ISSN 2220-6124 (online)

World Journal of *Nephrology*

World J Nephrol 2018 January 6; 7(1): 1-50

Published by Baishideng Publishing Group Inc

World Journal of Nephrology

Contents

Bimonthly Volume 7 Number 1 January 6, 2018

REVIEW

ORIGINAL ARTICLE

Observational Study

World Journal of Nephrology
Volume 7 Number 1 January 6, 2018

Contents

NAME OF JOURNAL
World Journal of Nephrology

ISSN
ISSN 2220-6124 (online)

LAUNCH DATE
February 6, 2012

FREQUENCY
Bimonthly

EDITORIAL OFFICE
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World Journal of Nephrology
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
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PUBLISHER
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7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
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E-mail: bpgoffice@wjgnet.com
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PUBLICATION DATE
January 6, 2018

INSTRUCTIONS TO AUTHORS
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ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Nephrology

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World J Nephrol 2018 January 6; 7(1): 1-28

DOI: 10.5527/wjn.v7.i1.1

ISSN 2220-6124 (online)

REVIEW

Fluid balance concepts in medicine: Principles and practice

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Author contributions: Roumelioti ME reviewed the literature, wrote parts of the report and constructed two figures; Glew RH made extensive and critical revisions of the report; Khitan ZJ made additions to the report and constructed two figures; Rondon-Berrios H, Argyropoulos CP, Malhotra D, Raj DS, Agaba EI, Rohrscheib M and Murata GH made changes and additions to the report; Shapiro JI made important corrections in the report and constructed one figure; Tzamaloukas AH conceived this report, reviewed the literature, and wrote parts of the text.

Conflict-of-interest statement: Dominic SC Raj is supported by RO1 DK073665-01A1, 1U01DK099914-01 and IU01DK09924-01 from the National Institutes of Health. Joseph I Shapiro is supported by HL105649, HL071556 and HL109015 from the National Institutes of Health. The other authors declare no conflicts of interest.

Manuscript source: Unsolicited manuscript

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Received: September 14, 2017
Peer-review started: September 19, 2017
First decision: October 23, 2017
Revised: November 16, 2017
Accepted: November 27, 2017
Article in press: November 27, 2017
Published online: January 6, 2018

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

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.

Roumelioti ME, Glew RH, Khitan ZJ, Rondon-Berrios H, Argyropoulos CP, Malhotra D, Raj DS, Agaba EI, Rohrscheib M, Murata GH, Shapiro JI, Tzamaloukas AH. Fluid balance concepts in medicine: Principles and practice. *World J Nephrol* 2018; 7(1): 1-28 Available from: URL: http://www.wjgnet.com/2220-6124/full/v7/i1/1.htm DOI: http://dx.doi.org/10.5527/wjn.v7.i1.1

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: $[Na]_S$ = (Exchangeable Na + Exchangeable K)/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 euvolemic, 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 (^3H_2O)[47], deuterium oxide-heavy water-(^2H_2O)[48] and antipyrine[49]. Other markers, *e.g.*, urea, thiourea and ethanol, have enjoyed only limited application. Heavy water does not subject patients to

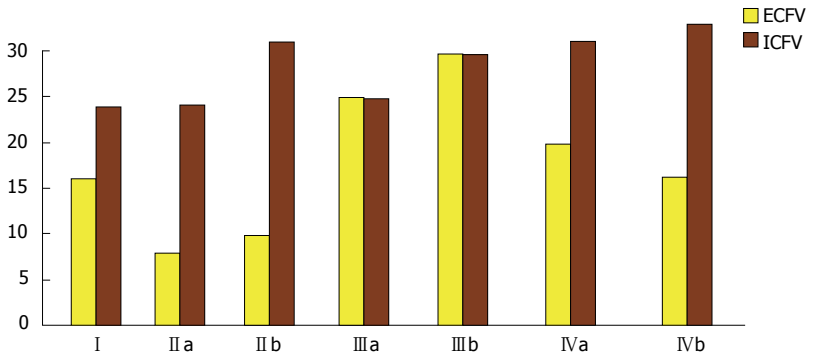

Figure 1 Body compartment volume (L) in the three categories of hyponatremia. I: Normal state: ECFV = 16 L, ICFV = 24 L, serum sodium concentration ($[Na]_S$) = 140 mmol/L. II: Hypovolemic hyponatremia; IIa: Loss of 8 L of isotonic sodium solution: ECFV = 8 L, ICFV = 24 L, $[Na]_S$ = 140 mmol/L; IIb: 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 tree 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

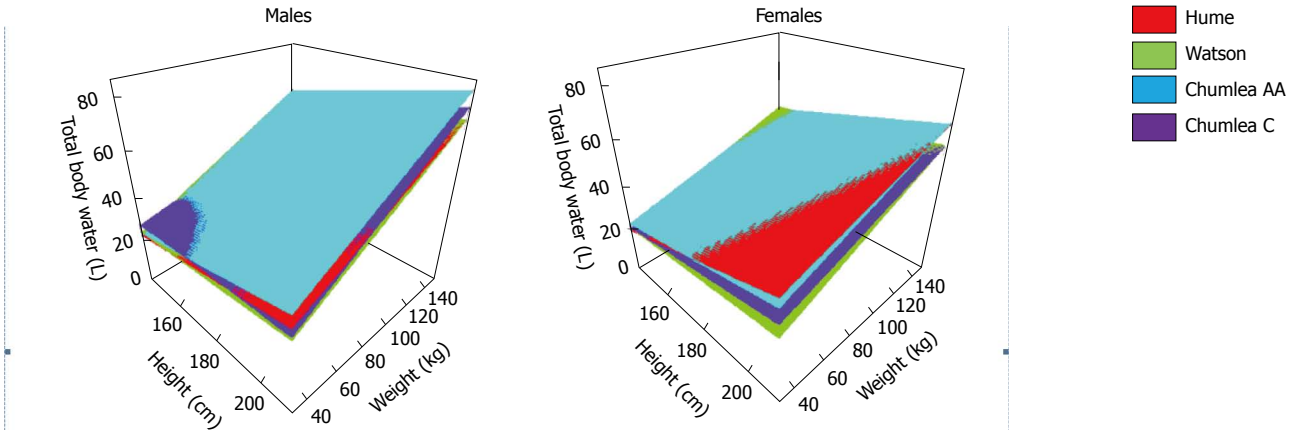

Figure 2 Total body water estimates from anthropometric formulas. Estimates of total body water computed by the Hume *et al*[63], Watson *et al*[64] and Chumlea *et al*[65] anthropometric formulas for men and women with the same age (40 years) and varying height and weight. AA: African American; C: Caucasians.

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 *et al*[64] formulae
….Women: TBW = -2.097 +0.1069H + 0.2466W
Men: TBW = 2.447 - 0.09516A + 0.1074H + 0.3362W
Chumlea *et al*[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 ≤ 110.8 cm: TBW = 0.076 + 0.013H + 0.507W
Girls, H > 110.8 cm: TBW = -10.313 + 0.154H + 0.252W
Boys, H ≤ 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 *et al*[71] formula
TBW = 0.07493713A - 1.01767992G + 0.57894981D + 0.12703384H - 0.04012056W - 0.00067247W2 - 0.03486146 (A × G) + 0.11262857 (G × W) + 0.00104135 (A × W) + 0.00186104 (H × W)
Adults, peritoneal dialysis
Johansson *et al*[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 [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 [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 [Na]$_S$ can develop. Frequent measurement of [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 [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 [Na]$_S$ are based on the same principles as those used to treat hyponatremia[37]. Table 2 shows these formulas. Too rapid decline in [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 [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 [Na]$_S$ during treatment of dysnatremia must be monitored. Clarification of the quantitative impact of these other determinants on changes in [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 [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. Adrogué-Madias formula[41]:
$[Na]_{Final} - [Na]_{Initial} = ([Na]_{Infusate} - [Na]_{Initial})/(TBW_{Initial} + 1)$
Volume of saline required for a targeted serum sodium concentration[84]:
$V_{Infusate} = TBW_{Initial} \times ([Na]_{Targeted} - [Na]_{Initial})/[Na](_{Infusate} - [Na]_{Targeted})$
Hypernatremia
Volume of D5/W required for a targeted serum sodium concentration[37]:
$V_{Infusate} = TBW_{Initial} \times ([Na]_{Initial} - [Na]_{Targeted})/[Na]_{Targeted}$
Volume of hypotonic saline required for a targeted serum sodium concentration[37]:
$V_{Infusate} = TBW_{Initial} \times ([Na]_{Initial} - [Na]_{Targeted})/([Na]_{Targeted} - [Na]_{Infusate})$

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

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]
51cromium ethylenediamine tetra-acetic acid (^{51}Cr-EDTA)	[141-143]
Iohexol	[144]
Technetium diethylene triamine penta-acetic acid (^{99}mTC-DTPA)	[145,146]
Iothalamate	[147]

GFR: Glomerular filtration rate.

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 (^{40}K) and TBW usually by $^{2}H_2O$ 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 $^{2}H_2O$ 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 excesses or deficits of this volume. To quantify ECFV excess, Chamney *et al*[50] measured TBW by $^{2}H_2O$ 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,

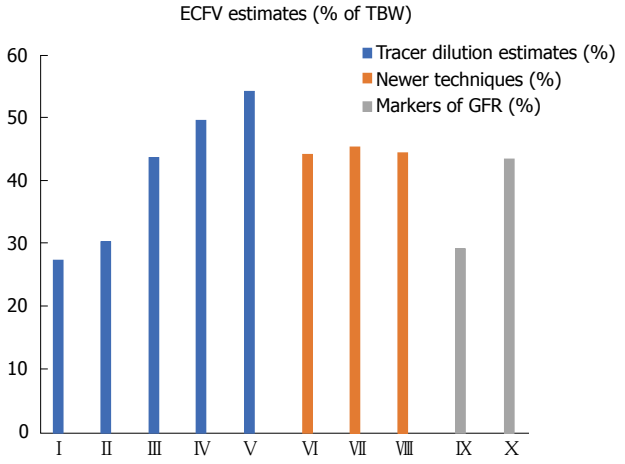

Figure 3 Average extracellular fluid volume estimates expressed as percentages of total body water. Ⅰ-Ⅴ: Tracer dilution estimates[46]; Ⅰ: Sucrose, thiosulfate; Ⅱ: Mannitol, sulfate; Ⅲ: Bromide, chloride; Ⅳ: Sodium; Ⅴ: Thiocyanate; Ⅵ-Ⅶ: Newer techniques; Ⅵ: Dual-energy X-ray absorptiometry[130]; Ⅶ: Bioelectrical 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 $^{3}H_2O$ 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: ECFV = (152 × TBW | 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 $^{2}H_2O$-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 $^{2}H_2O$, 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

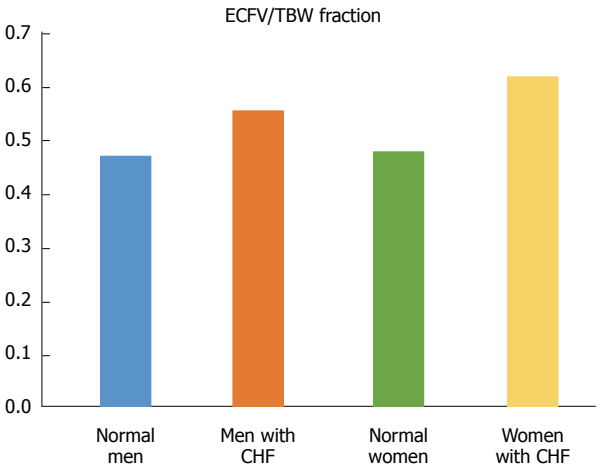

Figure 4 The fraction extracellular volume over total body water in elderly subjects with relatively compensated congestive heart failure and healthy controls. Mean values ECFV/TBW in the study of Sergi *et al*[228]. The mean ejection fraction of elderly patients with relatively compensate congestive heart failure (CHF) and absence of pleural effusion was 40%. Total body water (TBW) was measured by $^{2}H_2O$ 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 hypothesi[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 pre-renal 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 in 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 patien. 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 Ca 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 between the

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 (^{131}I-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 (^{51}Cr-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 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].

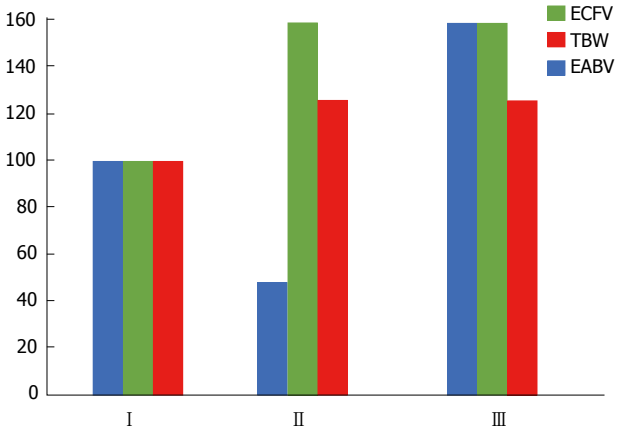

Figure 5 Percent changes from normal of body fluid compartments in hypervolemic states. Ⅰ: Normal body fluid state; Ⅱ: Congestive heart failure, hepatic cirrhosis, nephrotic syndrome with underfill mechanism of fluid retention; Ⅲ: Nephrotic syndrome with overfill mechanism of fluid retention. EABV: Effective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

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 Svenningsen *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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P- Reviewer: Markic D, Stavroulopoulos A, Tanaka H, Yong D
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Nephrology

Submit a Manuscript: http://www.f6publishing.com

World J Nephrol 2018 January 6; 7(1): 29-40

DOI: 10.5527/wjn.v7.i1.29

ISSN 2220-6124 (online)

REVIEW

Immunoglobulin G4-related kidney diseases: An updated review

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Author contributions: Salvadori M and Tsalouchos A contributed equally to the manuscript; Salvadori M designed the study, performed the last revision and provided answers to the reviewers; Tsalouchos A collected the data from literature; Salvadori M and Tsalouchos A analyzed the collected data and wrote the manuscript.

Conflict-of-interest statement: The authors do not have any conflict of interest in relation to the manuscript, as in the attached form.

Manuscript source: Invited manuscript

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Received: November 6, 2017
Peer-review started: November 9, 2017
First decision: December 1, 2017
Revised: December 15, 2017
Accepted: December 28, 2017
Article in press: December 28, 2017

Published online: January 6, 2018

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

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.

Salvadori M, Tsalouchos A. Immunoglobulin G4-related kidney diseases: An updated review. *World J Nephrol* 2018; 7(1): 29-40 Available from: URL: http://www.wjgnet.com/2220-6124/full/v7/i1/29.htm DOI: http://dx.doi.org/10.5527/wjn.v7.i1.29

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 1st International symposium in Boston in 2011	
Pancreas	Lymphoplasmacytic sclerosing pancreatitis
Eye/orbit/lacrimal glands	Dacryadenitis/orbital inflammation/pseudotumour
Salivary glands	Sialoadenitis/Mikulicz disease/Kuttner'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
Limph 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 plasmocytosis
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-recognin 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 anydrases, 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 antinuclear 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)

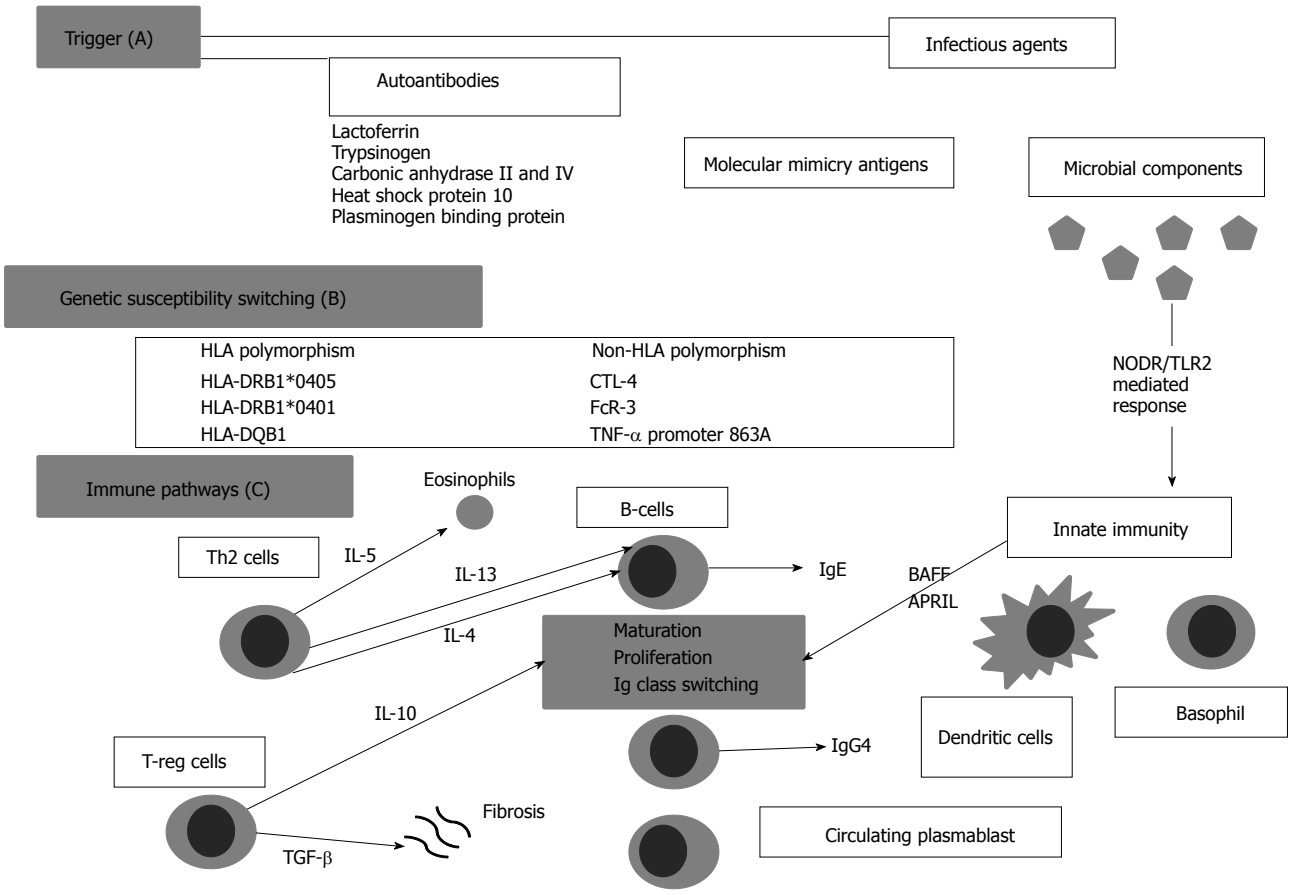

Figure 1 Pathogenesis of immunoglobulin G4-related disease. CTL-4: Cytotoxic T-lymphocyte-associated antigen 4; FcR-3: Fc receptor like 3; TNFα: Tumor necrosis factor alpha; NODR: Nucleotide-activating factor belonging to the tumor necrosis factor (TNF) family; TLR2: Toll-like receptor 2; BAFF: B cell activating factor; APRIL: A proliferative-inducing ligand; TGFβ: 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, hypodense 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, immunochemistry, 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 membrano proliferative 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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P- Reviewer: Kute VBB, Pedersen EB, Shrestha BM, Tanaka S, Yong D
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Lu YJ

World Journal of Nephrology

Submit a Manuscript: http://www.f6publishing.com

World J Nephrol 2018 January 6; 7(1): 41-50

DOI: 10.5527/wjn.v7.i1.41

ISSN 2220-6124 (online)

ORIGINAL ARTICLE

Observational Study

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

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Author contributions: Borrego WE, Vilay AM and Horowitz B were involved in study design, assisted with data collection, interpretation of data, revising the manuscript, providing intellectual content of critical importance, and approval of final version; Pailden J (statistician) was contributed to help with data analysis and interpretation, revising the manuscript, providing intellectual content of critical importance and approval of final version; Devraj R was responsible for idea concept, study design, development of data collection tools, data entry and cleaning, interpretation of data, providing intellectual content of critical importance, wrote and revised the manuscript.

Supported by SIUE STEP.

Institutional review board statement: This study was reviewed and approved by the Southern Illinois University Edwardsville Institutional Review Board and University of New Mexico Institutional Review Board.

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

Conflict-of-interest statement: None of the authors have any conflicts of interest.

Data sharing statement: Dataset available from the corresponding author at rdevraj@siue.edu. Consent was not obtained for data sharing, but the presented data are anonymized and risk of identification is low.

Manuscript source: Invited manuscript

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Received: August 17, 2017
Peer-review started: August 18, 2017
First decision: October 9, 2017
Revised: November 20, 2017
Accepted: December 1, 2017
Article in press: December 1, 2017
Published online: January 6, 2018

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 m^2. 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 (⩾ 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

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.

Devraj R, Borrego ME, Vilay AM, Pailden J, Horowitz B. Awareness, self-management behaviors, health literacy and kidney function relationships in specialty practice. *World J Nephrol* 2018; 7(1): 41-50 Available from: URL: http://www.wjgnet.com/2220-6124/full/v7/i1/41.htm DOI: http://dx.doi.org/10.5527/wjn.v7.i1.41

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 *n* (%), *n* = 150	CKD aware *n* (%), *n* = 132 (88%)	CKD unaware, *n* = 18 (12%)	*P* value[a]
Gender				0.087
Male	70 (47)	65 (49)	5 (27)	
Female	80 (53)	67 (51)	13 (72)	
Race				
White	60 (40)	54 (41)	6 (33)	0.625
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)				
21-40	15 (10)	10 (8)	5 (28)	0.027
41-60	67 (45)	61 (46)	6 (33)	
⩾ 61	68 (45)	61 (46)	7 (39)	
Education				
Some high school	22 (15)	21 (16)	1 (6)	0.258
High school graduate or GED[d]	38 (25)	31 (61)	7 (39)	
Some college and above	90 (60)	80 (61)	10 (56)	
Health Insurance				
Medicare	35 (23)	33 (25)	2 (11)	0.437
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				
< $15000	69 (46)	64 (48)	5 (28)	0.176
$15000-30000	42 (28)	34 (26)	8 (44)	
> $30000	39 (26)	34 (26)	5 (28)	
CKD stage (KDOQI guidelines)				
Stage 1	8 (5)	4 (3)	4 (22)	< 0.001
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				
Hypertension	30 (20)	28 (21)	2 (11)	0.088
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				
Low	95 (63)	84 (64)	11 (61)	0.513
Adequate	55 (37)	48 (36)	7 (39)	

[a]χ^2 contingency coefficient comparing demographics and CKD awareness; bold numerals, $P < 0.05$; [b]Race: Other: Asian 6 (4%) and other 3 (2%); [c]Health 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; % (*n*)	Total aware, *n* = 132 Percent aware giving correct answer % (*n*)	Total unaware, *n* = 18 Percent unaware giving correct answer % (*n*)	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 *n* = 63)	(*n* = 57)	(*n* = 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

[a]Fishers' 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, % (*n*)	Total aware (*n* = 132) Percent aware that performed the activity in past 3 mo, % (*n*)	Total unaware (*n* = 18) Percent not aware that performed the activity in the past 3 mo, % (*n*)	Odds ratio (95%CI)[b]	*P* 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	(*n* = 63)	(*n* = 58)	(*n* = 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]$P < 0.05$; [b]Reference 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 m^2. 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

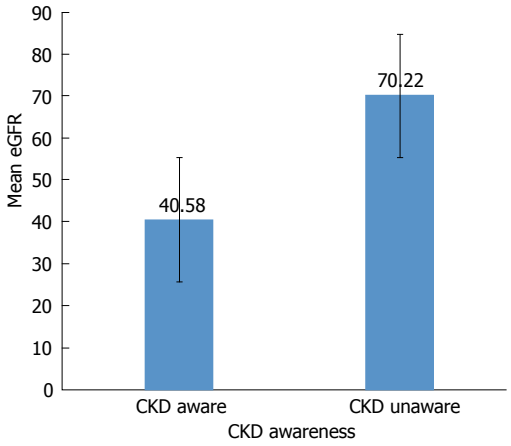

Figure 1 Comparison of mean eGFRs between those who are aware of their chronic kidney disease *vs* those who are unaware (*P* = 0.003)[a]. [a]Figure shows mean eGFRs and standard errors for the chronic kidney disease (CKD) aware and CKD unaware group.

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 patents 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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P- Reviewer: Robles NR, Taheri S **S- Editor**: Kong JX
L- Editor: A **E- Editor**: Lu YJ

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