr
Disthabanchong <i>et al</i> ^[24]	Total: 41 Intervention: 21	Oral sodium bicarbonate to maintain serum bicarbonate > 24 mmol/L	< 35	< 22	2-3	HCO ₃ ⁻ group: Preservation of eGFR Non treated group: 1.3

RCT: Randomised control trials; eGFR: Estimated glomerular filtration rate; F and V: Fruits and Vegetables

in GFR of 1.3 mL/min per 1.73 m² in the control group over the time period studied.

In 2012, a systematic review with a meta-analysis consisting of six RCTs on oral alkali therapy and its effects on renal function found a net improvement in GFR of 3.2 mL/min per 1.73 m² (based on 248 patients) compared to the non bicarbonate therapy group. The authors of this study suggested recommendations similar to the KDIGO 2012 CKD guidelines^[25].

Goraya *et al*^[26] compared a fruit and vegetable diet with oral bicarbonate supplementation in 71 CKD G4 hypertensive nephropathy patients with serum bicarbonate levels less than 22 mmol/L who were followed for one year. Markers of kidney injury, as proposed by the research team, included 8 h urine excretion of N-acetyl β -d-glucosaminidase, albumin and TGF- β , all of which were lower at the one-year follow-up compared to baseline. Notably, GFR was preserved in both groups. Both groups demonstrated an improvement in serum bicarbonate levels, but more was seen with oral alkali supplementation (21.2 $\pm$ 1.3 mmol/L vs 19.5 $\pm$ 1.59 mmol/L baseline and 19.3 $\pm$ 1.9 mmol/L baseline vs 19.9 $\pm$ 1.7 mmol/L). Interestingly, plasma potassium did not change significantly in the fruit and vegetable group (all patients were on furosemide, and patients with serum potassium more than 4.6 mmol/L were excluded).

Goraya *et al*^[27] performed another RCT over a three-year period looking at CKD G3 hypertensive nephropathy patients with serum bicarbonate levels (total venous CO₂) between 22-24 mmol/L. These patients were divided into three groups of 36: An oral bicarbonate supplementation group, fruit and vegetable group and

standard treatment group. All three groups received an angiotensin-converting enzyme (ACE) inhibitor with the goal to maintain a target systolic blood pressure of less than 130 mmHg. The outcome was a greater reduction in urinary albumin in both the bicarbonate and fruit and vegetable group compared to the standard care group, a reduction in N-acetyl β -d-glucosaminidase and urinary angiotensinogen in the bicarbonate and fruit and vegetable groups compared to a rise in the standard care group, and slower progression of GFR decline in the bicarbonate and fruit and vegetable group compared to the standard care group.

There are a few RCTs currently ongoing or actively recruiting, which may further shed light on the effectiveness of oral alkali therapy in preserving renal function, as well as other potential benefits such as an improvement in muscle strength and cardiac function^[28-32]. The Bicarb Trial is perhaps the most comprehensive of the current ongoing RCTs, involving multiple United Kingdom centers with 380 CKD G4-5 participants aged 60 or older and with serum bicarbonate levels < 22 mmol/L^[29]. The trial will look at the efficacy of oral sodium bicarbonate supplementation on physical performance, renal function, blood pressure, proteinuria and cost-effectiveness. Another ongoing RCT looking at renal transplant recipients with serum bicarbonate levels < 22 mmol/L and GFR between 15-89 mL/min per 1.73 m² could potentially enhance our understanding of the benefits of treating metabolic acidosis on transplant physiology^[32]. It will also cover a cohort of patients (renal transplant recipients) that have not formally been studied regarding chronic metabolic acidosis. The results of these RCTs are highly anticipated (Table 1).

OTHER POTENTIAL BENEFITS

CKD patients have a higher risk of fractures compared to the general population, largely due to a decrease in 1,25 hydroxylation of calcidiol (25-OH-vitamin D) and secondary hyperparathyroidism. Bone is also used as a buffer for excess hydrogen ions in chronic metabolic acidosis, which leads to a loss of calcium and an exacerbation of bone fragility^[33].

The preservation of bone health and the stabilisation of parathyroid hormone by the correction of metabolic acidosis has been demonstrated in a few studies^[34-36]. Furthermore, a decrease in protein degradation is seen, at a biochemical level, with an increase in muscle mass and an improvement in physical function^[7,37-39].

POTENTIAL ADVERSE EFFECTS

There has always been a concern regarding the worsening of hypertension, fluid overload and congestive heart failure (CHF) after the administration of oral sodium-based alkali supplementation in the CKD population due to sodium loading. These potential theoretical adverse effects have not been proven in a clinical setting, although a majority of participants in the RCTs were excluded if uncontrolled hypertension or clinically overt CHF was present^[7,25]. In one RCT, blood pressure was noted to be similar between the bicarbonate and standard care groups, with no CHF-related hospitalisation, and a similar increase in the use of diuretics and antihypertensive agents over the course of the study^[7]. Goraya *et al.*^[27] reported a similar finding, with no significant difference in blood pressure between the standard care and bicarbonate-treated groups, and a similar requirement for enalapril. Two RCTs by Goraya *et al.*^[26,27] also demonstrated that a fruit and vegetable diet allowed better blood pressure control compared to both bicarbonate supplementation and standard care.

TRC 101, a novel sodium-free, non-absorbed hydrochloric acid binder, has shown efficacy in alleviating MA-CKD without effecting blood pressure, and may become widely available in the near future^[40].

A plausible risk of increased vascular calcification exists once an acidotic environment has been resolved with oral alkali supplementation. However, there is currently a scarcity of studies to conclusively demonstrate this phenomenon^[41].

RECOMMENDATIONS

An appraisal of current evidence is necessary for the appropriate management of MA-CKD, which could have a significant impact on CKD care in Ireland.

A few RCTs demonstrated that a fruit and vegetable diet reduced the overall acid load and had a renoprotective effect^[26,27]. Two interesting observations can be noted. Firstly, the RCT with serum bicarbonate levels < 22 mmol/L in the CKD G4 hypertensive

nephropathy population did not achieve the desired aim of serum bicarbonate levels of > 22 mmol/L with fruits and vegetables. Despite this, however, the urinary indices of renal injury were lower and GFR was preserved^[26]. Secondly, the RCT on the CKD G3 hypertensive nephropathy population with serum bicarbonate levels between 22-24 mmol/L, above the current treatment guidelines, also demonstrated a slower progression of GFR decline and a reduction in urinary indices of renal injury with oral alkali supplementation^[26,27]. Even when oral alkali therapy was used in patients with CKD G2 and normal serum bicarbonate levels, a decline in the reduction of GFR was observed^[20]. These findings correlate with the understanding that western, high animal meat diets are indirectly renotoxic due to their overall acid-inducing effect, and that alkaline agents, either fruits and vegetables or oral sodium bicarbonate, help to neutralize this excess acid^[42,43].

It can be postulated that when fruits and vegetables associated with an alkaline effect are incorporated into a diet, they will be renoprotective at any CKD stage because of their ability to buffer acid. However, CKD G4-G5 patients have a tendency towards hyperkalemia. The RCT involving CKD G4-G5 patients managed with fruits and vegetables were on furosemide. Thus, the use of high potassium-containing fruits and vegetables in this category remains controversial^[26].

Based on the current evidence, it can be suggested that the CKD population maintain a serum bicarbonate level above 22 mmol/L, and that oral alkali therapy should be utilised to achieve this, especially in CKD G4-G5 patients^[7,20,24-27]. Since none of the RCTs included uncontrolled hypertension and overt CHF patients, clinical judgment should be used when initiating oral alkali therapy in patients with an underlying history of CHF or hypertension requiring more than three agents to control^[7,20,26,27,37].

The upper limit of serum bicarbonate levels once on oral alkali therapy is still speculative, with limited data available. In one cohort study, a serum bicarbonate level of > 26 mmol/L was associated with increased mortality and a risk of heart failure, while another study on haemodialysis patients demonstrated an association with increased mortality when serum bicarbonate levels were > 27 mmol/L^[44,45].

Maintaining serum bicarbonate levels between 22-26 mmol/L in the CKD population would be closest to the evidence base available at the moment. In four of the RCTs, an average of 0.3 mEq/kg per day to 1 mEq/kg per day of oral sodium bicarbonate was used to achieve the desired aim of serum bicarbonate levels > 22 mmol/L^[7,20,26,27,37].

It is further suggested that dieticians in renal units get involved in designing a program for CKD G1-G3 regardless of serum bicarbonate that incorporates fruits and vegetables to reduce the overall acid load, and commence community programs to promote this.

DOSING AND COST

A 1 mg dose of sodium bicarbonate approximately equates to 0.0123 mEq. A 600 mg sodium bicarbonate tablet contains 7.4 mEq of bicarbonate, and the usual commencing dose is 600 mg three times daily. In a 70 kg patient, this is approximately 0.3 mEq/kg per day. Three additional tablets may have patient compliance issues, as sodium bicarbonate can lead to abdominal bloating. However, until preparation is optimized and other formulations including sodium citrate are commonly available, oral sodium bicarbonate tablets will need to be titrated as required to achieve the desired serum bicarbonate levels between 22–26 mmol/L. An unconventional approach is to utilise natural baking soda (sodium bicarbonate), of which one teaspoon is equal to approximately 5000 mg of sodium bicarbonate. Thus, one-half of a teaspoon mixed in water should produce 2500 mg, which is equivalent to 31 mEq (2500 × 0.0123) of sodium bicarbonate. The cost per 600 mg of sodium bicarbonate tablets (including enteric-coated tablets) is approximately 0.1–0.15 Euros. If used at 0.3 mEq/Kg per day, it would cost 109–170 Euros/year (for a 70 kg patient).

CONCLUSION

MA-CKD is a complication that is often overlooked in clinical practice. Current evidence suggests that it contributes to renal function decline, and that appropriate management would lead to better CKD outcomes in terms of renal function preservation, muscle function, bone health and economic burden. Oral alkali therapy has the potential, when combined with other known interventions like blood pressure control and glycaemic control, to prolong the time before reaching end-stage renal disease. Irish nephrology practices currently hold very diverse opinions on managing MA-CKD. The recommendations offered here can be used as a basis to develop more detailed guidelines in the Republic of Ireland and around the world. Larger ongoing RCTs highlighted in this review will perhaps provide more conclusive evidence.

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Observational Study

Bicarbonate levels in hemodialysis patients switching from lanthanum carbonate to sucroferric oxyhydroxide

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Abstract

AIM

To examine possible alterations in acid-base parameters in patients switching from lanthanum carbonate (LanC) to sucroferric oxyhydroxide (SFOH).

METHODS

Fifteen stable hemodialysis patients were switched from LanC to SFOH. Only nine continued on SFOH, three returned to LanC and the other three switched to sevelamer carbonate. The later six patients served as a control group to the SFOH group of nine patients. Blood was sampled on the 3-d and the last 2-d interval of the week prior to switching and six weeks after. Bicarbonate levels (HCO_3^-), pH, pO_2 , pCO_2 were measured, and the mean of the two measurements (3-d and 2-d interval) was calculated.

RESULTS

Comparing pre-switching to post-switching measurements

in the SFOH group, no statistically significant differences were found in any of the parameters studied. The mean pre-switching HCO_3^- was 22.41 ± 1.66 mmol/L and the mean post-switching was 22.62 ± 2.25 mmol/L ($P = 0.889$). Respectively, the mean pH= 7.38 ± 0.03 vs 7.39 ± 0.03 ($P = 0.635$), mean pCO_2 = 38.41 ± 3.29 vs 38.37 ± 3.62 mmHg ($P = 0.767$), and Phosphate = 1.57 ± 0.27 vs 1.36 ± 0.38 mmol/L ($P = 0.214$). There were not any significant differences when we performed the same analyses in the control group or between the SFOH group and control group. No correlations were found, either between pre-switching LanC daily dose or between post-switching daily dose of the new binder and the measured parameters.

CONCLUSION

In our small study, switching from LanC to SFOH did not have any significant effect on blood bicarbonate levels and gas analysis, indicating that there is no need to change hemodialysis prescription regarding these parameters.

Key words: Gas analysis; Hemodialysis; Lanthanum carbonate; Acidosis; Bicarbonate; Phosphate binder; SuCroferric oxyhydroxide

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Core tip: Phosphate binders used for the control of hyperphosphatemia contribute to acid-base balance through their effect on serum phosphate and through the effect of the binders' constituents that have alkaline or acidic properties. This is the first study showing that switching from Lanthanum Carbonate to the novel phosphate binder suCroferric oxyhydroxide did not have any significant effect on blood bicarbonate levels and gas analysis. Thus, there is no need to change hemodialysis prescription regarding these parameters.

Stavroulopoulos A, Aresti V, Papadopoulos C, Nennes P, Metaxaki P, Galinas A. Bicarbonate levels in hemodialysis patients switching from lanthanum carbonate to suCroferric oxyhydroxide. *World J Nephrol* 2018; 7(6): 123-128 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v7/i6/123.htm> DOI: <http://dx.doi.org/10.5527/wjn.v7.i6.123>

INTRODUCTION

Metabolic acidosis is a characteristic complication of end stage kidney disease (ESKD) and is associated with major systemic effects and increased mortality^[1,2]. Hyperphosphatemia, another common complication of ESKD, partially contributes to metabolic acidosis and affects the acid-base status of the patients^[1]. Phosphate binders used for control of hyperphosphatemia contribute to acid-base balance through their effect on serum phosphate and through the effect of the binders'

constituents that have alkaline or acidic properties^[3]. The most characteristic is the case of sevelamer hydrochloride (SevH), which is associated with dose-dependent aggravation of metabolic acidosis in ESKD patients due to its hydrochloride content^[4,5]. This acidosis is ameliorated after switching to sevelamer carbonate (SevC) or other phosphate binders with alkaline content, such as calcium carbonate (CaC) or lanthanum carbonate (LanC)^[6-9]. However, despite the above mentioned studies, a recent meta-analysis suggests that the effect of phosphate binders in clinically important outcomes, such as metabolic acidosis, remains understudied^[10].

SuCroferric oxyhydroxide (SFOH) is a polynuclear iron(III)-oxyhydroxide-based phosphate binder recently approved for the treatment of hyperphosphatemia in patients with ESKD. It is a safe and potent phosphate binder with increasing use among hemodialysis patients, both as an initial treatment choice or as an alternative when other binders fail^[11,12]. However, little is known regarding the influence of this novel binder on the acid-base status of hemodialysis patients. Aim of our study was to examine possible alterations in acid-base parameters in hemodialysis patients switching from LanC to SFOH.

MATERIALS AND METHODS

Study population

We prospectively evaluated 15 clinically stable, Caucasian, anuric patients from the same unit who switched from LanC to SFOH (Table 1). The patients were taking LanC in the form of 750 mg chewable pills (Fosrenol, Shire Pharmaceuticals Cont. Ltd, United Kingdom) for at least 6 mo, but they had to change phosphate binder due to logistic reasons (disposal and access to the drug limitations). The new binder SFOH (Velphoro, Vifor Fresenius Medical Care Renal Pharma Ltd) was chosen as it is chewable with low pill burden, like LanC. SFOH pills of 500 mg were gradually introduced and titrated within two weeks to a maintenance dose. However, only nine continued on the new binder. The main reasons for discontinuation were gastrointestinal symptoms and taste of the product; thus, three patients returned to LanC and the rest switched to SevC. Therefore, we decided to use these six patients as a control group to the SFOH group of nine patients. No significant differences in the basic characteristics (age, gender, ESKD cause, dialysis vintage, Kt/V, dialysis modality) existed between the two groups. All patients were dialyzed using polysulphone membranes with 1.8-2 m² surface area, blood flow rate of 300-350 mL/min, and dialysate flow rate of 600 mL/min. Fifty-percent of them were on online hemodiafiltration. All patients had a well-functioning vascular access and dialyzed adequately within the recommended targets (12 h weekly, spKt/V = 1.32-2.14). Dialysis fluid had the following composition:

Table 1 Baseline characteristics of the study population (*n* = 15)

	SFOH group, <i>n</i> = 9	Control group, <i>n</i> = 6	<i>P</i> value
Age (yr)	78 (35-90)	73 (49-91)	NS
Male/Female	9/0	4/2	NS
Cause of ESKD	4 DM, 2 GN, 2 UN, 1 ADPKD	2 DM, 2 HN, 1 GN, 1 UN	NS
Dialysis vintage (mo)	53 (19-131)	49 (21-67)	NS
Arteriovenous fistula/Graft	6/3	4/2	NS
Single pool Kt/V	1.56 ± 0.16	1.57 ± 0.29	NS
Dose of LanC pre switching (mg/d)	2250 (750-3000)	3000 (1500-3750)	NS
Number of LanC pills pre switching	3 (1-4)	4 (2-5)	NS
Calcium carbonate: <i>n</i> , dose (mg/d)	1, 750	1, 1250	NS
Cinacalcet: <i>n</i> , dose (mg/d)	1, 60	1, 30	NS
Paricalcitol: <i>n</i> , dose (mcg/wk)	6, 10 (7.5-15)	4, 5 (5-10)	NS

ADPKD: Adult dominant polycystic kidney disease; DM: Diabetes mellitus; ESKD: End stage kidney disease; GN: Glomerulonephritis; HN: Hypertensive nephrosclerosis; LanC: Lanthanum carbonate; NS: Non-significant; SFOH: Sucroferic oxyhydroxide.

Sodium: 138 mmol/L, Potassium: 2.0 mmol/L, Calcium: 1.25-1.75 mmol/L, Magnesium: 0.5 mmol/L, Chloride: 108.5-109.5 mmol/L, Acetate: 3 mmol/L, Bicarbonate: 32 mmol/L, and Glucose: 5.55 mmol/L. Dialysate composition and doses of vitamin D analogs, cinacalcet and CalC, as well as hemodialysis prescription (including bicarbonate conductivity), remained unchanged throughout the study for each patient. Ultrafiltration rates were adjusted to the individual needs of the patients. Dietary consultation regarding phosphorus, potassium and protein intake was the same before and during the study. The study was performed in accordance with the Declaration of Helsinki and with the approval of the hospital ethics committee. Informed written consent was obtained from all patients before they entered the study.

Blood analysis

Blood was sampled from the "arterial needle" of the vascular access in all studied patients before dialysis sessions. Samples were collected on the 3-d and the last 2-d interdialytic interval of the week prior to switching (Baseline) and six weeks after at the same intervals. Whole blood pH, pO₂, pCO₂, bicarbonate levels (HCO₃⁻), base excess (BE) and potassium (K⁺) were measured using a Cobas B221 blood gas analyzer (Roche Diagnostics Limited, CH-6343 Rotkreuz, Switzerland). Serum phosphate levels were measured the same days using standard laboratory methods. The arithmetic mean (average) of the two pre-switching (baseline) measurements (2 and 3-d interdialytic interval) and the respective mean of the two post-switching measurements (6 wk) were also calculated for each of the above mentioned parameters.

Statistical analysis

All data are presented as mean ± SD and median with (minimum-maximum), according to the distribution. Due to the small sample size, non-parametric tests were used. Differences in parameters between studied groups of patients were analyzed using the Wilcoxon signed-rank test for paired samples and the Mann-

Whitney *U* test for independent samples. Bivariate correlations were performed using Spearman's rank correlation analysis. Statistical significance was set at *P* < 0.05.

RESULTS

Patients who switched to SFOH (SFOH group) had an effective phosphate control (Table 2), without increasing the pill burden, [number of LanC pills: 3 (1-4) vs SFOH pills: 2 (1-6), *P* = 0.849]. Comparing the mean values of the measured acid-base balance parameters, pre- and post-switching, no difference was found in any of them (Table 2). No statistically significant differences were found even when we analyzed the data for the 3-d and the 2-d interdialytic intervals separately (Supplementary Tables 1 and 2), or when we performed the same analyses in the control group or between the two groups (data not shown).

No correlations were found, either between pre-switching daily LanC dose and the measured parameters, or between post-switching daily dose of the new binder and the measured parameters (data not shown).

The only significant differences that we found were between the 3-d and 2-d measurements. HCO₃⁻, BE, and pH were significantly lower and K⁺ was higher at the 3-d vs 2-d interdialytic interval, as expected. For example, in the whole group of patients, baseline 3-d HCO₃⁻ were 21.2 ± 2.17 mmol/L, BE: -3.5 (-4.8 to -2.3) mmol/L, pH: 7.373 ± 0.031, and K⁺: 4.69 ± 0.46 mmol/L. Respective values for the baseline 2-d interval were: HCO₃⁻: 22.53 ± 2.68 mmol/L (*P* = 0.005, comparing to 3-d), BE: -2.2 (-3.3 to -0.4) mmol/L (*P* = 0.001), pH 7.389 ± 0.029 (*P* = 0.003) and K⁺ 4.29 ± 0.42 mmol/L (*P* = 0.04). Accordingly, 3-d pCO₂ was lower (37.2 ± 3.34 mmHg) vs 2-d (38.19 ± 4.51 mmHg), however the difference did not reach statistical significance (*P* = 0.061). Phosphate levels were the same, 1.42 ± 0.4 mmol/L vs 1.46 ± 0.26 mmol/L (*P* = 0.801), indicating that phosphate binders are effective in maintaining stable phosphate levels all days. When we performed the same analyses in the post-switching

Table 2 Paired comparisons, pre- and post-switching in the two groups

	SFOH group, <i>n</i> = 9			Control group, <i>n</i> = 6		
	Baseline	6 wk	<i>P</i> value	Baseline	6 wk	<i>P</i> value
HCO ₃ ⁻ (mmol/L)	22.41 ± 1.66	22.62 ± 2.25	0.889	21.05 ± 3.14	21.12 ± 2.27	0.917
pH	7.38 ± 0.03	7.39 ± 0.03	0.635	7.37 ± 0.033	7.36 ± 0.019	0.917
pCO ₂ (mmHg)	38.41 ± 3.29	38.37 ± 3.62	0.767	36.62 ± 4.55	37.82 ± 4.97	0.173
pO ₂ (mmHg)	93.1 ± 12.04	97.4 ± 10.08	0.953	82.8 ± 11.47	79.9 ± 14.35	0.463
BE (mmol/L)	-2.55 (-3.8 to -0.98)	-2.9 (-3.92 to -0.22)	0.722	-3.27 (-5.6 to -2.1)	-3.85 (-5.5 to -2)	0.917
K ⁺ (mmol/L)	4.47 ± 0.32	4.38 ± 0.64	0.678	4.52 ± 0.23	4.6 ± 0.23	0.600
Phosphate (mmol/L)	1.57 ± 0.27	1.36 ± 0.38	0.214	1.34 ± 0.33	1.57 ± 0.48	0.249

The laboratory values refer to the average of the respective 2- and 3-d interdialytic interval and are expressed as mean ± SD or as median (min.-max.), *P* value denotes in group comparison (Wilcoxon signed rank test). SFOH: Suroferric oxyhydroxide; BE: Base excess.

measurements or in the different groups, the findings were similar (data not shown).

DISCUSSION

In our study, we found that when hemodialysis patients are switching from LanC to SFOH, despite the loss of carbonate provided by LanC, there is no significant consequence on acid-base balance. Several explanations may exist for this finding. First, the iron oxide hydroxide binds phosphate in the gastrointestinal tract through a direct ionic interaction between the negatively charged oxygen ions on the phosphate and the ferric ions in the ferric oxide, forming FePO₄^[13]. During this interaction, hydroxyl groups are released^[13], indicating that SFOH acts as a base. An additional explanation could be that the effect of the alkali contained in LanC is small and its loss is compensated by endogenous adaption from blood and bone buffering and residual renal function, when present. This may be particularly true when doses of LanC are not very high or when there is no severe acidosis, like in our patients. There was only one prospective study found where LanC was introduced in phosphate binder-naïve patients. There, serum bicarbonate levels remained stable after 9 mo of LanC in 28 patients with moderate CKD (21.9 ± 2.9 mmol/L at baseline vs 21.8 ± 2.4 mmol/L at 9 mo), indicating that the effect of the carbonate is small^[14]. Furthermore, it is well known that switching to LanC can ameliorate the acidosis caused by SevH^[7,8]. However, this may not be the result of the alkalinizing agent of LanC, but rather the consequence of the withdrawal of the hydrochloride of SevH. Treatment with SevH results in a significant increase in dietary acid load, and this is the main cause of the observed acidosis^[4]. In favor of this is the observation that patients who switch from SevH to bicalomer, a non-hydrochloride and non-carbonate phosphate binder, improve their metabolic acidosis. This indicates that the withdrawal of chloride without the additional effect of carbonate is sufficient to ameliorate the acidosis^[15]. Lastly, in our study, no correlation was found between LanC dose and acid-base parameters. The above support the hypothesis that the effect of the carbonate content of LanC on

acid-base status is rather small. Moreover, concomitant use of CalC could compensate for the effects of loss of carbonate provided by the LanC on acid-base status. However, only two of our patients were on CalC, and the doses remained stable throughout the study. Finally, due to the small sample size of our study, a type II error cannot be excluded. Nevertheless, the harmful effect of SevH on acid-base balance was shown even in studies with 8 to 16 patients^[7,15,16]. Thus, the effects of SFOH switching would probably be detected in our study if they were significant. In addition, finding a significant difference between the acid-base status of 2-d and 3-d interdialytic interval could be considered a supporting finding that despite the small sample size, differences were detected when they were significant.

In our study, SFOH was effective in controlling phosphate without increasing the pill burden, in accordance with previous studies^[17,18]. However, some of our patients could not tolerate the new binder, as treatment with SFOH appears to be predominantly complicated by gastrointestinal disturbances^[17,19].

Finally, we observed that patients were more acidotic in the long interdialytic interval. This has been already shown in previous studies^[20], and this is why we decided to perform measurements both in the long and the short interdialytic interval in an effort to increase the possibility of detecting potential effects of SFOH switching on acid-base status.

The main limitation of the present study is the small sample size, as possible effects of switching on acid-base parameters may not be detected, even if present. Yet, the small number of patients allowed for stable conditions and better compliance, and this, together with the prospective nature, can be considered a strength of the study. Another limitation is that we did not measure the protein dietary intake that can affect acid-base balance. However, nutritional instructions remained the same during the study, and albumin and cholesterol levels did not change, supporting that there were no major changes in dietary habits. Finally, we cannot generalize our findings in patients with severe acidosis or in patients with ESKD on peritoneal dialysis.

To the best of our knowledge, this is the first study that evaluates acid-base status in patients receiving the

new phosphate binder SFOH. Therefore, it can serve as a pilot for further studies with a larger number of patients, different binders and extended durations to better understand their effect in clinically important outcomes, such as metabolic acidosis.

In conclusion, switching from LanC to SFOH did not have any significant effect on blood bicarbonate levels and gas analysis, indicating that there is no need to change hemodialysis prescription regarding these parameters. However, when selecting a phosphate binder, potential consequences on acid-base balance should be considered, and monitoring of serum bicarbonate levels is part of good clinical practice.

ARTICLE HIGHLIGHTS

Research background

The effect of phosphate binders in clinically important outcomes, such as metabolic acidosis, remains understudied.

Research motivation

There are no studies examining the effect of the novel phosphate binder sucroferric oxyhydroxide (SFOH) on acid-base status.

Research objectives

Examine possible alterations in acid-base parameters in hemodialysis patients switching from lanthanum carbonate (LanC) to SFOH.

Research methods

Fifteen stable hemodialysis patients switched from LanC to SFOH. We compared pre- and post-switching blood gas analyses, whilst hemodialysis conditions and medications remained stable.

Research results

Switching from LanC to the novel phosphate binder SFOH did not have any significant effect on blood bicarbonate levels and gas analysis. No correlations were found, either between pre-switching LanC daily dose or between post-switching daily dose of the new binder and the measured parameters.

Research conclusions

This is the first study that evaluates acid-base status in patients switching from LanC to the new phosphate binder SFOH, showing that there is no need to change hemodialysis prescription regarding these parameters.

Research perspectives

Our study can serve as a pilot for further studies with a larger number of patients, different binders and extended durations, to better understand their effect in clinically important outcomes, such as metabolic acidosis.

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Confounding risk factors and preventative measures driving nephrolithiasis global makeup

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Abstract

Nephrolithiasis is increasing in developed and developing countries at an alarming rate. With the global spike in kidney stone diseases, it is crucial to determine what risk factors are influencing the current global landscape for kidney stones. Our aims for this review are: to identify and analyze the four categories of risk factors in contributing to the global scale of stone formation: lifestyle, genetics, diet, and environment; and discuss preventative measures for kidney stone formation. We also performed data search through the published scientific literature, *i.e.*, PubMed® and found that there is a significant link between lifestyle and obesity with cases of calcium stones. Food and Agriculture Organization of the United Nations and World Health Organization factor indicators for dietary intake and obesity, along with climate data were used to create the projected total risk world map model for nephrolithiasis risk. Complete global analyses of nephrolithiasis deplete of generalizations is nearly insurmountable due to limited sources of medical and demographic information, but we hope this review can provide further elucidation into confounding risk factors and preventative measures for global nephrolithiasis analysis.

Key words: Nephrolithiasis; Epidemiology; Risk factors; Global factors

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Core tip: We analyzed diet, lifestyle, genetics, and environment, four categorical risk factors that play major roles in the contribution of nephrolithiasis. Calcium stones and lifestyle factor obesity had a significant link; dietary factor of high protein and low intake of negative regulators increased the risk; and environmental factor of climate had a relatively high correlation to nephrolithiasis. Together, a model was formed to map a prevalence of nephrolithiasis of the world.

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INTRODUCTION

Kidney diseases affect hundreds of millions of people globally. The number of people affected by the disease continue to grow by each year, with 200 million people affected worldwide according to current estimations by the World Health Organization (WHO)^[1]. One of the most common forms of debilitating kidney disease is the formation of kidney stones known as nephrolithiasis. Kidney stones are an aggregation of crystalline structures that build up in the nephrons of the kidney. These crystalline structures impair the normal functioning of the kidney and often require costly interventions such as pharmacological treatment, laser and radio bombardment, and surgical interventions (if severe). Earlier, diseases like kidney stones had been restricted to developed countries; however, over the past decade there has been a global spread of chronic non-communicable diseases. As such, nephrolithiasis is on the rise in developed and developing countries at an alarming rate. With this global spike in kidney stone diseases, it is incredibly important to determine what risk factors are influencing the current global landscape for kidney stones. By understanding the root causes for the increase in prevalence of kidney stones, we can develop health interventions and recommendations to curb nephrolithiasis' global burden of disease.

Significant key risk factors that play the greatest role in kidney stone formation can be divided into 4 major categories: Dietary, genetic, environmental, and lifestyle. The main aim and scope of this study is to update the current knowledge on global prevalence, incidence, and risk of kidney stones. We have performed an extensive literature search to understand the development of the four different kidney stone types: Calcium (calcium oxalate and calcium phosphate), uric acid, struvite (magnesium ammonium phosphate), and cysteine. Throughout this literature search, we focused on our causes of stone formation to make a list of risk factors that play the largest role in the development of stones. Understanding these risk factors will allow us to create

a geographical model to map national and global areas of risk for kidney stones. Food and Agriculture Organization Corporate Statistical Database (FAOSTAT) and WHO data has been used to project the world map for nephrolithiasis.

There are 4 different types of kidney stones: Calcium stones, uric acid stones, struvite stones, and cysteine stones. These stones are comprised of different materials and have different causes. Calcium stones are the most common type of stone in most countries. Calcium phosphate stones are less common and are comprised of calcium and phosphate aggregation; however, these stones do account for a large percent of the economic burden because they are very difficult to treat^[2]. Brushite stones are an aggregation of calcium monohydrate phosphate, a slightly modified form of calcium phosphate. Precipitation of these crystals occurs at a lower urinary concentration level than normal calcium phosphate crystals, and once stones start to form, they become very difficult to treat due to the strength of ionic bonds. Calcium oxalate stones, the more common calcium stones, are comprised of oxalate calcium salts. Together, these account for 75%-80% of global stone prevalence in most countries^[3]. Uric acid stones are the third most common type of stone in the globe. They are the result of having supersaturated urea which can be caused by a multitude of factors. In addition, uric acid concentrations and aggregation also stimulates the crystallization of calcium oxalate *via* deposition of a crystalline overlay on a crystalline substrate^[4]. The uric acid crystal serves as a base allowing the formation of other stones based on the ionic make-up of the surrounding urine. The fourth most common type, struvite stones, are a result of bacterial imbalances which cause elevated levels of ammonia, decreased phosphate solubility, and carbonate imbalance in the body. All of which lead to precipitation of these phosphate rich struvite salts^[3]. Cysteine stones are the last type of stone. They are globally rare because they are a direct result of a genetic mutation that causes malabsorption in the renal tubal^[3].

LIFESTYLE

Age, race, demographic

Nephrolithiasis is a long-term disease that develops over time and is usually found much later in a patient's life. While people of young ages are not immune to or free from the development of kidney stones, ranging from ages 18 to 95, this disease is most commonly found in individuals 43 and older, with the highest incidence rate in people among ages 40 to 65^[5]. Additionally, stone development is more commonly found in male patients than female patients. A study focusing on the prevalence of stone development in the United States places the difference between men and women as high as 2 times^[6]; however, this is rapidly changing. Females ages 40 and older are now seeing a rise in stone development that has placed them much closer the incidence of men^[7].

Table 1 Summary of confounding risk factors (diet intake, obesity, and environment) for each country

Country	Diet ^[15]	Obesity ^[16]	Climate
United States	High in sugar and meat	Highly obese (30%-40%)	Varies, Southern states tend to have on average warmer temperatures than the north; though the eastern states tend to have more tropic conditions ^[17]
Scotland	High in sugar and meat	Highly obese (27.7%)	Temperate ^[18]
British Isles	High in sugar and meat	Highly obese (14%-27.7%)	Mild winter, warm summers
Australia	High in sugar, meat, and dairy	Highly obese (20%-30%)	Warmer climates
Malayan Peninsula	High in meat and fish	Moderate obesity (16.3%)	Equatorial climate
Spain	Moderate in sugar	Moderate obesity (15.6%)	Mediterranean climate ^[19]
	High in meat		
Germany	Very high in sugar	Moderate obesity (12.9%)	Temperate
Sweden	High in sugar	Moderate obesity (12%)	Very mild climate ^[20]
	Moderate in meat		
Italy	High in caffeine	Moderate obesity (9.8%)	Mediterranean climate
Pakistan	High in meat	Low obesity (3.4%)	Weather is extreme depending on the season
Japan	High in fish	Low obesity (3.1%)	Warm and humid
China	High in fish	Low obesity (2.9%)	Temperate, facing lead epidemic
India	High in meat and fish	Low obesity (0.7%)	Hot, tropical climate

There has been a higher amount of nephrolithiasis incidence in younger women, specifically calcium phosphate stones over the past years; however, the exact cause of increase is not well known^[8]. An explanation could be that women tend to have higher urine pH levels even after controlling for diet, possibly due to a differential rate of absorption of GI anions, which would also explain why they are more prone to calcium phosphate stone formation^[9]. Moreover, it is known that higher urine pH has more influence on the supersaturation of calcium phosphate than the compositions of calcium and phosphate^[10].

All ethnic groups were equally represented in the affected population. This is partly due to the fact that metabolic risk factors for nephrolithiasis seem to have very little variation when looking at differences in ethnic background^[11]. However, a recent cohort questionnaire study of approximately 42000 Southeastern United States white and black adult men and women from 2002-2009 found that, with adjustment for age, white adults had a greater risk for kidney stones compared to black adults with a hazard ratio of 2.23^[12]. When comparing men and women, risk was slightly higher with a hazard ratio of 1.12; however, white men were significantly associated for kidney stone incidence compared to white women with a hazard ratio of 1.45, though the correlation was not significant for men and women among blacks^[12].

Obesity

Obesity is one of the fastest growing epidemics in the world. It is a complex metabolic disorder that leads to serious, long term medical problems like cardiovascular disease, musculoskeletal disorders, and chronic kidney disease (CKD)^[7]. Recent publications have found a direct correlation between patients who are obese, overweight, and have higher body fat percentages to the development of nephrolithiasis^[13]. Calcium stones account for nearly 80% of kidney stone development

globally^[1] and have specifically been linked to obesity. Along with urinary calcium stone, obesity affects the overall excretion levels of uric acid, sodium, calcium, and citrate increasing the risk for developing uric acid stones^[14]. Increases in prevalence of both uric acid stones and calcium stones can be seen in obesity plagued countries over the past 10 years.

Recent estimates suggest that over 34% and 35% of men and women are classified as overweight respectively, and 10% and 14% of men and women are obese in the United States. Recent estimates of obesity rates according to WHO have shown that a majority of nations such as United States, Germany and Sweden were reported to have higher obesity rates than eastern countries. While Eastern countries such as Japan, China, and India were reported to have low prevalence rates of obesity (Table 1).

Childhood obesity rates have been increasing over the years as well. According to the WHO, for in children from age 0-5, the global obesity prevalence rate from 2005 to 2015 is 5.8% to 7.8% and is projected to increase to 9.1% by 2020^[21]. Moreover, a recent population based study which uses Israeli Defense Forces medical records found that the prevalence rate for having a history of nephrolithiasis before reaching 17 years old was 88.6 per 100000, more skewed toward those with BMI > 30 kg/m²^[22].

Through the FAOSTAT and the WHO data, we averaged the two data sets and attributed low, medium, and high obesity rates to each country by whether the percentage of those who are overweight and obese was greater than 30%, and/or by whether the obese population make up 40% of those who are obese and overweight (Figure 1).

Comorbidities

There is a continuing amount of evidence that ascertains co-existing conditions such as hypertension, diabetes, and CKD^[23-27] can increase the risk of kidney

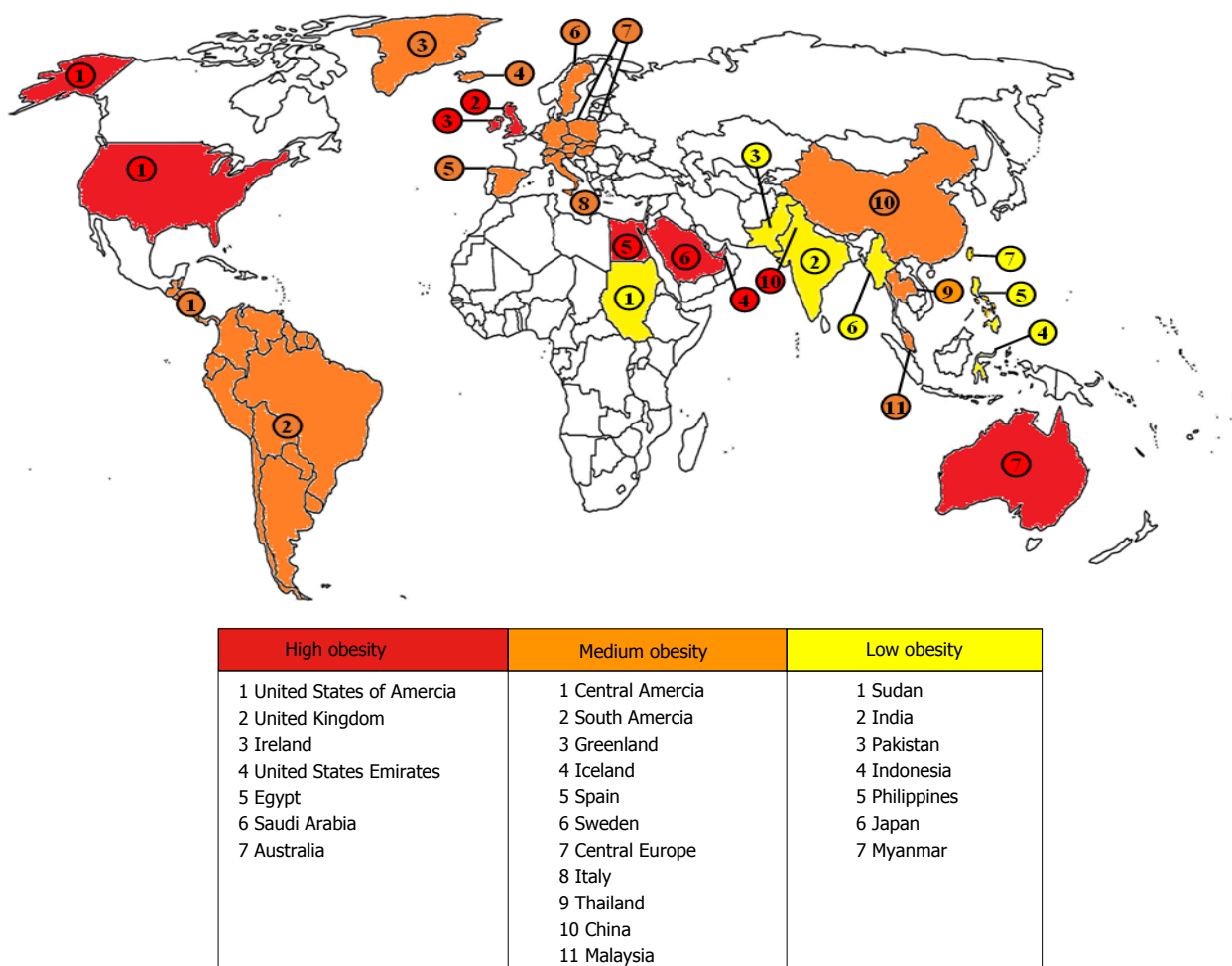


Figure 1 World map projection of obesity prevalence. Red countries are countries with high prevalence of obesity; orange countries have an either a greater than 40% of obese population of obese + overweight population; and yellow countries have lower prevalence of obesity. Obesity defined as measurement of body mass index ≥ 30 . Data retrieved from the Food and Agriculture Organization of the United Nations and the World Health Organization.

stone formation. Not only do these comorbidities force kidney stone formation into a more difficult prognosis, research shows their geographical location may affect their prevalence in comparison to other places in the world.

Type 2 diabetes is another metabolic syndrome that is consistently increasing globally, and with the overall stress that diabetes places on the kidneys, it has become the focus of interest for CKDs. In terms of nephrolithiasis, type 2 diabetes is a very important risk factor because the development of insulin resistance has a drastic effect on ammonia transport and production, altering urine pH significantly^[28]. The changing in urinary pH, as stated earlier, leads to an increase in concentration of uric acid, citrate, and sodium all of which increase uric acid stone formation and calcium stone formation.

Nephrolithiasis can lead to renal damage, which in turn, could lead to hypertension. Kidney stones can plague hypertensive patients disproportionately compared to normotensive individuals. Many patients who are hypertensive were shown to have increased 24-h output urinary Ca^{2+} ^[24]. The high levels of Ca^{2+}

of hypertensive patients put them at risk for possible development of nephrolithiasis. An individual with a history of nephrolithiasis is more likely to develop hypertension; however, whether hypertension increases the risk for nephrolithiasis is not well known^[24]. Hypertension prevalence in the United States and globally can also rise depending on where the person lives.

CKD, an incapacitating disease, affects 7% of those > 30 years old, translating to at least 70 million within developed countries worldwide and number may be higher given the unknown prevalence in underdeveloped countries^[27]. Since CKD is usually asymptomatic and diagnosing would rely on biomarkers which do not clearly differentiate between normal and disease, identifying CKD can be difficult. However, CKD can be an important predictor for cardiovascular related diseases and mortality before ESRD. Nephrolithiasis is a risk factor to CKD, and so patients with kidney stones are recommended to screen for subclinical CKD.

Physical activity

Physical activity frequency and intensity are lifestyle factors that are commonly recommended to treat

kidney stones. Levels of physical activity not only affect the severity of importation metabolic diseases such as obesity and diabetes, but they have a direct impact on the body's physiological waste excretion mechanisms. Physical activity encourages people to increase their water intake while simultaneously increasing the frequency of urine excretion. Both of these factors would likely reduce the risk of nephrolithiasis. A study found that women who had high risk of stone development based on age and weight were less likely to develop nephrolithiasis over time if they had moderate levels of physical activity compared to women with lower levels of physical activity^[29]. Conversely, high levels of physical activity and low levels of fluid intake perform the complete opposite physiological function, by decreasing urine pH and increasing urinary concentration of uric acid, Calcium, and oxalate causing higher rates of nephrolithiasis^[30]. Moreover, a self-reported survey from 1988-2002 states that physical activity within the United States amongst adults have actually increased, despite the increase in obesity rates, though the increase in sedentary lifestyle (automobile travel, less physically demanding occupations, etc.) may explain the discrepancy^[31].

Migration

One factor for nephrolithiasis prevalence that is not well known is migration. Migration can potentially create an artificial trend on the prevalence of nephrolithiasis for a country. According to the United Nations, Department of Economic and Social Affairs, high percentage of international migrants are 30-34 years old of both sexes, skewed toward the lower spectrum of the working ages (20-64), possibly because they would need to be fit enough for labor^[32]. Parks *et al.*^[33] states that the peak age for kidney stones for men is 30 while the women have a bimodal distribution of 35 and 55. While this may suggest that the risk of kidney stones overall for the countries receiving the migrants, various ethnical or cultural factors may play a role which may affect the risk differently. Meanwhile, it is not known as to whether the aging immigrant population would affect the prevalence of nephrolithiasis within a country.

DIET

Micronutrient consumption

The most important, overlooked risk factor for nephrolithiasis is the overall quality of a patient's diet. Dietary influences on the rates of nephrolithiasis have been well documented. There are 3 essential micronutrients that are required for the development of kidney stones: Sodium, oxalate, and calcium.

Sodium plays an important role in calcification and nephrolithiasis. Sodium has an effect on the absorption rate of cells in the proximal tubule in kidneys^[34]. Sodium levels affect the urea concentration and influence the degree of supersaturation of other minerals by attracting

surrounding water molecules. This, in turn, raises the concentration of all other dangerous crystalline salts in the urine like calcium oxalate, calcium phosphate, and uric acid crystals^[3].

Oxalate is an organic waste molecule that when in high levels can be very dangerous when found in foods. Oxalate easily binds with calcium in the kidneys to form calcium oxalate crystals. The aggregations of these crystals are calcium oxalate stones and they comprise the largest portion of global nephrolithiasis. Urinary oxalate levels are highly influenced by dietary intake of oxalate in foods. Foods high in oxalate are usually plant based; however, oxalate can also be formed through the metabolism of amino acids and the breakdown of vitamin C^[35]. Glycine and hydroxyproline account for the highest production of oxalate due to amino acid metabolism^[35].

Calcium is the driving mineral that interacts with all stones. It is responsible for the formation of every type of stone. Calcium is a vital mineral used for musculoskeletal contraction and bone density support, so dietary levels of calcium are essential for a healthy patient. If dietary calcium levels are normal, the body absorbs less calcium in the small intestine and more in the distal tubule of the nephron; however, if there are low levels of calcium in the diet, the body will compensate by releasing more calcium into the blood from calcium storage locations like the bone. The calcium is absorbed in the small intestine and very little is absorbed in the kidney, leading to higher concentrations of calcium ions in the urine^[29]. With more calcium in the urine, there is a greater chance that these ions will bind to other dietary promoters of stones to form crystals that can aggregate to cause kidney stones^[36]. Calcium will bind to these stone forming molecules like oxalate and phosphate anywhere in the body, but they are easily excreted when they bind in the intestinal tracts, which can be improved by higher dietary levels^[5,37]. Some vitamins and minerals inhibit the development of stones. These minerals either compete with the harmful micronutrients creating less harmful salts and biological compounds or react with the harmful micronutrient neutralizing them. There are three known helpful, negative regulator micronutrients: Magnesium, citrate, and potassium.

Magnesium is a competitive inhibitor and binds to oxalate and excess phosphates much faster than calcium^[38]. The main reasons magnesium is an effective treatment is that it can easily be excreted *via* urinary excretion and has a minimal risk of developing into traditional stones^[39]. Higher urinary and intestinal concentrations of oxalate magnesium serve no threat to the individual; however, given the appropriate physiological conditions some calcium phosphate stones may be encouraged^[3]. There is an association with magnesium phosphate aggregation and formation of a calcium phosphate stone called brushite stone as well as struvite stones if urinary phosphate levels are high enough^[40]. Additionally, magnesium intake must also be monitored

carefully for patients who may be suffering from CKDs because the levels of filtration in the blood are reduced in CKD patients^[3].

Citrate is a common organic compound that when in normal concentrations has many anti-stone forming properties. Citrate blood levels have been shown to cause a significant decrease in individuals supplementing their diet with extra citrate medication^[41]. Citrate acts as a buffer regulating the urinary pH and calcium crystallization by means of increasing their solubility.

Similarly, Potassium is used as a regulator in calcium crystal formation. Potassium is inversely related to the development of kidney stones^[40]. Citrate and potassium are commonly used to increase urinary pH through oral potassium citrate supplementation, and has been shown to be 96% effective in treating patients with recurrent stone formation due to low blood citrate levels^[41]. Foods high in citrate have been shown to provide similar benefits to oral potassium citrate supplementation. A study looking into lemon juice as an alternative for potassium citrate to alter citrate concentrations found that it provided a 2.5 fold increase in original levels of urinary citrate whereas potassium citrate provided 3.5 fold increase^[42]. This dramatic increase in the urinary citrate levels has a direct effect on 2 major contributors of all stone formation, pH and ion concentration.

Animal protein

There is a common consensus that excessive animal protein consumption is one of the main dietary contributors to the development of stone disease^[43-45]. If excessive animal protein is consumed in the diet, the body will begin to metabolize the proteins. When the body metabolizes amino acids (two that cause most problems are proline and hydroxyproline) the body then converts these into harmful organic waste molecules like oxalate. Animal proteins have much higher concentrations of hydroxyproline and proline. The levels of these organic waste molecules in the blood will find their way into the kidney through normal filtration function. These increased levels of waste molecules in the urine are more likely to crystalize with surrounding calcium ions that have not been absorbed. Additionally, amino acid metabolism increases the acidity of the surroundings. The metabolism of animal proteins pose a double-sided threat to the development of nephrolithiasis by increasing two precursors: lowering the pH of the body and urine and increasing the blood concentrations of organic waste molecules that crystalize with ionic calcium. The result of these precursors leads to increased stone formation. All animal protein is not the same, with each different type carrying different concentrations of these high risk amino acids^[46]. Meat, Poultry, and Eggs are considered to be complete sources of essential amino acids because they contain adequate levels of the 20 essential amino acids; however, they also contain much higher levels of harmful amino acids that raise the pH and increase

urinary stress on the kidneys^[47,48]. Proteins from fish have fewer oxalate forming amino acids, a lower overall sulfur amino acid concentration, and a higher concentration of vitamin B6. Vitamin B6 is inversely correlated with the development of calcium oxalate stones^[49]. Animal protein intake also has an effect on the development of confounding metabolic diseases like obesity and type 2 diabetes^[50]. Countries where animal proteins intake accounts for a majority of their population's dietary energy intake have higher rates of type 2 diabetes than other countries. The link between diets high in animal protein and nephrolithiasis must be considered with caution because diets high in animal protein are also commonly associated with diets high in fat and sodium intake, but low in vitamin intake^[50].

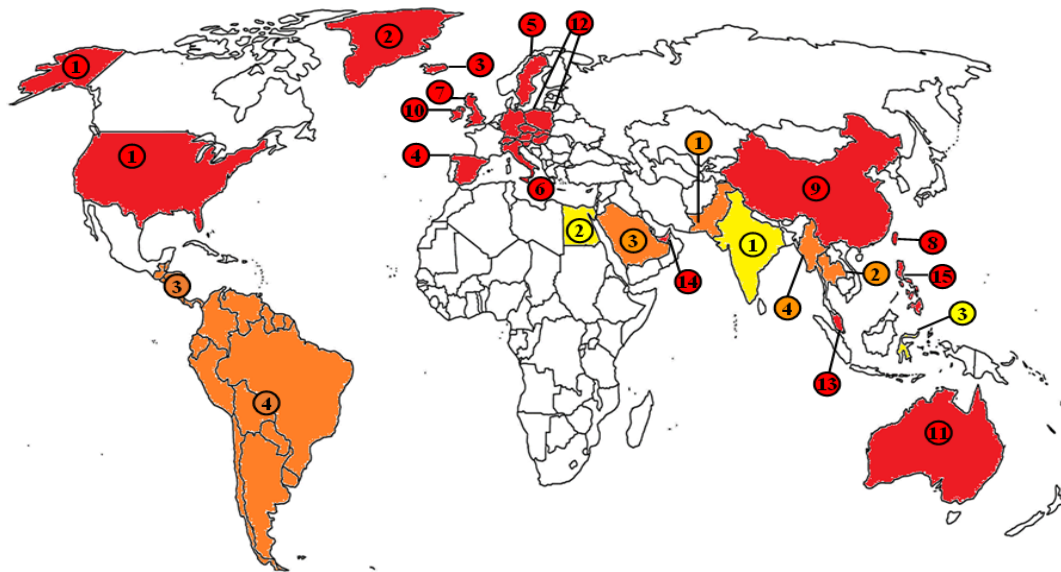
The protein intake world map was projected using the Food and Agricultural Organization of the United Nations database for 3-year averages of daily average protein supply per capita and daily average animal protein supply per capita (Figure 2). Total overall daily protein intake > 60 g for individual and whether the percentage of which comprises of animal proteins > 35% were used as indicator for animal protein intake magnitude of each country.

Sugars and sweeteners

The sugar and sweeteners in an individual's diet can play an important role in many metabolic disorders. Excess amounts of sugar intake lead to the overworking of the pancreas and can lead to an increase in heart disease, diabetes, and CKD^[51]. Both sugar and artificial sweeteners reduce water availability in urine if supersaturated with sugar in the blood, and would raise risk for the formation of all stone crystals which can aggregate to form stones^[51]. Different sugars have more of an effect on the biochemical content and concentrations of blood. Fructose metabolism raises the levels of uric acid in the blood. Not only does this cause a greater risk of uric acid kidney stones, but it also reduces nitric oxide levels which is important for insulin function and over a long period of time can induce insulin resistance. The lack in function of insulin in the blood leads to the development of type 2 diabetes, which increases the likelihood of stone formation.

Bacterial influences

With advancements in microbiology research, the scientific community has a much better understanding of the symbiotic relationship between microbial organism and normal physiological function. Different microbiomes in areas of the body work together to protect individuals from pathogenic invaders and in helping us metabolize foods our body normally could not. The gut microbiome is one of the most importance base of this very reason. *Oxalobacter formigenes* is a bacterium that is commonly found in the gut microbiome^[52]. These bacteria are capable of breaking down dietary oxalate before it can be absorbed *via* intestinal absorption^[53]. This bacterium



High protein intake	Moderate protein intake	Low protein intake
1 United States of America	1 Pakistan	1 India
2 Greenland	2 Thailand	2 Egypt
3 Iceland	3 Saudi Arabia	3 Indonesia
4 Spain	4 Myanmar	
5 Sweden		
6 Italy		
7 Scotland		
8 Japan		
9 China		
10 Ireland		
11 Northern Australia		
12 Central Europe		
13 Malaya		
14 United Arab Emirates		
15 Philippines		

Figure 2 World map projection of animal protein consumption. Protein retrieved from the Food and Agriculture Organization of the United Nations. High protein intake countries are red; moderate protein intake countries are orange; and low protein intake countries are yellow. Source: Food and Agriculture Organization of the United Nations, <http://www.fao.org/faostat/en/#country>. Reproduced with permission.

does not originate in the body at infancy. The bacteria is colonized through environmental exposure from foods^[53]. There is an indirect link between drastic changes in the GI microbiome and an increase in kidney stone formation^[52]. When one analyzes the urinary composition of individuals who have gone through bariatric surgery to control weight related problems, there is a dramatic spike in oxalate levels leading calcium oxalate formation^[52]. By breaking down oxalate before it can be absorbed into the blood stream, the bacteria prevent excess oxalate from accumulating in the urine which causes calcium oxalate crystal formation. By examining bacterial influences and sugar intakes of individuals and patients, it can lead to new findings between the link of an individual's diet and the risk of kidney stone formation.

Success of dietary interventions

Dietary interventions are commonly used to combat the formation of stone diseases by understanding the

levels of micronutrient regulators as well as protein intake. Recently dietary changes have been shown to have a direct effect on nephrolithiasis and stone formation^[54]. A recent push by dieticians to prevent the rise of chronic diseases due to cardiovascular disease is the implementation of the Dietary Approach to Stop Hypertension (DASH) diet, which was based off the Mediterranean diet. The implementation of this diet also has shown to be beneficial in preventing nephrolithiasis. The DASH diet consists of high dairy intake, low animal protein intake, and higher fruit and vegetable consumption^[55]. These diets show a significant increase in regulating micronutrients like magnesium, potassium, and citrate through the limitation of high risk foods resulting in overall decrease in stone erudition.

ENVIRONMENT

Temperature and humidity

Surrounding geographical environments have a varying

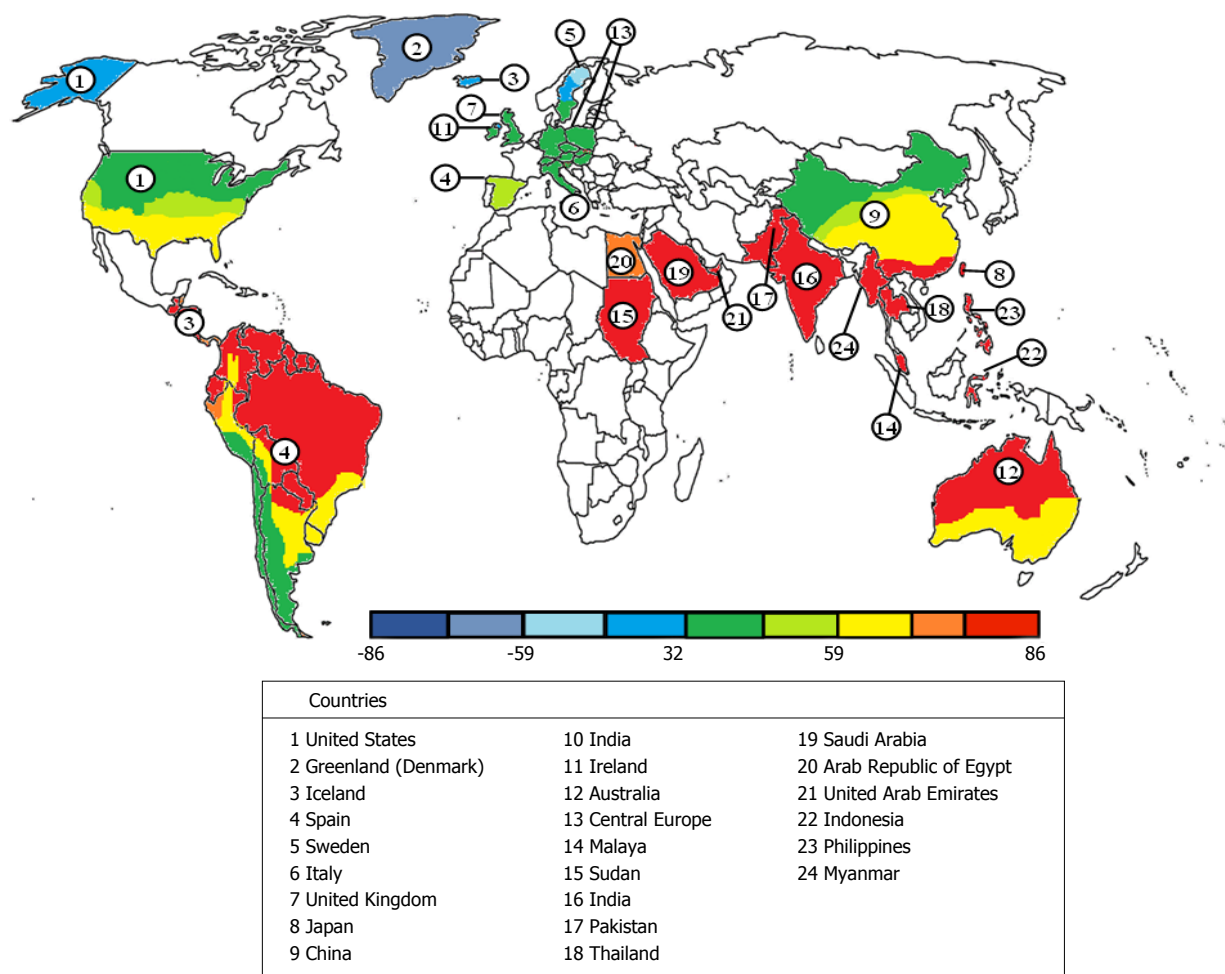


Figure 3 World map annual temperature projection. Annual mean temperature (°F) data estimate of countries. Color spectrum correlates to estimated annual temperature. Data retrieved from: The Nelson Institute Center for Sustainability and the Global Environment, University of Wisconsin-Madison.

effect on metabolic and physiological function, and this is especially true in the formation of stone disease. The urinary system dramatically changes based on the temperature and aridity of an individual's surrounding environment^[3]. Urinary ion concentrations are altered by the temperature of the patient by reducing urinary volume excretion^[56]. A multivariate study using 599 patient data, showing the effects of both seasonal and temporal change in urinary composition, found that urinary calcium, urinary oxalate, and uric acid^[57]. The longer a patient is exposed to higher temperature environments, the more at risk these individuals are for developing stones. When examining the relationship between humidity and urinary ion concentration through different seasons of the year, however, the study did not find significant correlations^[57]. An observational study focusing on the rise in stone prevalence as they relate to average mean temperature in the United States alone shows a correlation between areas with a temperature greater than 10 °C over the course of a year, with higher prevalence of stone formation in these populations^[13]. This suggests that temperature may play as a significant indicator for predicting nephrolithiasis prevalence. We created a projected

world map indicating different mean temperature for each country (Figure 3).

Urban heat islands and urbanization

Temperature change due to global warming is important to consider when looking at the long term rise in nephrolithiasis; however, we are seeing a much more rapid increase in the prevalence of stone disease in urban, high density locations known as "urban heat islands"^[58]. Urban environments are 1-3 degrees higher ambient temperature annually than rural areas but temperatures can be as high as 12 degrees higher during high heat months such as the summer season^[59]. The ambient temperature changes due to these heat islands is much more apparently affecting urban populations to a much larger degree than global warming, increasing rates of nephrolithiasis in urban populations globally. Exposure to higher temperatures is associated with a greater risk for stone development in males; however, the association with higher temperatures and stone development in females is less significant which brings into question the overall affect that temperatures have on prevalence of nephrolithiasis when adjusted for age, race, and gender^[60].

Exposure to harmful chemicals

Heavy metals are common environmental and occupational toxins that can have detrimental effects on physiological function in many body systems, including kidney function. Even minute exposure to metals that are not biologically needed by the body lead to serious diseases like lung disease, cardiovascular disease, certain types of cancer, and renal failure^[39]. Heavy metals induce calcium stone aggregation due to their similar charge and ease of substitution with other bioavailable ions in the urine^[61]. Cadmium is a heavy metal used in construction and manufacturing, usually to prevent the corrosion of steel. The metal is considered highly toxic and there is no biological use for cadmium in organisms. Cadmium is a competitive inhibitor to calcium, in turn can increase urinary calcium concentration. Acute chronic exposure to cadmium causes severe renal damage as a result of tubular protein-urea^[62]. Lead is the most common heavy metal contaminate and it can be found in almost all products^[63]. The widespread use of lead in manufacturing, paint, gasoline, and construction have ceased in modern developed countries due to a general consensus on the harmful effects of lead on people's health; however, it is still commonly used in developing countries despite global warnings of health impacts on populations^[63]. Exposure to low levels of lead can have drastic effects on kidney function. One of such effect is the increased formation of uric acid. This increase in uric acid and subsequent decrease in kidney reabsorption of nutrients can contribute to the development of nephrolithiasis.

Melamine exposure and contamination

Melamine is an industrial additive that is commonly found in plastics and cleaning supplies^[64]. It is a molecule high in nitrogen content that manufacturers add to dilute food products in an attempt to increase levels of protein content by deceiving protein tests that measure for nitrogen levels^[64]. An addition of this chemical to food products even in trace amounts has been known to cause renal damage and kidney failure. Though melamine toxicity cases are not frequent and consistent, the outbreak can have a devastating epidemiological impact. In 2008, a reported 294000 infants and young children affected by melamine in China were sent to the emergency room^[65]. Among those cases, 51900 were hospitalized, and among the 2085 children screened, 348 children had kidney stones; however, the method of detection did not account for smaller urinary stones and the actual number may be underrepresented^[65].

In 2004 and 2007, a discovery of melamine in animal food products exported by China in the past has led to widespread animal death due to renal failure with calcification in the kidneys^[66]. Interestingly, pet food in the United States during the 2007 outbreak shows similar melamine levels as the contaminated infant milk products in China. Pet food has also shown cyanuric acid, a chlorine-stabilizing agent used in swimming

pools^[64]. Melamine's role in altering renal reabsorption rates and the overall development of melamine crystal formation are under investigation, but this compound is known to cause serious problems and must be taken into careful consideration^[67].

ADDITIONAL FACTORS TO CONSIDER

Genetics

A familial history of kidney stone disease is one of the strongest causes of penetration for kidney stone formation. The overall impact of genetic disorders contributing to the development of nephrolithiasis in patients is astonishingly high. Roughly 10% of individuals affected by nephrolithiasis can attribute some aspect of their condition directly to a heritable disease^[68]. An autosomal recessive genetic disease Cystineuria, is directly responsible for 1% of all kidney stones^[69]. This disease leads to the development of cysteine stones, which are highly infectious and affect people of all ages. This disorder is commonly found in children and account for roughly 25% of childhood nephrolithiasis^[70]. Hypercitraturia in family members with nephrolithiasis may also be the result of inheriting a genetic disease from stone-forming families, in addition to environmental factors. Many diseases such as Hypertension or Diabetes can form potential higher risks for kidney disease by passing it on through future familial generations.

There is also a possible heritability for urinary osmolality and volume, which could implicate genetic regulation of thirst^[71], while studies have considered urine volume as a risk factor for stone disease. Nephrolithiasis found in adults will most likely be a strong indicator for kidney stone formation in their children and carried on in future familial diseases. Individuals will have to be aware of the possibility of the reoccurrence of stone formation.

Genes which potentially affect the predisposition only influences the risk factors of nephrolithiasis; such as comorbidities or phenotypical symptoms which may increase the risk of nephrolithiasis in the longer run. Several genes which code for TRPV5^[72], SLC26A6 and NaDC-1^[73] can play a physiological role in contributing to calcium stone formation because they play a major role in homeostasis in maintaining physiological conditions. Other genetic factors may have an indirect correlation to nephrolithiasis by contributing to common comorbidities or risk factors to nephrolithiasis.

Reoccurrence of stone formation and family history

While there is no direct genetic predisposition of nephrolithiasis, there is in fact a correlation to family history of stone formation and nephrolithiasis. Nephrolithiasis offspring can possibly carry several urinary metabolic risks predisposing to stone formation that are similar to their parents. Kidney stones develop about 3 times more frequently for individuals with positive family history^[74]. A correlation has been expressed between

Table 2 Prescription medications and treatment of condition with contributions to nephrolithiasis

Medication	Treatment of condition	Function
Acetazolamide	Glaucoma	Diuretic used to prevent and reduce the symptoms of altitude sickness
Vitamin D supplements	Osteoporosis	Mineralization in bone and calcium reabsorption
Vitamin K	Excessive bleeding	Assists blood clots, bones, heart disease
Calcium supplements	Osteoporosis	Assists calcium building, bones, cardiovascular
Warfarin	Blood clotting	Reduce blood pressure/vitamin K inhibitor
Lithium chloride	Mental illness	Psychiatric medication

family history of kidney stones and the onset of nephrolithiasis in patients. Patients are 2 times more likely to develop stone disease, with some studies showing relative risk rates as high as 2.5^[37]. This is one of the strongest associations with the development of stones disease. If a patient develops nephrolithiasis, there is a 50% chance that they will develop another stone within the next 5 years. These cases of recurrence are equally spread out amongst the different type of kidney stones^[3]. Moreover, descendants with nephrolithiasis display urinary metabolic disorders associated with kidney stones^[75]. These abnormalities may also be observed in the parents or predecessors. Although the reoccurrence of stone formation and family history can be observed through genetics, diseases occurring simultaneously with kidney stone formation pose a risk as well.

Medications

Available medications may work well for a patient's kidney stone treatment; however, some medications can not only have adverse side effects but can also contribute to alleviating or worsening potential onset of nephrolithiasis. Medications that pertain to this possibility include acetazolamide, vitamin K, vitamin D, Ca²⁺ supplements, beta blockers such as warfarin, and lithium chloride.

Acetazolamide, a carbonic anhydrase inhibitor, is commonly used to combat glaucoma^[76]. It can cause renal tubular acidosis which can result in calcium phosphate calculi^[77]. Vitamin K is used to counteract excessive bleeding. Vitamin K deficiency could be considered as a main cause of osteoporosis, atherosclerosis and other calcium deposit issues throughout the body.

An individual taking Ca²⁺ supplements may use it to supplement calcium deficiency. Calcium supplements are widely available for the general population. A study of thirty-two healthy navy privates have shown that taking calcium supplements can result in a reduction in urinary oxalates and an elevation in urinary citrate^[78]. Vitamin D supplements, fat-soluble vitamins, are commonly prescribed to treat osteoporosis because of its role in calcium regulation. 50% of woman with osteoporosis are found to have inadequate vitamin D levels^[79], while its deficiency is also associated with other comorbidities such as cardiovascular disorders, cancer, and kidney disorders. Moreover, a study of 456 idiopathic stone

formers have shown that 31% among them were vitamin D deficient^[80], raising up the question of its role in calcium stone formation. The summary of the medications are shown above (Table 2).

Warfarin is used to treat blood clots. It can cause renal damage in patients with CKD and is also associated with progression of renal disease. The mechanism leading to renal damage is hemorrhage and red blood cell tubular casts. Individuals are usually prescribed lithium chloride and used as an anti-depressant. Chronic intake of high lithium amounts causes renal damage. However, lithium chloride acts as an anomaly. There is accumulating evidence from animal studies that indicates that low lithium administration may benefit in kidney disease prevention caused by oxidative stress or inflammation^[81]. The availability of these medications worldwide is not always in abundance, however for patients and individuals taking them, they must be wary of the possibility of kidney stone formation and nephrolithiasis regardless of their living environment.

GLOBAL INTERCOUNTRY COMPARISON

Analysis of United States (Northern/Southern)

Lifestyle and diet are highly influential factors for kidney stone formation in the United States, especially lifestyle, in comparison to the world (Figure 4).

The United States is primarily divided by its latitude and longitude between northern, southern, western, and eastern regions. Most obviously seen, the effects of a state's geographical location on kidney stone formation can be easily discerned between the Northern and Southern states in America (Figure 5). In all, while prevalence in stone formation is elevated from the west to the east side of the United States, formation is also more pronounced from the north to the south side of the United States^[82]. Therefore, Alabama, Mississippi, Tennessee, North Carolina, and other Southern states are considered in the "stone belt"^[13]. This incidence can be attributed to the temperature of Southern region and states as well as the dietary intake of residents inhabiting these States. Men who usually live in southern most latitudes are 60% more likely to report a history of stones than those living in the northern most latitudes^[13].

Analysis of Japan/Iceland

The ambient temperature of these 2 island countries is

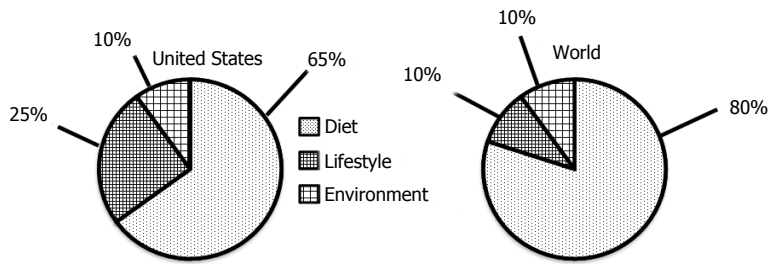
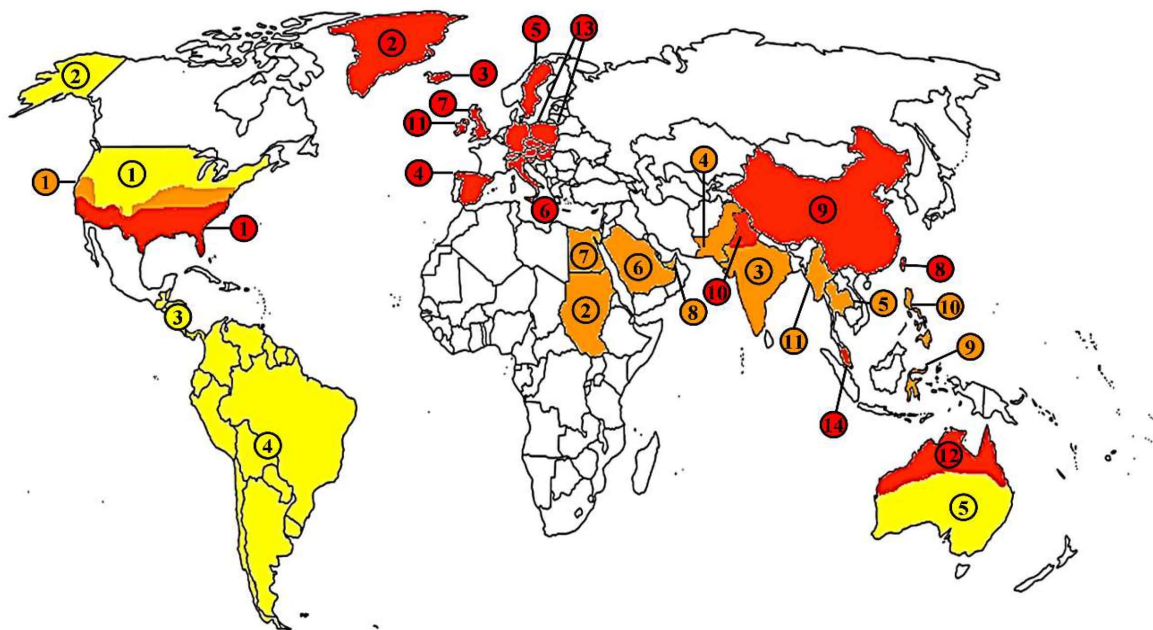


Figure 4 Proposed risk factor percentage distribution for diet, lifestyle and environment. Percentage was determined upon literature review. Lifestyle and diet were the more influential factors for the United States than the world. The environment percentage was about the same for both the United States and the rest of the world.



High prevalence	Moderate prevalence	Low prevalence
1 United States (South)	1 United States of America (Northeast/West)	1 North America
2 Greenland	2 Sudan	2 Alaska
3 Iceland	3 India	3 Central America
4 Spain	4 Pakistan	4 South America
5 Sweden	5 Thailand	5 Southern Australia
6 Italy	6 Saudi Arabia	
7 Scotland	7 Arab Republic of Egypt	
8 Japan	8 United Arab Emirates	
9 China	9 Indonesia	
10 Northern India	10 Philippines	
11 Ireland	11 Myanmar	
12 Northern Australia		
13 Central Europe		
14 Parts of the Malayan, Peninsul		

Figure 5 Projected world map of magnitude of nephrolithiasis prevalence. Magnitude of nephrolithiasis in each country using conglomeration of risk factor indicators dietary intake, obesity, and climate. Degree of prevalence is color coded in red (high prevalence), orange (moderate prevalence), and yellow (low prevalence). High prevalence information obtained through Romero *et al.*^[82].

distinctly different, with Iceland ranging from 0 °C-10 °C and Japan 10 °C-20 °C. One would then expect that Iceland would have a lower prevalence of kidney stone; however, Iceland actually has much higher rates of kidney stones. Iceland rates of stone prevalence are

very similar to western rates of stone prevalence^[48]. This is partly due to the fact that Iceland has a much higher degree of risk for nephrolithiasis due to the average diet and lifestyle risk factors that affect the majority of the country. In a comparison between the two countries,

almost all risk factors for developing kidney stones can be seen in the Icelandic population whereas very few can be found in the Japanese population. According to data from the Food and Agricultural Organization of the United Nations and WHO, an Icelandic diet is calorie dense and consists mainly of animal protein and sugars. They account for roughly 30% of caloric intake per day for someone living in Iceland^[16]. On the contrary, Japan has a much smaller overall consumption of animal protein and sugars, as they only account for 15%^[16]. This dietary difference between the two countries is enough to cause such a dramatic difference in the prevalence of nephrolithiasis in these countries.

Analysis of Australia (Northern/Southern)

Australian rates of kidney stones have had a measured increase over the past decade, similar to that of western countries as they have a similar diet to that of industrialized western countries. Individuals in developed countries like Australia and the United States are more likely to develop nephrolithiasis because they are at a much greater risk of developing metabolic diseases that increase risk. Over 60% of Australians are overweight and obese, with little amounts of physical activity^[16]. Average ambient temperature within the country ranges based on geographical location. The northern part of the country has a harsher hot climate when compared to the southern part of the country.

CONCLUSION

The overall consensus of experts and researchers in this field is that there is no salient contributing factor to the development of nephrolithiasis, but rather it is a combination of risk factors that can cause this disease. Different countries and their populations have different risk factors that they are exposed to over the course of their lifetime. The creation of a model that will fit the current global epidemic of nephrolithiasis is bound to have different degrees of accuracy. It is important to note that these risk factors are an indirect causal relationship, meaning that not all risk factors are necessary for the development of the disease; however, the few that have been listed are well understood or play the largest role in shaping the etiology of the disease.

It is difficult to accurately determine dietary differences within a country because it is nearly impossible to monitor dietary fluctuations and changes by region based on current publicly available data. One can extrapolate the idea the diets of rural individuals will have diets that are very different than individuals living in an urban area due to factors like access to different types of technology and food sources; however, this cannot be quantified nor easily estimated. Certain lifestyle factors like obesity, type 2 diabetes, and metabolic disorders that play a role in the formation of different stones are monitored closer by countries and

international health organizations than other lifestyle contributors like physical activity. While these other factors play an important role in shaping the global nephrolithiasis breakdown, an accurate quantification of factors would be required to enhance the global understanding of kidney stone risk factors.

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Awakening the sleeping kidney in a dialysis-dependent patient with fibromuscular dysplasia: A case report and review of literature

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Abstract

Renal artery stenosis is a common cause of secondary hypertension and chronic kidney disease. We present here a case of fibromuscular dysplasia that was treated with surgical revascularization, resulting in recovery of kidney function with eventual cessation of chronic dialysis. The case involves a 25-year-old female with coincidentally discovered hypertension, who underwent further investigations revealing a diagnosis of renal artery stenosis due to fibromuscular dysplasia. She subsequently developed two episodes of malignant hypertension, with flash pulmonary oedema and worsening renal failure that resulted in dialysis dependence. After evidence was obtained that the right kidney was still viable, a revascularization procedure was performed, improving blood pressure control and restoring kidney function, thereby allowing dialysis to be stopped. This case highlights the importance of evaluating patients with renal artery stenosis for revascularization before committing them to a life of chronic dialysis.

Key words: Renal artery stenosis; Fibromuscular dysplasia; Revascularisation; Dialysis; Caes report

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Core tip: Renal failure requiring dialysis support is a rare complication of renal artery stenosis due to fibromuscular dysplasia. We present a 25-year-old woman with fibromuscular dysplasia who developed dialysis dependence following acute loss of kidney function after suspected renal arterial dissection. Surgical revascularization resulted in dialysis cessation and improved blood pressure control. This case illustrates that in well-selected dialysis-dependent patients with renal artery stenosis secondary to fibromuscular dysplasia, surgical revascularization may not only improve the control of blood pressure but also restore enough kidney function for dialysis cessation.

Chothia MY, Davids MR, Bhikoo R. Awakening the sleeping kidney in a dialysis-dependent patient with fibromuscular dysplasia: A case report and review of literature. *World J Nephrol* 2018; 7(7): 143-147 Available from: URL: <http://www.wjgnet.com/2220-6124/full/v7/i7/143.htm> DOI: <http://dx.doi.org/10.5527/wjn.v7.i7.143>

INTRODUCTION

Renal artery stenosis (RAS) is a common cause of secondary hypertension and chronic kidney disease. The most common cause of RAS is atherosclerosis, while fibromuscular dysplasia (FMD) is regarded as a rare aetiology. The latter is regarded as a non-atherosclerotic, non-inflammatory vascular disease, most frequently affecting the renal arteries (60%-75%) followed by the carotid arteries (25%-30%); however, many other vascular beds have been described^[1].

The pathological classification of FMD is based on the arterial layer primarily affected. The most common pathological type is medial fibroplasia, which has a characteristic "string-of-beads" appearance on renal angiography. The cause of FMD remains unknown but may have a genetic component since the disease tends to affect first-degree relatives of affected individuals^[2]. The disease is frequently asymptomatic and may only be identified coincidentally. Studies have reported that FMD represents < 10% of cases of renovascular hypertension^[3]. Even more uncommon is renal failure due to FMD, despite studies reporting that up to 63% of patients have loss of kidney volume^[4].

We present herein a case of FMD that resulted in severe dialysis-dependent renal failure, where there was recovery of kidney function following revascularization and eventual cessation of chronic dialysis.

CASE REPORT

A 25-year-old female was seen in August 2015 at our medical outpatient clinic after hypertension was diagnosed following surgery for a distal tibia-fibula fracture. During hospitalisation, the patient's systolic and diastolic blood pressure (BP) was noted to be in the range of

180-225 mmHg and 110-130 mmHg, respectively, despite anti-hypertensive therapy that included hydrochlorothiazide 25 mg daily and amlodipine 10 mg daily.

The patient showed no symptoms related to her hypertension. On clinical examination, she had a normal body habitus with a body mass index of 23 kg/m² and no syndromic features for an endocrine cause of hypertension. All pulses were palpable and equal in volume, with no radio-femoral delay. There were no differences in BP between the right and left upper limbs, or between the upper and lower limbs. No renal or carotid arterial bruits were audible. There was a prominent, pressure-loaded apical impulse. Her serum creatinine concentration was 67 µmol/L.

Since parenchymal kidney disease and renovascular disease are the two most common causes of secondary hypertension, a radiological examination of these systems was performed. Ultrasound measurements of the patient's left and right kidney showed a discrepancy in sizes of 72 mm and 117 mm, respectively. Resistive index could not be determined for the left kidney, due to very poor perfusion; however, the right kidney had normal perfusion, with a resistive index of 60%. Computed tomography angiography (CTA) revealed normal cortico-medullary enhancement in the right kidney, while the left kidney had cortical infarcts and fibrous tissue that encased the left renal artery, originating approximately 8 mm from the ostium up to the level of the renal hilum with near-complete occlusion. The right renal artery had nearly 50% stenosis that originated 17 mm from the ostium. The rest of the aorta and its branches were otherwise normal in configuration.

A diagnosis of FMD was made, since the CTA was most consistent with this condition (as opposed to Takayasu's arteritis). The lumina of the aorta and its branches were not narrowed and had a smooth wall, and no post-stenotic dilatations were noted. Also, the origins of the stenosis in the renal arteries were not at the ostia but rather at the mid-vessel level.

During this time, the patient's serum creatinine had increased slightly to 87 µmol/L and she developed resistant hypertension. Her antihypertensive regimen included atenolol at 50 mg daily, furosemide at 160 mg daily, amlodipine at 10 mg daily and minoxidil 5 mg daily. Antagonists of the renin-angiotensin system were avoided due to the concern of effects that this class of drugs may have on renal function.

In January 2016, the patient presented with malignant hypertension, flash pulmonary oedema and a serum creatinine level that had risen to 1807 µmol/L. Despite this, her urine volumes ranged from 700 mL to 1000 mL daily. Repeat ultrasound showed that the right kidney size was now 92 mm and that the resistive index had increased to 70%. A diuresis renogram revealed a differential function of 80% in the right kidney and 20% in the left, with poor global function. The patient was initiated on haemodialysis and her serum creatinine improved to 650 µmol/L. Dialysis was stopped. However, 3 wk later, she re-presented with a second episode



Figure 1 Three-dimensional computed tomography reconstruction. Extensive collateral blood supply to the right kidney (blue arrows) and origins of the renal arterial stenosis (yellow arrows) are shown.

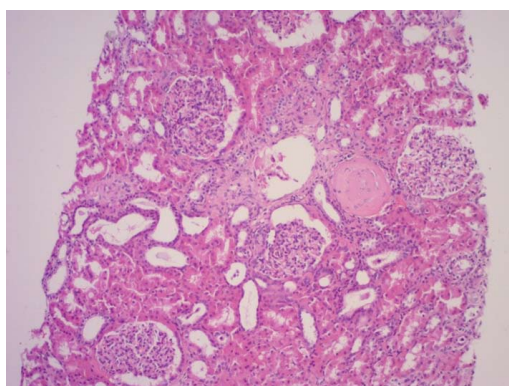


Figure 2 Results of the kidney biopsy. Normal appearing tissue (haematoxylin and eosin stain, at 100 × high power field magnification).

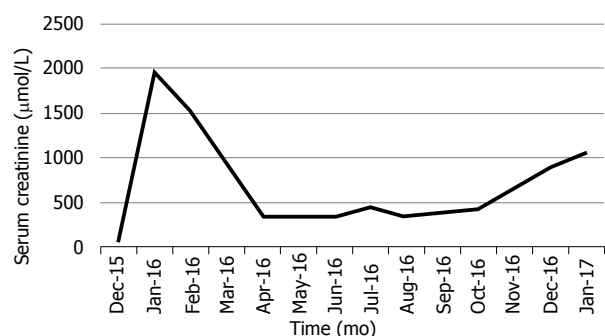


Figure 3 The patient's serum creatinine levels over time.

of malignant hypertension and flash pulmonary oedema and her serum creatinine had again increased to 1509 μmol/L. Haemodialysis was then re-initiated.

Notably, the patient's urine volumes throughout this entire period remained at nearly 1000 mL daily, which was an indication of ongoing right kidney perfusion, possibly *via* collateral blood vessels. This was confirmed on a repeat CTA (Figure 1). A kidney biopsy of the right kidney was performed and revealed viable, normal-appearing tissue (Figure 2).

Due to the abrupt loss of kidney function, arterial

dissection and/or thrombosis involving the right renal artery was suspected. Because of limited experience with the endovascular treatment of complicated renal arterial lesions at our centre, a decision was made to attempt primary surgical revascularization. Due to the negligible contribution to overall kidney function, no interventions were planned for the left kidney.

In April 2016, the patient underwent *ex vivo* reconstruction of the right renal artery using a saphenous venous graft from the left leg. A long segment of arterial dissection up to the branch vessels was identified. The occluded arterial segment was resected, and the venous graft was interposed with end-to-side anastomoses. Post-operative Doppler ultrasound showed that the kidney size had increased to 132 mm and excellent renal perfusion was noted.

Approximately 1 wk post-operatively, the patient complained of right flank pain. An ultrasound examination revealed a right perinephric haematoma and suspected kinking of the ureter, causing hydronephrosis. A pigtail catheter was placed to drain the haematoma, and a double-J-stent was inserted to relieve the obstruction. There was a dramatic improvement of both kidney function and BP control. Haemodialysis was tapered and eventually discontinued. Her serum creatinine settled at 350 μmol/L, nearly 2 mo following surgery. BP control was achieved with a single agent. The patient remained dialysis-free for 9 mo before her chronic kidney disease progressed and she eventually returned to chronic dialysis (Figure 3).

DISCUSSION

The "sleeping" kidney is a term used to describe a non-functioning but viable kidney, usually due to RAS. Most of the reported cases have involved those with atherosclerotic RAS, with fewer cases involving FMD.

The main blood supply to the kidneys is *via* the renal arteries; however, they also have a rich collateral blood supply. These pre-formed collateral vessels originate from branches of the renal capsular, peri-pelvic and peri-ureteric systems^[5]. We suspect that our patient must have had an extensive collateral blood supply to the right kidney since she maintained good urine volumes of up to 1000 mL per day despite the demonstration on CTA of extremely poor perfusion *via* the main right renal artery.

Renal arterial dissection may cause renal infarction and subsequent chronic kidney disease; however, FMD as a cause of chronic kidney disease is very uncommon and cases that progress to end-stage kidney disease are rare^[6,7]. A large registry of FMD patients showed that out of a total of 447 vascular events, 4.3% of patients had renal arterial dissection and that only 1.6% and 0.9% of patients had renal failure and renal infarction, respectively^[7]. In our case, renal arterial dissection and/or thrombosis was suspected as a cause of acute kidney injury due to the unexplained, abrupt loss of kidney

function.

The indications for renal revascularization, as recommended by the American Heart Association (commonly known as the AHA), include resistant hypertension, new-onset hypertension, branch disease, dissection and aneurysm, and the preservation of kidney function^[7]. Regarding the latter, the AHA recommends revascularization when there is progressive decline in kidney function and/or reduction in kidney mass. We decided to offer our patient a revascularization procedure because she had resistant hypertension that was complicated by episodes of malignant hypertension and flash pulmonary oedema. Also, the on-going urine production despite the negligible perfusion seen on radioisotope renogram and CTA suggested a potentially viable right kidney.

There are no guidelines regarding revascularization of RAS in dialysis-dependent patients. A study that investigated 15 hypertensive patients with non-functioning kidneys due to either complete or segmental renal arterial occlusion found that the presence of viable glomeruli on kidney biopsy, angiographic evidence of collateral blood supply, and the presence of a patent distal renal artery were associated with successful revascularization and salvage of non-functioning kidneys^[8]. In addition, others have recommended kidney length of at least 90 mm and renal vein renin sampling as an additional measure of nephron viability^[9-11]. Our case demonstrated three of these criteria: the right kidney size being 92 mm; detection of collateral perfusion on CTA as well as on Doppler ultrasound; and, kidney biopsy showing normal glomeruli without tubular atrophy or significant interstitial fibrosis.

Guidelines recommend percutaneous transluminal angioplasty (PTA) as the primary revascularization procedure for renal FMD, with surgery as a secondary procedure if PTA is unsuccessful^[7]. However, these studies predominantly focussed on the effect of PTA on the rates of hypertension cure and/or control. Evidence for PTA to restore or preserve renal function is less robust, with many studies, albeit their representing a small number, reporting unclear outcomes with none of the patients established on dialysis^[12-18]. One study demonstrated that 12 of 14 patients had improved renal function following PTA, with a mean serum creatinine concentration of 212 $\mu\text{mol/L}$ at baseline that improved to 150 $\mu\text{mol/L}$ after a mean follow-up period of 33 mo^[19]. Again, none of these patients were dialysis-dependent. There have been few documented case reports of successful renal revascularization in dialysis-dependent patients. In a case of presumed FMD that was dialysis-dependent for 6 mo, the patient became dialysis-independent following surgical correction that involved a spleno-renal bypass procedure^[20].

In our case, the decision to surgically repair the right renal artery instead of attempting PTA was largely influenced by the abrupt loss of kidney function, which suggested arterial dissection and/or thrombosis. Also,

the lack of local experience with regards to renal arterial stenting was an additional factor that influenced our decision. Because our patient was dialysis-dependent and had a potentially salvageable solitary kidney, we believed that surgical repair would offer the greatest chance for successful revascularization.

The outcomes of revascularization in dialysis-dependent patients are not well known. In the case mentioned above, the patient remained dialysis-free for 17 mo, with a serum creatinine of 203 $\mu\text{mol/L}$. In a study that included 6 patients with FMD and required a secondary revascularization procedure after a failed primary procedure, all cases were dialysis-free after an average follow-up of 58 mo^[21]; however, none of those patients were dialysis-dependent prior to surgery. The initial indication for revascularization in all cases was for BP control rather than improvement of kidney function. Our patient had improvement of both hypertension as well as kidney function but eventually returned to dialysis after 9 mo.

In conclusion, the case presented herein illustrates that in well-selected dialysis-dependent patients with RAS, revascularization may not only improve BP control but also restore kidney function. Patients with RAS should be evaluated for revascularization before fully committing them to a life of chronic dialysis.

ARTICLE HIGHLIGHTS

Case characteristics

We report the case of a young woman with renal artery stenosis (RAS) due to fibromuscular dysplasia who became dialysis dependent following arterial dissection; after surgical revascularization, the patient was able to stop dialysis.

Clinical diagnosis

Renal artery stenosis secondary to fibromuscular dysplasia complicated by arterial dissection and subsequent dialysis dependence.

Differential diagnosis

Renal artery stenosis secondary to Takayasu's arteritis.

Imaging diagnosis

Three-dimensional computed tomography reconstruction indicating a rich collateral renal blood supply and confirming the origins and extent of the renal artery stenosis.

Pathological diagnosis

Kidney biopsy confirming viable tissue.

Treatment

Surgical revascularization by *ex vivo* repair of the renal artery using a saphenous venous graft.

Related reports

The paper by Libertino *et al* is important for readers to appreciate how to identify those patients that are likely to have a good response to revascularization.

Term explanation

The "sleeping" kidney refers to a non-functional but potentially viable kidney that may recover function following revascularization.

Experiences and lessons

Patients with RAS should be evaluated for revascularisation before fully committing them to a life of chronic dialysis.

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WJN covers topics concerning kidney development, renal regeneration, kidney tumors, therapy of renal disease, hemodialysis, peritoneal dialysis, kidney transplantation, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of nephrology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, etc.

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Palliative care for acute kidney injury patients in the intensive care unit

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Abstract

Patients with acute kidney injury (AKI) in the intensive care unit (ICU) are often suitable for palliative care due to the high symptom burden. The role of palliative medicine in this patient population is not well defined and there is a lack of established guidelines to address this issue. Because of this, patients in the ICU with AKI deprived of the most comprehensive or appropriate care. The reasons for this are multifactorial including lack of palliative care training among nephrologists. However, palliative care in these patients can help alleviate symptoms, improve quality of life, and decrease suffering. Palliative care physicians can determine the appropriateness and model of palliative care. In addition to shared decision-making, advance directives should be established with patients early on, with specific instructions regarding dialysis, and those advance directives should be respected.

Key words: Palliative care; Acute kidney injury; Intensive care unit; Dialysis; Advance directives

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Core tip: Role of palliative medicine in nephrology is not well defined and the patients with acute kidney injury in the intensive care unit may not receive the most comprehensive care surrounding their illness due to scarcity of established palliative care guidelines and lack of palliative care training among nephrologists. A multidisciplinary approach involving palliative care physician early in the course of illness may help in comfort care of acute kidney injury patients in the intensive care unit. Shared decision-making and advance directives play an important role guiding the physician as to what patient wishes are, and those decisions should be respected.

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INTRODUCTION

Intensive care unit (ICU) patients with acute kidney injury (AKI) have a high mortality rate and renal replacement therapy is not cost-effective in these patients^[1]. Physicians in the ICU often face challenging situations when potentially inappropriate treatment has to be withdrawn in critically ill patients^[2]. Various factors make these situations more complex; incapacitated state of ICU patients, the option of temporary dialysis due to reversible nature of AKI, and inadequate knowledge of surrogate decision-makers about the goals of care and prognosis^[2]. Palliative medicine has a well-established role in many chronic disease states and principles of palliative care are well established for the management of end-stage disease symptoms. However, the role of palliative medicine in the field of nephrology is not well defined and patients with AKI leading to fluid overload, acidosis, hyperkalemia, acute respiratory distress syndrome, respiratory failure and multisystem organ dysfunction with hypotension and sepsis in the ICU may not receive the most comprehensive or appropriate care surrounding their illness. A multitude of factors contribute to this; lack of palliative care training among nephrologists, lack of epidemiological research on outcomes and scarcity of established palliative care guidelines for management of AKI patients in the ICU results in a substandard level of care. However, a multidisciplinary approach by involving palliative care physician early in the course of illness may help in comfort care of AKI patients in the ICU. In this review, we discuss the use of palliative medicine in this specific patient population.

PALLIATIVE CARE IN ACUTE KIDNEY INJURY IN THE ICU

One of the main reasons why palliative care is rarely offered to AKI patients in the ICU setting is the lack of palliative medicine training in most nephrology programs. As a result, most nephrologists may not feel comfortable or compelled to provide these services at an appropriate time. To help solve this issue, nephrology fellows in the future during their training should receive some exposure to palliative care, especially in the ICU setting. There are well-established prognostic indicators from multitudes of epidemiological research on disease progression and outcomes in end-stage renal disease (ESRD) patients. Due to this, nephrologists frequently consult palliative medicine in situations when it may be appropriate for the ESRD patient to withdraw from chronic dialysis. However, AKI patients on dialysis in the ICU may not have palliative care offered at an appropriate time due to the lack of guidelines/recommendations to make a clinical judgment. The following discussion may serve as a guide to nephrologists for providing palliative care to patients with AKI in the ICU.

Risk factors associated with poor outcome in critically ill AKI patients

Kao *et al*^[3] conducted a retrospective cohort study to investigate in-hospital mortality and long-term survival rates in critically ill patients with AKI or ESRD receiving renal replacement therapy. This study found that overall in-hospital mortality was 66.5% and there was no significant difference in mortality rates between AKI and ESRD groups (adjusted odds ratio: 0.93; 95%CI: 0.84-1.02)^[3]. Hypertension was found to be a high-risk factor for in-hospital mortality in patients with AKI while older age, chronic liver disease and history of cancer were found to be independent risk factors for in-hospital mortality in both AKI and ESRD groups^[3]. In addition, older age, coronary artery disease, and ICU admissions were found to be risk factors in AKI patients for long-term dialysis dependence^[3]. In another study, Bagshaw *et al*^[4] investigated risk factors and outcomes associated with critically ill septic AKI patients in ICU. Compared to non-septic AKI group, septic AKI group had greater severity of illness ($P = 0.0001$), hypotension ($P = 0.0001$), tachycardia ($P = 0.0001$), worse lung function measures ($P = 0.0001$), higher white cell counts ($P = 0.0001$) and significant acidemia ($P = 0.0001$)^[4]. Also, septic AKI group was associated with a higher crude mortality rate in the ICU (19.8% vs 13.4%, $P \leq 0.001$) and in the hospital (29.7% vs 21.6%, $P <$

0.001) compared to non-septic AKI group^[4]. Furthermore, a recent prospective cohort study involving septic AKI patients undergoing dialysis in the ICU found that norepinephrine use, hepatic failure, medical condition, blood lactate, and pre-dialysis creatinine level were associated with early mortality (seven days)^[5].

Models of palliative care

Palliative care should be considered for all high-risk AKI patients in the ICU determined by the presence risk factors associated with poor outcome or high mortality rates as discussed earlier. Three palliative care models have evolved over two decades with an aim to improve quality of care and reduce suffering in the ill patients^[6]. These models of care may be considered in the ICU setting for AKI patients as appropriate.

Conventional model of care: This is also called as the traditional dichotomous model of palliative care where ICU patients receive curative or disease-specific care for AKI till it fails following which palliative care will be initiated^[7]. This dichotomous model offers AKI patients either curative/disease-specific care or palliative care but not both simultaneously, which leads to a sudden transition from curative to palliative care without enough transition time (Figure 1)^[6,7]. The Conventional model of care is suitable for young AKI patients in the ICU without high-risk factors associated with the poor outcome such as septic shock, acidemia, hypertension, coronary artery disease, chronic liver disease and history of malignancy. Given higher resolution rates in this patient population, curative or disease-specific therapy is given first for the management of AKI till it is unsuccessful and then palliative care is initiated.

Comprehensive model of care: This is also called as the overlapping model of palliative care where ICU patients receive both curative or disease-specific care for AKI and palliative care simultaneously (Figure 2)^[7]. Although this model of care is dichotomous, it offers both curative/disease-specific and palliative care simultaneously to the patients with a gradual increase in palliative care over time and slow withdrawal of curative/disease-specific care^[6,7]. However, both of these dichotomous models of care have the disadvantage of providing one model of care at the cost of the other^[6]. The Comprehensive model of care is suitable for older AKI patients in the ICU with multiple comorbid conditions in addition to the presence of high-risk factors for the poor outcome such as septic shock, acidemia, hypertension, coronary artery disease, chronic liver disease, history of malignancy and history of prior ICU admissions. Due to the poor outcome and higher mortality rates in this patient population, concurrent initiation of palliative care early in the course of medical management helps to prevent and relieve suffering from pain and other physical, psychological, emotional and spiritual distress^[7].

Conceptualization model of care: This is also called as the individualized integrated model of palliative care where ICU patients concurrently receive both palliative care and curative or disease-specific care for AKI, but individualized to suit the needs of the AKI patients and family members^[7]. In this model of care, palliative care extends beyond the death of the patient to include bereavement care for the family members^[7]. In addition, the intensity of palliative care varies based on the needs of the patient or family member during the course of management^[7]. Conceptualization model of palliative care is best suited for poor prognostic AKI patients in the ICU with multiple comorbidities and multi-organ failure. This model of care classifies all the interventions and options of care based on goals allowing more flexible management^[6]. Once the palliative care is consulted for the impending death of a family member or friend that entails life-changing events and dynamics, the conceptual model helps in supportive intervention to educate family caregivers about stress coping strategies and creates a perception that they have necessary skills to confront problematic situations. (1) Cure-seeking care: Aim to eliminate the underlying disease/medical problem with medical treatment^[6]. For example, treatment of sepsis, hypotension, acidosis, electrolyte imbalance, and underlying connective tissue and immunological disorders in AKI patients; (2) Life-extending care: Aim to prolong life in chronic disease states with the help of medical treatment while also enhancing the quality of life^[6]. For examples, AKI patients with long-term dialysis dependence; (3) Quality of life and comfort maximizing care: Aim to improve function, reduce suffering and enhance the quality of life in AKI patients in the ICU, and these interventions may also prolong life^[6]; (4) Family supportive care: Aim to address the grief and emotions of the family members from the time of diagnosis to past death^[6]. The key variables that should be considered for supportive care interventions for family members are^[8]; preparedness of the caregivers for the tasks and demands of the role, mastery to manage stress, competence to adapt more quickly to the situation, self-efficacy to manage a situation with coping behaviors,

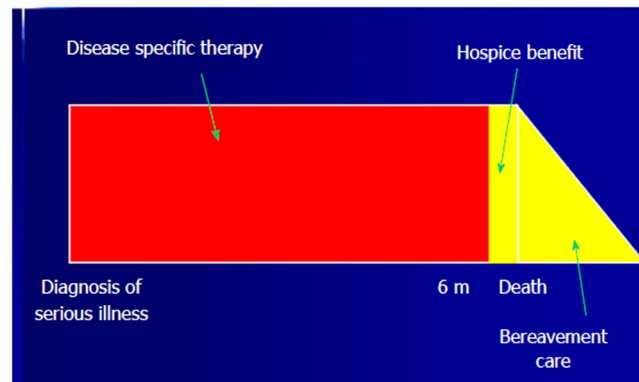


Figure 1 Conventional model of care. Patients receive curative or disease-specific care till it fails following which palliative care will be initiated.

social support to the caregivers, positive emotions to reframe the stressful situations in a positive way, optimism of caregivers to neutralize some potentially negative aspects of caregiving^[8]; (5) Healthcare staff supportive care: Aim to address the grief and emotions related to the management of these AKI patients in the ICU^[6].

Shared decision-making and advance directives

Patel *et al*^[9] described outcomes and decision-making process for nephrologists in the management of AKI in the ICU setting. Expected outcomes and prognosis for patients with AKI remain poor with the mortality rate of 28%-90%^[10]. The highest prognostic indicators for mortality were concomitant multi-organ failure, mechanical ventilation, liver-failure, and malignancy^[9,11,12]. These prognostic indicators aid physicians to offer palliative care at an appropriate time in this patient population. Furthermore, the use of the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria to establish predicted mortality was around 80%-85% and that, while not perfect, could still be an acceptable tool to help establish the prognosis for AKI patients in the ICU^[9,13]. However, in those patients who survive, 70%-90% have a recovery of kidney function^[12,13]. Hence RIFLE criteria can be considered when making clinical decisions regarding the discontinuation of dialysis in AKI patients^[12,13]. The Renal Physicians Association/American Society of Nephrology (RPA/ASN) guideline, Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis, helps to establish general recommendations in certain situations in which dialysis may be discontinued^[14]. These situations are: (1) a patient with full capacity for judgment who asks for dialysis to be discontinued; (2) a patient who lacks capacity but previously expressed a desire not to continue dialysis; (3) a patient without capacity but power of attorney asking to withdraw dialysis; (4) a patient who has irreversible, profound neurological impairment; (5) a patient who has a terminal illness (severe cirrhosis, end stage pulmonary disease, advanced stage of cancer) with a life expectancy of ≤ 6 mo. In these situations, it is appropriate to consult palliative care and develop a plan to proceed with the discontinuation of dialysis.

Advance directives also play an important role in clinical decision-making. The presence of an advance directive gives clinicians a guide as to what patient wishes are, and those decisions should be respected^[9]. However, one study involving cancer patients in the ICU demonstrated that the presence of an advance directive did not alter decision-making regarding life-supporting interventions^[15]. This alone is concerning; however, this issue becomes more complex when it is considered that most advance directives typically do not directly address acute dialysis in the setting of AKI. Nephrologists are often left without a guide for advance directives to determine the continuity of care in this specific setting.

Cost-effectiveness of renal replacement therapy

Cost is another factor, which must be considered in these patients. The SUPPORT trial helped to establish the cost-effectiveness of AKI treatment involving 490 patients^[1]. This trial determined that overall cost of renal replacement therapy per quality-adjusted-life-year in AKI patients in the ICU was \$128200 with \$274100 for patients in worst prognostic group and \$61900 for patients in the best prognostic group. However, it surpassed the cost-effective limit of \$50000 per quality-adjusted-life-year^[1]. In another study by Gopal *et al*^[16], the outcomes of 85 survivors of multi-organ failure who required the use of renal replacement therapy in ICU found that the cost of each year of survival was \$50000, and the majority of survivors felt that their

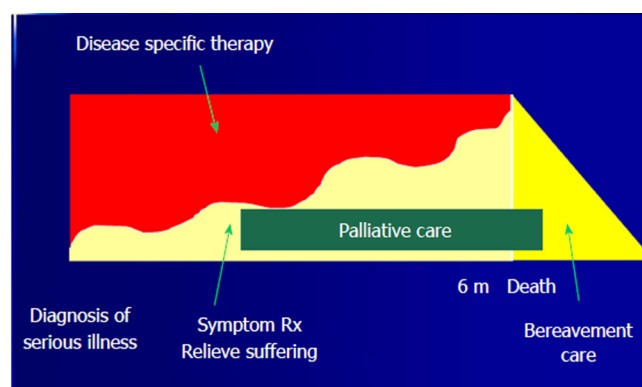


Figure 2 Comprehensive model of care. Patients receive both curative/disease-specific and palliative care simultaneously with a gradual increase in palliative care over time and slow withdrawal of curative/disease-specific care.

treatment was worthwhile and their quality of life was satisfactory. With a high mortality rate of up to 90% for ICU patients with AKI^[10], the ethical principle of justice and the equitable distribution of resources must be considered when treating these patients. In these situations, a palliative care consult would provide a more cost-effective treatment apart from better symptom management and a better quality of life.

RECOMMENDATIONS

AKI in ICU patients has a host of symptoms, including pain, pruritus, anorexia, sleep disturbances, fatigue, sexual dysfunction, and others^[17]. The appropriateness of palliative care in AKI patients in the ICU will be judged based on the complications and prognosis. However, a study done by Aslakson *et al*^[18] establishes the role of palliative care in the ICU and determined that “palliative care is increasingly accepted as an essential component of comprehensive care for critically ill patients, regardless of diagnosis or prognosis”. AKI in the ICU comes with a host of complications regarding treatment decisions. Among the most difficult decisions a physician must make is whether to withdraw dialysis from these patients. Due to difficulty in establishing the prognosis, this decision may not come lightly. Following is a list of recommendations and justifications for the palliative care in these critically ill AKI patients: (1) Palliative care is appropriate in patients with AKI in the ICU: Patients with AKI in the ICU are often appropriate for palliative care due to the multitudes of symptoms they can experience. These patients have historically not been provided this service due to multifactorial reasons. However, palliative care in these patients can help to alleviate problematic symptoms, improve quality of life, and decrease suffering. Palliative care physicians, with the teamwork of the patient’s nephrologist, are equipped with the appropriate training and knowledge to make determinations regarding the appropriateness of palliative care for individual patients. Depending on the clinical situation and the presence of risk factors for poor outcome, one of the three models of care is recommended; (2) Establish an advance directive with patients early on, with specific instructions regarding dialysis, and respect those advance directives^[9]: This will help to establish patient wishes early on, and with the ethical respect of these wishes, a physician can make a sound clinical judgment regarding the withdrawal of dialysis as well as the establishment of palliative care in that patient; (3) Discontinuation of dialysis should occur in the situations outlined by the RPA/ASN guidelines^[14]: The RPA/ASN guidelines help to establish evidence-based ethical considerations when making the clinical decision to withdraw dialysis. Clinicians can use these guidelines combined with informed consent to educate patients and patient advocates about the risks, benefits, outcomes, and prognosis for each patient’s condition.

LIMITATIONS AND ETHICAL CONSIDERATIONS

AKI in the elderly population has been shown to be associated with significant morbidity and mortality^[19]. Furthermore, dialysis is associated with poor outcomes, suffering, and limited life prolongation at the cost of dignity and quality of life in the

elderly AKI patients admitted to ICU with multiple comorbidities^[19]. Expectations of today's society about the standard of care have lead to indisputable provisions of dialysis in this patient population necessitating the reevaluation of these approaches^[19]. Although RPA/ASN guidelines are applicable in the acute care setting, there are few factors that may limit its use in AKI patients in the ICU^[20]. Shared decision-making is often difficult given decisions are urgent and physicians have not known patients and their family members prior to ICU admission in most cases^[20]. In contrast, shared decision making in chronic kidney disease patients progressing to ESRD is much easier due to the long-standing relationship between caregiver, patients and their family members^[20]. Some clinical scenarios may challenge caregivers with ethical and legal issues as few patients and their relatives may demand initiating or continuing dialysis even after it is considered futile^[2]. In such situations, informed decision-making plays a crucial role in proving the legality of withholding or withdrawing dialysis^[2]. All the discussions and communications with the patient and his/her family members or surrogate decision makers should be properly documented at all the times during the entire course of management^[2]. In addition, a multidisciplinary approach involving palliative care team, nephrologists, intensivists, and institutional ethics committee may help to settle conflicts between the caregivers, and the patient and family members^[2].

CONCLUSION

AKI patients in the ICU have a host of symptoms and most often suitable for palliative care that can help relieve symptoms, improve quality of life and reduce suffering. The appropriateness of palliative care in this patient population is determined with the teamwork of the patient's nephrologist and palliative care physician. Shared decision-making and advance directives play an important role in the management and guide the physician as to what patient wishes are, and those decisions should be respected. Either comprehensive or conceptualization model of palliative care is recommended for these patients.

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Clear cell papillary renal cell carcinoma: A case report and review of the literature

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Abstract

Clear cell papillary renal cell carcinoma (ccpRCC) was recently established as a distinct type of epithelial neoplasm by the International Society of Urological Pathology Vancouver Classification of Renal Neoplasia. Here, we report a case of partial nephrectomy for a ccpRCC detected during the routine follow-up of a previously treated liposarcoma in a 70-year-old male patient. The patient was referred to the urology department for a right-sided renal mass (size: 2 cm) detected during routine annual imaging follow-up for a malignant right inguinal fibrous histiocytoma and liposarcoma that had been diagnosed 6 and 4 years earlier, respectively, and treated with surgery and adjuvant radiation therapy. Following partial nephrectomy, the renal mass was pathologically diagnosed as ccpRCC, and immunohistochemistry revealed carbonic anhydrase 9 (CA9) expression. No recurrences or metastases were detected on follow-up imaging for 6 months. This is the first report of partial nephrectomy for incidentally discovered CA9-positive ccpRCC.

Key words: Clear cell; Papillary; Renal cell carcinoma; Partial nephrectomy; Carbonic anhydrase 9; Case report

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Core tip: Clear cell papillary renal cell carcinoma (ccpRCC) was recently established as a distinct type of epithelial neoplasm. Here, we report a case of partial nephrectomy for a ccpRCC detected during the routine follow-up a previously treated liposarcoma in a 70-year-old male patient. The patient received partial nephrectomy, the renal mass was pathologically diagnosed as ccpRCC, and immunohistochemistry revealed carbonic anhydrase 9 (CA9) expression. No recurrences or metastases were detected on follow-up imaging for 6 mo. This is the first report of partial nephrectomy for incidentally discovered CA9-positive ccpRCC.

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INTRODUCTION

Clear cell papillary renal cell carcinoma (ccpRCC), which is also known as clear cell tubulopapillary renal cell carcinoma, is a rare type of malignant renal tumor that differs markedly from other malignant tumor subtypes in terms of visual, microscopic, and immunohistochemical characteristics^[1-4]. Cytopathologically, ccpRCC comprises epithelial cells with clear cytoplasm in both tubular and papillary arrangements, and thus exhibits characteristics of both clear cell renal cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC). These clear tumor cells harbor a linear array of low-grade nuclei distal from the basement membrane and develop a range of tubular, papillary, and cystic structures. By contrast, atypical and mitotic cells, vascular invasion, necrosis, hyaline globules, foamy macrophages, and pleomorphism are rarely observed.

Although Tickoo *et al*^[5] first identified ccpRCC in the context of end-stage kidney disease in 2006, this entity mainly occurs in normal kidneys and is rare in patients with end-stage or cystic kidney disease^[1,2,6]. Recently, the International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia^[7,8] recognized ccpRCC as a distinct epithelial tumor that could be distinguished from ccRCC and pRCC by genetic differences in the *von Hippel-Lindau* (VHL) tumor suppressor gene mutation and 3p loss status and the extreme rarity of gains in chromosomes 7 and 17 or the loss of chromosome Y, despite significant morphological, immunohistochemical, and genetic similarities among the three tumors^[9]. Here, we report a case in which partial nephrectomy was used to treat a ccpRCC that was incidentally diagnosed during a recent imaging follow-up in a patient with a history of previously treated liposarcoma and malignant fibrous histiocytoma.

CASE REPORT

A 17-year-old man was referred to department of urology after a routine computed tomography (CT) scan detected a right-sided enhancing mid-pole renal mass measuring 2.3 cm (Figure 1). He was previously treated for a right-sided inguinal lymph nodal malignant fibrous histiocytoma and right-sided pelvic high-grade pleomorphic and spindle cell sarcoma 6 and 3 years earlier, respectively, *via* surgical excision in the orthopedic department and radiation therapy (adjuvant dose of 60 Gy/30 fractions to the pelvis) in the radiology department. He had no other underlying diseases such as hypertension or diabetes. The follow-up of the patient included biannual pelvic magnetic resonance imaging (MRI) and chest CT and annual positron emission tomography (PET)-CT. No signs of recurrence or metastasis were identified until the currently described renal mass (Figure 1).

Following a full metastatic work-up, the patient underwent open right-sided partial nephrectomy. Subsequent pathology revealed a tumor measuring 1.7 cm × 1.4 cm × 1.0 cm with a capsule abutting, leading to a diagnosis of a grade 2 ccpRCC without necrosis and a final pathologic stage of T1aN × M0 (Figure 2). The patient was routinely followed at the urology outpatient clinic without any further adjuvant plan for 9 mo postoperatively.

DISCUSSION

According to the ISUP (ISUP) Vancouver Classification 2012, ccpRCC, which has also been described as clear cell tubulopapillary RCC or renal angio adenomatous tumor (RAT), is a recently recognized type of indolent epithelial tumor of the renal cortex, with a prevalence rate of 1%-4% among all resected asymptomatic renal tumors^[7,10]. These tumors exhibit no age or sex prevalence, and no cases of local or nodal recurrence or distant metastasis have been reported^[11,12]. However, despite the generally asymptomatic nature of ccpRCC, some patients, including the subject of this case, complain of abdominal or flank pain. Although these tumors may occur in patients with end-stage renal disease or von Hippel-Lindau (VHL) syndrome, most

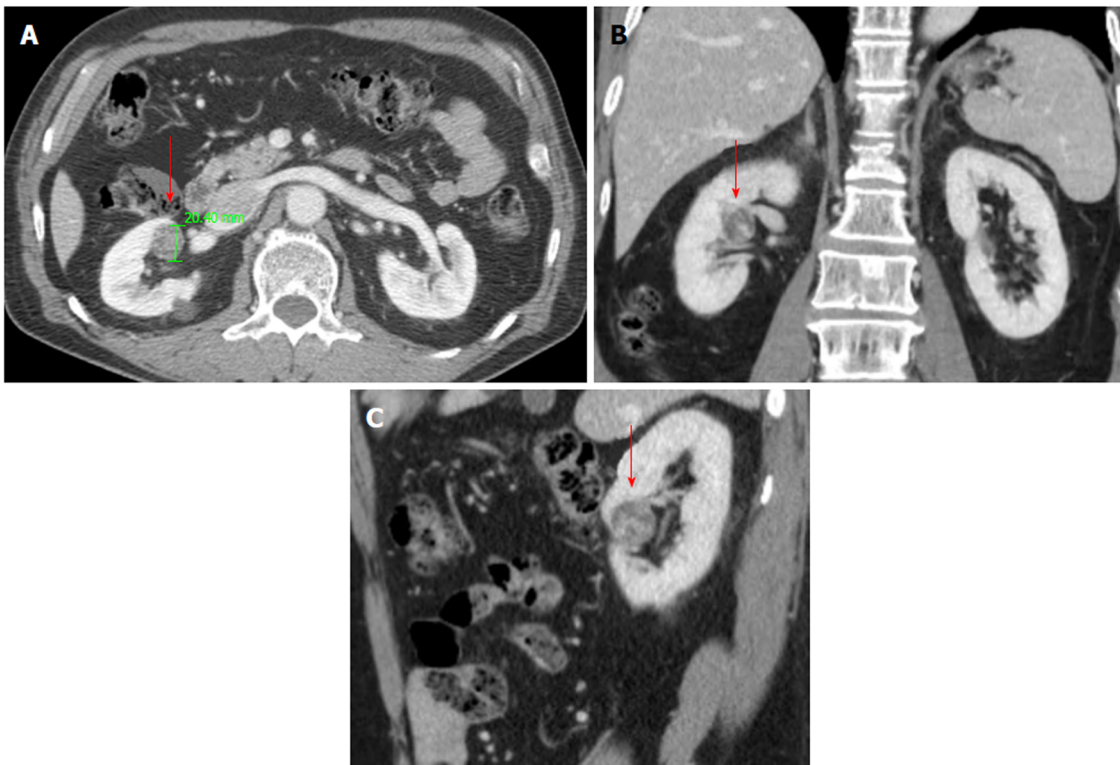


Figure 1 Computed tomography findings of clear cell papillary renal cell carcinoma. A 2-cm mass with an area of irregular enhancement is visible in the right kidney. A: Axial view; B: Coronal view; C: Sagittal view.

affect normal kidneys^[1,2]. The finding that most ccpRCCs are diagnosed as stage 1 (excepting two stage 2 cases)^[2,4,9,11] led to the designation of “low malignant potential” in the recent ISUP classification^[12].

Imaging studies of ccpRCC indicate hypodense areas with cystic changes or cyst formation on CT and areas of isointensity and hypointensity on T1- and T2-weighted MRI, respectively^[13]. ccpRCC frequently appears as a well-defined, well-encapsulated tumor with cystic changes or the formation of cysts^[11,12] filled with serosanguinous fluid or colloid-like regions^[9]. Morphologically, ccpRCC appears to be an intermediate between ccRCC and pRCC, with low nuclear grading, tubular and papillary arrangement of clear epithelial cells, a predominantly linear nuclear alignment distal from the basement membrane, and a distinctive immunohistochemical profile similar to that of RAT. Multifocality and bilaterality are rarely reported^[8,10]. Macroscopically, the cut surface is whitish-tan, with variable surface coloration. Microscopically, most ccpRCCs are small and lack necrosis or invasion of the lymphatic vasculature and renal sinus, but are well-circumscribed and encapsulated with common cystic changes. Proteinaceous secretions are often observed within the lumina or acini of tubules^[3]. Although foamy macrophages, psammoma bodies, and hemosiderin deposits are rarely observed^[14], fibrous stroma is common^[1] and usually indicates the association of a smooth muscle metaplasia with the tumor capsule^[11]. Some previously diagnosed renal angiomyoadenomatous tumors with a predominantly smooth muscle histology have since been recognized as examples of ccpRCC.

Immunohistochemically, ccpRCC is positive for cytokeratin (CK)-7, CA-9, high-molecular-weight CK, Pax2 and Pax8, and 34βE12 and negative for CD10 and alpha-methylacyl-CoA racemase^[7,8,10]. Concurrent strong, diffuse CK-7 expression and a cup-shaped CA-9 expression pattern is usually considered an immunohistochemical hallmark of ccpRCC; this pattern corresponds with the shape of the neoplastic cell, which is typically cuboidal to low columnar, with round and generally uniform nuclei and inconspicuous linearly arranged nucleoli distal from the basal membrane.

Genetic analysis can be used to further differentiate ccpRCC from ccRCC and pRCC, and comparative genomic hybridization can differentiate sporadic ccpRCC from cases associated with end-stage renal disease. Although *VHL* mutation is a hallmark of ccRCC, mutations in this gene have been described in 15%-30% of ccpRCC cases. Furthermore, pRCC exhibits a loss of heterogeneity, although this is not accompanied by mutation or promoter methylation. Rather than *VHL* alterations, pRCC is known to harbor trisomies of chromosomes 7 and 17 and losses of Y, whereas ccpRCC does not exhibit these changes^[15]. ccpRCC may occur in normal kidney, non-

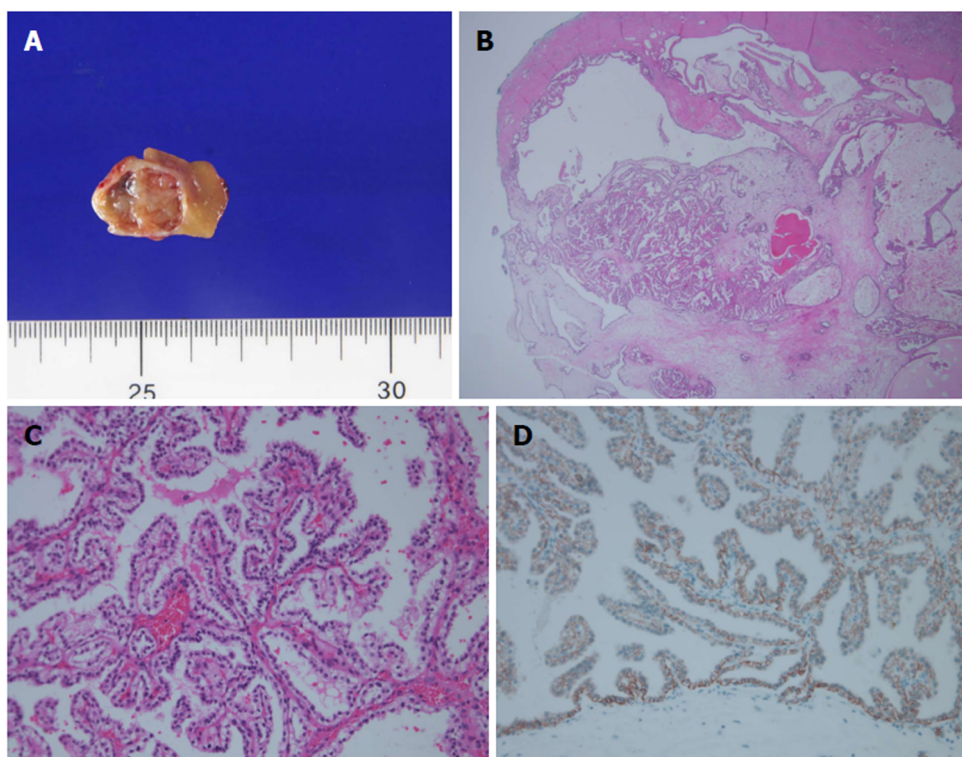


Figure 2 Photomicrographs of clear cell papillary renal cell carcinoma. A: Gross findings; B: H and E: The tumor showed papillary, cystic and tubular patterns in low powered magnification (original magnification $\times 12.5$); C: The tumor is composed of clear cells with uniform nuclei typically showing a linear arrangement away from the basal membrane (original magnification $\times 200$); D: The typical immunohistochemical staining of carbonic anhydrase IX. The staining pattern is a cup-like distribution typical feature of clear cell papillary renal cell carcinoma (original magnification $\times 200$).

cystic end stage renal disease and acquired cystic disease^[3,11,16,17]. Two cases of ccpRCC occurred within 10 years of hemodialysis^[18].

Some cases have been associated with von Hippel-Lindau disease^[19]. The association with other renal cancers such as papillary RCC, clear cell RCC, chromophobe RCC, multilocular cystic RCC, acquired cystic disease-associated RCC and renal oncocytoma have also been reported^[11,16,20].

Total or partial nephrectomy is generally performed when surgical resection is feasible and the tumor is solitary^[1]. Because these tumors are generally indolent, active surveillance with strict follow-up may be possible in selective cases.

In conclusion, this report describes the first case of partial nephrectomy for a ccpRCC that was incidentally diagnosed in an elderly male patient during the imaging follow-up of previously treated tumors. More comprehensive sampling may be warranted to identify the characteristics of ccpRCC with prognostic variables.

ARTICLE HIGHLIGHTS

Case characteristics

The patient was referred to the urology department for a right-sided renal mass (size: 2 cm) detected during routine annual imaging follow-up for a malignant right inguinal fibrous histiocytoma and liposarcoma that had been diagnosed 6 and 4 years earlier, respectively.

Clinical diagnosis

A routine computed tomography (CT) scan detected a right-sided enhancing mid-pole renal mass measuring 2.3.

Differential diagnosis

Immunohistochemistry revealed carbonic anhydrase 9 (CA9) expression could be helpful for differential diagnosis.

Imaging diagnosis

A routine CT scan detected a right-sided enhancing mid-pole renal mass measuring 2.3 cm.

Pathological diagnosis

pathology revealed a tumor measuring 1.7 cm $\times$ 1.4 cm $\times$ 1.0 cm with a capsule abutting, leading

to a diagnosis of a grade 2 ccprCC without necrosis and a final pathologic stage of T1aN × M0.

Treatment

The patient underwent open right-sided partial nephrectomy.

Experiences and lessons

Patients who have previously been treated with tumor need careful follow-up.

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