P. Bolasco • K. Kalantar-Zadeh • C.M. Rhee

CONSERVATIVE MANAGEMENT OF
CHRONIC KIDNEY DISEASE

How to avoid or defer dialysis

PREFACE

Piergiorgio BOLASCO, Kamyar KALANTAR-ZADEH, Connie M. RHEE

This book is dedicated to the *"Conservative management of chronic kidney disease: how to avoid or defer dialysis."* This scholarly endeavor is the product of an international collaboration that brings together the expertise and experiences of the Nephrologic Schools of Thought in Europe and North America.

In North America, there has been growing interest on identifying novel and effective strategies that can protect the residual kidney function of chronic kidney disease patients, given its importance in the survival and health-related quality of life of this population. For example, there has been increasing interest in incremental hemodialysis as a potential means to preserve residual kidney function among advanced chronic kidney disease patients transitioning to conventional dialysis.

Meanwhile, the Italian School has been a pioneer in promoting dietary interventions that preserve kidney function, particularly the beneficial effects of a low-protein diet largely derived from amino acid supplements. While dietary patterns and practices as well as lifestyles differ across Europe and the USA, there is a mutual recognition of the importance of optimizing nutritional status across the entire spectrum of kidney function, including patients with early stages of kidney disease and those receiving maintenance dialysis treatment. Dietary modifications have indeed been a means by which nephrologists have successfully delayed dialysis among advanced chronic kidney disease patients.

In the same vein, this volume is almost entirely dedicated to the conservative management of uremic patients, with a comprehensive presentation of topics including the beneficial effects of proteinuria reduction; the well-established utility of low-protein diet implementation; the detrimental effects associated with hyperphosphatemia as a "silent killer" in chronic kidney disease patients; and the fundamentals of the sodium and fluid management in this population. Other innovative themes discussed in this book include the critical function of a balanced intestinal microbiota in reducing uremic toxic burden, and the use of novel intestinal

adsorbents. Last but not least, one must not forget the key role played by angiotensin-converting-enzyme inhibitors in preserving kidney function via an independent of optimal blood pressure control.

In conclusion, internists and nephrologists have the opportunity to utilize these interventions as tools in their armamentarium in an effort to avoid or defer the initiation of dialysis in advanced chronic kidney disease patients preserving and/or slowing the natural decline of residual kidney function. We thank all authors for our extraordinary expertise and contributions that make this a unique book.

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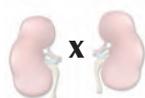*Harbor-UCLA,*
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CONSERVATIVE MANAGEMENT OF CHRONIC KIDNEY DISEASE: HOW TO AVOID OR DEFER DIALYSIS

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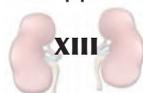
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SODIUM AND FLUID MANAGEMENT IN THE CONSERVATIVE MANAGEMENT OF CHRONIC KIDNEY DISEASE

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Chronic kidney disease (CKD) is a major public health concern that has reached epidemic proportions, affecting >20 million individuals (~13.1% of the population) in the United States alone.[1] The risk of cardiovascular mortality or a cardiovascular event in patients with CKD is significantly increased compared to those free from CKD, even in the presence of similar cardiovascular risk factors.[2-4] Of particu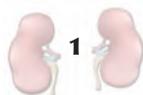lar concern to patients with CKD is the development of left ventricular hypertrophy (LVH), which is very prevalent in this population.[5] Indeed, ~80% of non-diabetic stage 3-5 CKD patients exhibit LVH, prior to the initiation of chronic dialysis.[6] The presence of LVH is an independent predictor of all-cause and cardiovascular mortality both in patients with CKD,[7, 8] as well as in the general population.[9, 10]

Patients with CKD also have a high prevalence of hypertension[11] and increased large elastic artery stiffness, as assessed by aortic pulse-wave velocity (aPWV).[12, 13] Although hypertension is a well-appreciated cardiovascular risk factor, increased aPWV also independently predicts incident cardiovascular events in patients with CKD, and actually improves prediction beyond traditional risk factors alone.[14, 15] In fact, recent evidence supports that increased large elastic artery stiffness, while long considered to be a complication of hypertension, may precede the pathogenesis of hypertension.[16-18] Furthermore, systolic hypertension and increased aPWV are strongly associated with LVH in patients with non-dialysis dependent CKD, and regression analysis suggests arterial stiffness contributes to the development of LVH.[5, 6] Aortic stiffening increases peripheral resistance, systemic arterial pressure and pressure pulsatility, systolic load, and ultimately contributes to ventricular remodeling.[5, 19] Thus, it is important to consider interventions targeting this sequeale of events (arterial stiffness → hypertension → LVH) as they may prevent incident CVD and recurrent cardiovascular events in patients with CKD.

Although the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI),[20] Kidney Disease: Improving Global Outcomes (KDIGO),[11] the American Heart Association (AHA),[21] and the U.S. Department of Agriculture (USDA)[22] all advocate for di-

etary sodium restriction in CKD, available data suggest that sodium intake remains high in this population (between 150-200 mmol/d).[23, 24] The recent Institute of Medicine (IOM) report on the topic reaffirmed that there is a positive relation between sodium intake and CVD.[25] However, the report stressed that there is lack of available intervention data, and further randomized controlled trials (RCTs) are recommended, particularly to determine the effects of sodium intake below 100 mmol/d (2300 mg/d) on cardiovascular risk. This was noted to be especially true among subgroups, including patients with CKD, a point that has also been emphasized recently by KDIGO.[11] Overall, there is a paucity of data on the effects of dietary sodium and fluid management in patients with CKD, as most clinical trials examining dietary sodium and fluid intake have specifically excluded this population. Despite standard of care recommending sodium restriction in CKD, actual intake remains high, and the efficacy of intensively modifying sodium intake is unknown. The purpose of this review is to examine the current evidence on the physiologic effects of sodium and fluid intake in renal disease as well as the barriers to the clinical practice of these conservative therapies.

DIETARY SODIUM RESTRICTION

Dietary Sodium Restriction is a promising lifestyle strategy for the prevention and treatment of not only hypertension, but also for large elastic artery stiffening and increased left ventricular mass index (LVMI).[26-28] New evidence indicates that dietary sodium restriction may be an even more effective intervention for prevention of CVD and cardiovascular events than previously recognized.[29-31] It was recently estimated that globally, 1.65 million annual deaths from cardiovascular causes are attributed to sodium intake above a reference level of 2000 mg/day.[29] Data project that even modest reductions in sodium intake could reduce the number of new cases of coronary heart disease by 60,000 to 120,000 per year and, over the lifetime of adults aged 40-85, avert 500,000 strokes and 480,000 myocardial infarctions, while increasing quality adjusted life-years by 2.1 million.[30] Projected health care savings from dietary sodium restriction are $32.1 billion annually.[31] However, the average American currently consumes well above the recommended amount of sodium at nearly 3.8 grams per day, which is attributed to both the evolutionary necessity of the kidney to preserve salt in order to prevent dehydration as well as the hypothalamic pathways stimulated by this compound that are similar to the addictive properties of illicit drugs.[32] Unfortunately, the Western diet promotes salt consumption through food preservatives as well as a flavor additive making patient attempts at sodium restriction extremely difficult. In order to understand the beneficial role of sodium restriction in CKD, it is important to examine the underlying physiology of sodium handling.

The kidney primarily controls the filtration and excretion of sodium in the human body in order to maintain vascular volume.[34] The bulk of sodium is reabsorbed in the proximal tubule coupled to the transport of other ions and then it is further reabsorbed by the Loop of Henle and distal tubule. Less than 1% of filtered sodium is normally excreted, therefore changes in glomerular filtration rate (GFR) will directly affect the amount of sodium in the urine. This process is
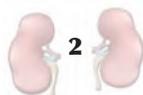
mediated by glomerulotubular feedback as well as autoregulation, which preserves blood pressure through balancing sodium delivery and excretion as well as maintaining renal perfusion. In addition, the primary hormonal axis that controls sodium and effective blood volume is the renin-angiotensin-aldosterone system (RAAS), which is influenced by the sympathetic nervous system or decreased renal perfusion with reduced delivery of sodium chloride to the macula densa of the nephron.[34] Activation of the RAAS system causes general arteriolar vasoconstriction, directly stimulates sodium reabsorption in the proximal tubule, and produces aldosterone secretion from the adrenal cortex in order to increase sodium reabsorption in the distal tubule and collecting duct.[34]

Several theories exist regarding the pathologic role of salt intake in hypertension and the progression of CKD. Primary hypertension is viewed as a "salt-sensitive" state with the inability of the kidney to excrete sodium appropriately in order to adjust intravascular volume. This condition causes activation of the sympathetic nervous system and the RAAS leading to oxidative stress, renal artery constriction, and ischemia which in turn causes more inflammation and tubulointerstitial injury[34] *(Figure 1.1)*. Supporting evidence includes rat studies showing that high sodium intake eliminates the effects of angiotensin-converting enzyme (ACE) inhibition on the conversion from angiotensin I to angiotensin II in vascular tissues.[35] Also, a study in 28 normotensive human subjects demonstrates enhanced conversion from angiotensin I to angiotensin II during high salt intake consistent with increased tissue RAAS activity.[36] Furthermore, salt may amplify the pro-fibrotic effects of aldosterone. In fact, a study in patients with resistant

hypertension revealed increased sodium excretion and proteinuria was progressively higher in subjects with elevated plasma aldosterone concentrations at any given blood pressure.[37] The mediators of salt-induced kidney injury may be endogenous inhibitors of the sodium-potassium ATPase including marinobufagenin and ouabain.[38] A study by Kolmakova and colleagues found that in patients with CKD, plasma marinobufagenin concentration was significantly higher when compared with healthy controls.[38] It is also hypothesized that salt induces hyper-filtration resulting in increased renal damage and proteinuria.[39] This phenomenon was observed in a study of 95 obese men with essential hypertension placed on a high salt
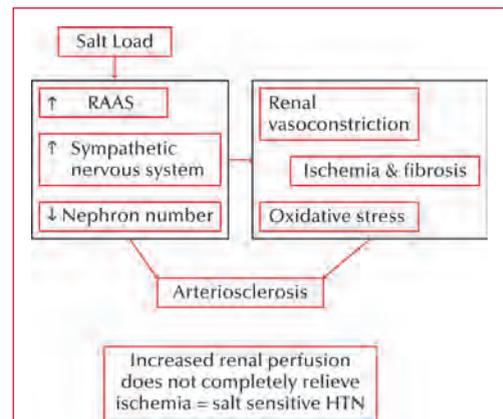
FIGURE 1.1.

Demonstrate renal physiology associated with consumption of a high salt load. In hypertension, salt intake activates the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) causing further oxidative stress and fibrosis in the kidney. Initially, the kidney attempts to compensate through autoregulation, however, in the presence of kidney disease, decreased nephron number coupled to arteriosclerosis furthers this process resulting in a "salt-sensitive" state.
HTN: hypertension; RAAS: renin-angiotensin-aldosterone system.
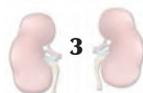
diet which increased effective renal plasma flow and albuminuria in comparison to a low salt diet.[39]

DIETARY SODIUM RESTRICTION AND CLINICAL OUTCOMES IN CKD

Observational studies on sodium restriction and progression of renal disease have yielded contradictory results. In a cohort study of over 2800 Finnish patients with type 1 diabetes, those with macroalbuminuria at baseline and the lowest urinary sodium excretion had the highest incidence of progression to ESRD.[40] Interestingly, results of the National Health and Nutritional Examination Survey (NHANES) in over 7000 participants, observed a 37% cardiovascular mortality and 28% all-cause mortality increase with dietary sodium restriction to <2.3 grams daily compared to the control group.[41] Also, a *post-hoc* analysis of two major trials, the Ongoing Telmisartan Alone in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE-tolerant subjects with Cardiovascular Disease (TRANSCEND) with over 28,000 patients combined with type 2 diabetes and no macroalbuminuria showed that there was no significant association between moderate sodium intake and risk of incident CKD. However, investigators found a significant relationship with increased cardiovascular risk with both high and low sodium diets.[42, 43] Limitations of this data include the use of single urinary sodium values extrapolated to 24hour urinary excretions which are subject to circadian fluctuation as well as the lack of generalizability to the general population.[43]

In contrast, The Ramipril Efficacy In Nephropathy (REIN) trial of non-diabetic patients with CKD Stages 3-5 revealed a 1.6 fold increased (95% confidence interval 1.15-2.24) in the risk of progression to ESRD for every 100 mmol per gram increase in urinary sodium to creatinine ratio.[44] In this study, a high sodium diet blunted the antiproteinuric effect of ramipril and increased the risk of progression to ESRD independent of blood pressure control.[44] In addition, a recent smaller study of Japanese patients with hypertension and no baseline CKD monitored over a ten year period, found that patients with an average salt excretion of <8 grams per day showed a significantly slower decline in renal function when compare to participants with an average salt excretion of greater than 8 grams per day independent of blood pressure control.[45]

Randomized controlled clinical trials regarding sodium restriction and CKD to date are limited in size. However, they consistently demonstrate that reduction in salt intake is associated with decreased cardiovascular risk and proteinuria *(Table 1.1)*.[46-50] In a multicenter crossover trial in Dutch patients with Stage 3 CKD without diabetes compared the effects of adding dietary sodium restriction or angiotensin receptor blockade (ARB) at maximum dose, or their combination, receiving background treatment with ACEI at maximum dose.[50] This study found that the group limiting salt intake resulted in a significant greater reduction in proteinuria and systolic blood pressure than the ARB group.[50] A recent double-blind, placebo controlled trial of 20 hypertensive Australian patients with Stages 3-4 CKD who were placed on either a low sodium (60-80 mmol daily) or high sodium (180-200 mmol daily) diet for 6 weeks,[48] showed a significant decline in both systolic and diastolic blood

pressure as well as a decrease in proteinuria and extracellular fluid volume.[48] While these studies provide a foundation for new dietary sodium guidelines, further randomized trials with larger sample size and longer-term follow-up are necessary in order to establish a definitive conclusion regarding the effects of dietary sodium restriction in CKD.

BARRIERS OF SODIUM RESTRICTION IN CKD

During 2007-2010, the prevalence of excess sodium intake ranged from 79.1% for U.S. children aged 1-3 years to 95.4% for U.S. adults.[51] The lack of federal restrictions on sodium has made it increasingly difficult for Americans to limit their salt intake given that nearly 80% of dietary sodium comes from processed foods as opposed to less developed countries where salt is added during cooking.[52] In fact, the salt content of a 100-gram serving of chicken nuggets from a fast food restaurant in the United States has more than double the amount of sodium content at 1.5 grams of salt *versus* only 0.6 grams of salt in the United Kingdom (UK).[53] This may be in part due to the active role the UK government has taken to lobby for reduction of salt content in national food chains. However, the amount of sodium per

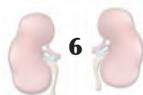| TABLE 1.I — Randomized controlled trials using dietary sodium restriction.					
Author/year	*N.*	*Characteristics*	*CKD stage*	*Intervention*	*Results*
Kwakernaak, AJ *et al.* (2014) [46]	45	Diabetes, microalbuminuria or macroalbuminuria	3 or above	HCTZ (50 mg/day) + Lisinopril (40 mg/day) *versus* placebo + Lisinopril (40 mg/day); + low sodium diet (50 mmol/day) *versus* no salt restriction	Both sodium restriction and hydrochlorothiazide significantly reduced albuminuria. (393 mg per day [258-599], P=0˙0002), (434 mg per day [306-618], P=0˙0003)
de Brito-Ashurst, *et al.* (2013) [47]	56	Diabetes 14%, BMImean 27.1	3-5	Reduce salt intake 50% in cooking	Decreased urinary excretion from 260 mmol/day to 103 mmol/day (P=0.001)
McMahon, *et al.* (2013) [48]	20	Diabetes 40%, BMImean 29.3, average proteinuria 586 mg/24 h	3-4	Salt restriction 60-80 mmol/day *versus* 180-200 mmol/day	Decreased blood pressures 10/4 mmHg (P<0.001); significant decrease in proteinuria and extracellular volume
Yu, W. *et al.* (2012) [49]	43	IgA nephropathy	3-5	Regular diet *vs.* low salt diet (<100 mmol/day)	Reduction in blood pressure (–11.1 mmHg *vs.* –5.0 mmHg, P=0.022) and proteinuria (-465 *vs.* -150, P=0.024)
Slagman, *et al.* (2011) [50]	52	Non-diabetic, proteinuria >1.0 g/day, on ACE inhibitor (Lisinopril 40 mg/day)	3 or above	ARB or placebo ±low salt (50 mmol/day) or high salt diet (200 mmol/day)	Dietary restriction of salt was more effective than dual-RAAS blockade for reduction of proteinuria and BP control
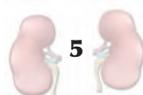
serving has increased significantly in every country for processed foods.[53] An additional obstacle to salt restriction is the coupled effect of decreased caloric intake associated with adherence to this type of diet. Patients with CKD and ESRD often struggle with poor nutrition, and hypoalbuminemia is associated with increased morbidity and mortality.[54] There are some published reports that discuss alleviation of this issue through the consumption of increased vegetarian protein intake that will lower sodium content as well as provide added benefits of low phosphorus and acid-producing nitrogen.[55] Unfortunately, unless action is taken on a national level to restrict the amount of sodium in commercial consumption as well as to increase patient awareness, the intake of a high salt diet will continue, further promoting the obesity epidemic as well as hypertension and renal disease.

Another barrier to management of patients with CKD and hypertension is the stigmata of diet and fluid restriction. According to multiple surveys, patients often find it difficult to preserve their personal relationships when they feel as though they are being constantly monitored and possibly scolded regarding their diet.[56] Many patients also feel social limitations on where they can go eat as well as feeling like a "burden" on friends and family. Furthermore, patients often feel overwhelmed by the amount of nutritional information they must learn, and they find it difficult to change their daily habits.[56] Interestingly, a recent published a meta-analysis of 46 studies involving all types of dialysis patients as well as kidney transplant patients with Stages 1-5 CKD regarding this topic, concluded that fluid and dietary restriction is an overwhelming challenge for patients with renal disease that often causes strain in their interaction with the medical team.[56]

In order to alleviate these feelings, clinicians must consider novel approaches to dietary education as well as to harness patient motivation so that they may adapt to lifestyle changes including salt restriction.

WATER MANAGEMENT IN CKD

In contrast to sodium handling, approximately 65% of water is reabsorbed in the proximal tubule prior to undergoing countercurrent exchange in the loop of Henle in order to concentrate or dilute urine.[34] The other major regulator of water in the kidney is vasopressin, which activates the vasopressin-2 (V2) receptors in the apical plasma membrane of the principal cells of the kidney to increase permeability of water in the collecting duct.[34] Vasopressin is controlled by both osmotic and non-osmotic stimulators in response to changes in vascular volume sensed by the cardiac atria as well as pain or nausea.[34] The mechanism of thirst is based on balances in plasma osmolality and stimuli for vasopressin release. However, one study reports that the evolution of thirst has changed in the past few decades to reflect the increased number of calories consumed through high sugar beverages such as soda as well as the interruption of homeostatic behaviors of eating and drinking based on new social contexts.[57] In CKD, structural damage due to interstitial inflammation and fibrosis causes impairment of the countercurrent system and the overall loss of nephrons compromises kidney function. Also, vasopressin release is decreased as V2 receptors are suppressed resulting in the loss of the kidney's ability for selective water diuresis.[58] Based on these changes, many patients with CKD search for recom-

mendations concerning their fluid intake, yet very few studies exist on this subject. Over recent decades, investigations have reported the benefits of high urine output in patients with nephrolithiasis.[59] One study prospectively followed nearly 200 patients with calcium-stones for five years and observed that low urine volume is the most important predictor of recurrent stones.[60] Several observational studies performed in the general population demonstrated up to a 42% reduction in the risk of nephrolithiasis through increasing urine volume to >2.5 liters per day.[61-64] In addition, retrospective studies in autosomal dominant polycystic kidney disease (ADPKD) show possible slowing of cyst enlargement with increased urine output.[65] Furthermore, in vitro data suggests that increased fluid intake may block V2 antagonists, thereby slowing cyst growth.[66] In fact, the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease (TEMPO 3:4) of 1445 patients with ADPKD and preserved renal function demonstrated that tolvaptan, a V2 receptor antagonist, as compared with placebo, slowed the increase in total kidney volume and the decline in kidney function over a 3-year period.[67] These results are promising outcomes of the possibility that increasing fluid intake may slow the progression of renal disease. However, the specific underlying pathophysiology of these diseases make it difficult to apply to the general CKD population.

FLUID OVERLOAD AND CARDIAC REMODELING IN ESRD

Although free water is equally distributed between body compartments and therefore should not have a large impact on intravascular volume, patients requiring chronic dialysis often make little to no urine and undergo insensible losses of only 500ml daily leading to intradialytic weight gain.[34] A study by Kalentar-Zadeh *et al.* in over 34,000 dialysis patients over a three-year period measured weight gain in 0.5 kg increments between dialysis sessions and found that after adjustments for demographics and malnutrition, higher weight gain was associated with increased cardiovascular and all-cause death risk (HR 1.25, CI: 1.12-1.39).[68] The similarities of ESRD patients to patients with congestive heart failure prompt theories of volume overload and activation of the renin angiotensin aldosterone leading to further inflammation and fibrosis. In a prospective study of 161 hemodialysis patients, echocardiographic data was performed twice during an 18-month period and the results were used to predict cardiovascular events.[69] Investigators found that the rate of increase of left ventricular mass index (LVMI) was associated with a 62% increase in risk of fatal and non-fatal cardiovascular events [HR 1.62, 1.13-2.33, P=0.009).[69] A similar study was done on patients with early CKD looking at 104 patients with a mean eGFR of 60 ml/min/1.73 m^2 using cardiac and vascular ultrasound and measurement of extracellular fluid by multi-frequency spectroscopic bio-impedance.[70] The results were consistent with ESRD studies in that decline in kidney function was associated with left ventricular remodeling as well as increased aortic stiffness.[70] Furthermore, a multivariate analysis revealed that extracellular fluid was an independent determinant of left ventricular hypertrophy, and the authors concluded that cardiovascular remodeling is associated with extracellular volume at a very early stage of CKD.[70]
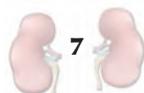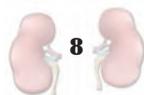
WATER INTAKE AND KIDNEY DISEASE PROGRESSION

Observational studies in patients with CKD have suggested that increased water intake could delay kidney disease progression. A prospective cohort of over 2,100 patients in Canada with Stage 3 CKD or greater had a lower risk of annual decline in eGFR with urine volumes of greater than 3 liters daily compared to patients with urine volumes less than 2 liters daily after adjustment for multiple variables including diabetes over a 5 year period.[71] A similar study administered a validated nutrition food questionnaire to people older than 50 years identified in a door-to-door census of a well-defined suburban area in Australia. The study found that the group with the highest self-reported fluid intake of a median of 3.2 liters per day had a lower risk of reduced creatinine clearance in comparison to the group who reported fluid intake of a median 1.8 liters daily.[72] While increasing water intake is a simple and economical intervention, many clinicians are also concerned about patient compliance as well as the risk of hyponatremia. Surprisingly, the kidney has a remarkable ability to regulate water balance at advanced stages of CKD, and in a study of 70 patients with a serum creatinine >10 mg/dL, serum sodium levels remained normal until initiation of dialysis.[73] However, in a larger recent study of 655,493 United States Veterans with Stages 1-5 CKD, 26% of all patients developed at least one episode of hyponatremia over a 5-year period.[74] Interestingly, the prevalence of hyponatremia did not correlate with stages of CKD at an eGFR of 30ml/min and above, and instead was associated with younger age, presence of proteinuria, a diagnosis of diabetes mellitus, heart failure, liver disease, and a low serum albumin or anemia.[74, 75] Therefore, the recommendation to increase fluid intake for the prevention of CKD may need to be tailored to a specific patient population without the risk factors of lowering serum sodium, which may have serious effects of cerebral edema and possibly death.

CONCLUSIONS

The incidence of recognized CKD in people over 65 years of age has more than doubled between 2000 and 2008. Furthermore, the amount of people requiring dialysis therapy for the treatment of ESRD has risen 600 percent since 1980 to nearly one million. Medicare spent over 99 billion on people with kidney disease not including prescriptions, and the majority of this was spent on patients with CKD. Risk of CVD is significantly elevated in patients with CKD. In order to mitigate the financial and healthcare burden of this disease, clinicians must find new ways to manage hypertension and prevent the progression of CKD. Dietary sodium restriction is a promising strategy for prevention of CKD-associated CVD. However, despite widespread clinical recommendations for patients with CKD to restrict dietary sodium intake, most trials on dietary sodium restriction have specifically excluded such patients; thus the feasibility and efficacy of these recommendations are unknown. Finally, there is little evidence for the recommendation of increased fluid intake in this population, which may also lead to side effects of hyponatremia and increased cardiovascular events given the decreased ability of patients to excrete free water in CKD. Further randomized controlled trials are necessary prior to mak-

ing guidelines regarding these conservative therapies. Other proposed dietary therapies including restricting alcohol intake, increasing consumption of alkali-generating foods, and switching to a very low protein diet (VLPD) have also shown promise in prevention for progression of CKD. Meanwhile, encouragement of a healthy diet and education for better patient understanding of food content should be adopted by clinicians for management of renal disease.

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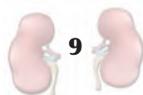
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