infections. Although gram-negative bacteria are generally HMB-PP positive, most of the common gram-positive causative microorganisms of peritoneal dialysis–related peritonitis are indeed HMB-PP negative, including *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus* species, and *Enterococcus* species. Interestingly, the authors suggested that the natural antibiotic fosmidomycin, which targets the HMB-PP pathway, could also mitigate the inflammatory reactions by inhibiting Vγ9/Vδ2 T cell–driven responses to HMB-PP–producing bacteria.

The study of Lin *et al.* deepens our understanding of the complex, local pathogen-host interactions. Such patient-based studies are important not only from a theoretical perspective but also for the prospect of future developments that could improve diagnosis and management of the various forms of peritonitis. The insights obtained by these patient-based studies may play an important role in the development of novel useful tests that may help to predict the causative microorganisms in an early stage of peritonitis (*i.e.*, before the results of bacterial cultures have become available).

DISCLOSURES

None.

REFERENCES

1. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, Johnson DW, Kuijper EJ, Lye WC, Salzer W, Schaefer F, Struijk DG; International Society for Peritoneal Dialysis: Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int* 30: 393–423, 2010
2. Szeto CC, Wong TY, Chow KM, Leung CB, Li PK: The clinical course of culture-negative peritonitis complicating peritoneal dialysis. *Am J Kidney Dis* 42: 567–574, 2003
3. Lin CY, Roberts GW, Kift-Morgan A, Donovan KL, Topley N, Eberl M: Pathogen-specific local immune fingerprints diagnose bacterial infection in peritoneal dialysis patients. *J Am Soc Nephrol* 24: 2002–2009, 2013
4. Rocklin MA, Teitelbaum I: Noninfectious causes of cloudy peritoneal dialysate. *Semin Dial* 14: 37–40, 2001
5. de Freitas DG, Gokal R: Sterile peritonitis in the peritoneal dialysis patient. *Perit Dial Int* 25: 146–151, 2005
6. Mangram AJ, Archibald LK, Hupert M, Tokars JI, Silver LC, Brennan P, Arduino M, Peterson S, Parks S, Raymond A, McCullough M, Jones M, Wasserstein A, Kobrin S, Jarvis WR: Outbreak of sterile peritonitis among continuous cycling peritoneal dialysis patients. *Kidney Int* 54: 1367–1371, 1998
7. Boer WH, Vos PF, Fieren MW: Culture-negative peritonitis associated with the use of icodextrin-containing dialysate in twelve patients treated with peritoneal dialysis. *Perit Dial Int* 23: 33–38, 2003
8. Blander JM, Sander LE: Beyond pattern recognition: Five immune checkpoints for scaling the microbial threat. *Nat Rev Immunol* 12: 215–225, 2012
9. Lee CC, Avalos AM, Ploegh HL: Accessory molecules for Toll-like receptors and their function. *Nat Rev Immunol* 12: 168–179, 2012
10. Fieren MW: The local inflammatory responses to infection of the peritoneal cavity in humans: their regulation by cytokines, macrophages, and other leukocytes. *Mediators Inflamm* 2012: 976241, 2012
11. Newton K, Dixit VM: Signaling in innate immunity and inflammation. *Cold Spring Harb Perspect Biol* 4: a006049, 2012
12. Eberl M, Roberts GW, Meuter S, Williams JD, Topley N, Moser B: A rapid crosstalk of human gammadelta T cells and monocytes drives the acute inflammation in bacterial infections. *PLoS Pathog* 5: e1000308, 2009
13. Davey MS, Lin CY, Roberts GW, Heuston S, Brown AC, Chess JA, Toleman MA, Gahan CG, Hill C, Parish T, Williams JD, Davies SJ, Johnson DW, Topley N, Moser B, Eberl M: Human neutrophil clearance of bacterial pathogens triggers anti-microbial $\gamma\delta$ T cell responses in early infection. *PLoS Pathog* 7: e1002040, 2011
14. Riganti C, Massaia M, Davey MS, Eberl M: Human $\gamma\delta$ T-cell responses in infection and immunotherapy: Common mechanisms, common mediators? *Eur J Immunol* 42: 1668–1676, 2012

See related article, "Pathogen-Specific Local Immune Fingerprints Diagnose Bacterial Infection in Peritoneal Dialysis Patients," on pages 2002–2009.

Sodium Reduction in CKD: Suggestively Hazardous or Intuitively Advantageous?

Cheryl A.M. Anderson* and Joachim H. Ix†

*Department of Family and Preventive Medicine, Division of Preventive Medicine and †Department of Medicine, Division of Nephrology-Hypertension, University of California San Diego School of Medicine, San Diego, California

J Am Soc Nephrol 24: 1931–1933, 2013.
doi: 10.1681/ASN.2013090923

In the United States and most countries worldwide, mean dietary sodium intake is much higher than daily requirements. Although the potential consequences of high dietary sodium intake, including higher BP, fluid retention, and cardiovascular disease (CVD) risk, are much more common in individuals with CKD;[1] few trials have been done, and to our knowledge, only one is underway in CKD patients based on a search of ClinicalTrials.gov.[2]

In the absence of clinical trials, guidelines for dietary sodium intake in CKD are based on expert opinion, observational studies, and extrapolation from general population studies. For example, recent Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines recommend "lowering salt intake to $<$ 90 mmol ($<$2 g) per day of sodium, unless contraindicated."[1] This recommendation corresponds to 5 g of sodium chloride. The recommendation is graded "1C," indicating that the KDIGO panel considered it important enough to serve as a candidate for making public policy decisions and as a performance measure, although

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Joachim H. Ix, 9500 Gilman Drive, MC-9111, La Jolla, CA 92093-9111. Email: joix@ucsd.edu

simultaneously indicating that the quality of evidence was low and that the true effect may be substantially different from the estimated effect. This grade appears consistent with the widespread belief that dietary sodium reduction is probably beneficial in CKD, albeit with little evidence to support it.

In this issue of *JASN*, McMahon and colleagues provide new clinical trial data in this area.[3] The elegant design and careful measurements in their study provide reassurance to the existing KDIGO guidelines, despite enrolling only 20 individuals. The authors report data from a randomized, double-blind, crossover trial in patients with stage 3–4 CKD. Participants were placed on a low-sodium diet for a 1-week run-in, then randomly assigned to a high-sodium arm (accomplished by the addition of a salt tablet on top of the low-sodium diet) or a low-sodium arm (low-sodium diet with the addition of a placebo tablet). Participants were treated for 2 weeks in one arm, followed by a 1-week washout period, and then crossed over to the other arm. Effects on BP, proteinuria, fluid status, body weight, plasma renin and aldosterone concentrations, and measures of arterial stiffness were examined.

Key strengths of the study include the use of slow-release sodium tablets to achieve contrast between the low- and high-sodium arms without influencing other aspects of diet. Thus, total caloric intake and potassium intake were held constant on both the high- and the low-sodium diet. This design feature allows clear insights into the effects of dietary sodium without confounding effects from changes in other dietary factors. Importantly, the sodium exposure categories (*i.e.*, 4140–4600 mg/d and 1380–1840 mg/d in the high- and low-sodium arms, respectively) are highly relevant to public policy because few data are available on outcomes at the range of intake <2000 mg/d, as currently recommended by KDIGO.

The authors found that mean systolic BP was 9.7 mmHg lower in the low-sodium arm than in the high-sodium arm; this level of BP reduction is substantial and clinically relevant. In addition, four participants required dose reductions of antihypertensive medications because of symptomatic hypotension while in the lower-sodium arm, suggesting that effects may have been even greater if use of antihypertensive medications were held constant. Moreover, proteinuria was decreased by about 50% during the low-sodium intervention, an effect that was statistically independent of BP changes. As expected, body weight and fluid status decreased, and plasma renin and aldosterone concentrations markedly increased during the low-sodium intervention. No effect on arterial stiffness was observed.

This study is salient because few intervention studies have evaluated dietary sodium reduction in patients with CKD.[4] The evaluation of other outcomes in addition to BP is an additional strength of the trial. Although BP is considered a valid surrogate outcome for estimating risk of CVD in the general population,[5] there are other considerations in the context of CKD. The reported effects on proteinuria, fluid status, and body weight in addition to the marked change in BP should all be beneficial.

Large trials with hard endpoints are costly and logistically challenging. One reason is the requirement for a high level of safety monitoring. Thus, contributions from trials such as that by McMahon and colleagues[3] are important additions to the field. It is also likely, therefore, that the preponderance of new evidence will continue to come from observational studies. These studies provide key insights. However, the limitations of observational studies and inaccuracies in 24-hour urine collections raise concerns about confounding and even reverse causality because the oldest, sickest, and least compliant participants will be those with the lowest apparent sodium intake if they systematically undercollect their urine. In this case, there is the possibility of paradoxical and even spurious associations of low sodium intake with risk of death and ESRD.[6]

To date, observational studies have provided inconsistent results. Studies in nondiabetic patients with CKD[7] and in dialysis patients[8] have reported that low sodium intake is associated with improved outcomes, as might be expected on the basis of the findings of McMahon *et al.*[3] On the other hand, there have also been reports that lower 24-hour urine sodium excretion is associated with higher risk of death and ESRD in individuals with type 1[9] and type 2[10] diabetes with overt proteinuria. As shown again in the study by McMahon and colleagues, dietary sodium reduction is known to increase plasma renin and aldosterone concentrations, and some authors have argued that long-term exposure to high plasma renin and aldosterone may promote atherosclerosis.[11] Others have argued that in the setting of diabetes, low dietary sodium intake may increase renal plasma flow and GFR and may contribute to hyperfiltration in the early stages of diabetic nephropathy.[12,13] Thus, although the study by McMahon *et al.* shows impressive results over a short 2-week intervention, the observational studies raise questions about the long-term effects of dietary sodium reduction in patients with CKD that may be independent of BP or proteinuria *per se*, and they underscore the need for larger well designed studies with longer follow-up.

Whether an intensive short-term dietary sodium restricted intervention in the closely monitored setting of a clinical trial will translate into similar improvements in routine clinical practice is unknown. Further, whether such diets are sustainable over the long term, and whether effects on surrogate or hard clinical outcomes will manifest, are uncertain. We must also be mindful that dietary recommendations are complex, particularly in CKD. Outside of a clinical trial, advice to restrict dietary sodium intake may influence absorption calcium, protein, net endogenous acid production, potassium, and calories. Nonetheless, this study makes us cautiously optimistic.

We commend the authors for providing important clinical trial data in support of current clinical practice consensus guidelines through this study. Their findings underscore the need for larger studies with longer follow-up specifically designed and carried out in CKD populations to help inform recommendations to both individual patients and policymakers. Until we have such studies, we are left uncertain of whether dietary

sodium reduction in CKD may be suggestively hazardous or intuitively advantageous.

DISCLOSURES

C.A.M.A. is supported, by a grant to the University of California San Diego from the National Heart, Lung and Blood Institute (K01HL092595). J.H.I. is supported by grants from the National Heart, Lung and Blood Institute (R01HL094555) and the National Institute of Diabetes and Digestive and Kidney Diseases (U01DK097093).

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group: KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2 (suppl): 337–414, 2012
2. Clinicaltrials.gov. Last accessed on September 1, 2013.
3. McMahon E, Bauer J, Hawley CM, Isbel N, Stowasser M, Johnson DW, Campbell KL: A randomized trial of dietary sodium restriction in CKD. *J Am Soc Nephrol* 24: 2096–2103, 2013
4. de Brito-Ashurst I, Perry L, Sanders TAB, Thomas JE, Dobbie H, Varagunam M, Yaqoob MM: The role of salt intake and salt sensitivity in the management of hypertension in South Asian people with chronic kidney disease: A randomised controlled trial. *Heart* 99: 1256–1260, 2013
5. IOM (Institute of Medicine): *Evaluation of biomarkers and surrogate endpoints in chronic disease*, Washington, DC, The National Academies Press, 2010
6. Institute of Medicine: *Sodium intake in populations: Assessment of evidence*, Washington, DC, The National Academies Press, 2013
7. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P: Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol* 23: 165–173, 2012
8. Mc Causland FR, Waikar SS, Brunelli SM: Increased dietary sodium is independently associated with greater mortality among prevalent hemodialysis patients. *Kidney Int* 82: 204–211, 2012
9. Thomas MC, Moran J, Forsblom C, Harjutsalo V, Thorn L, Ahola A, Wadén J, Tolonen N, Saraheimo M, Gordin D, Groop PH; FinnDiane Study Group: The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care* 34: 861–866, 2011
10. Ekinci EI, Clarke S, Thomas MC, Moran JL, Cheong K, MacIsaac RJ, Jerums G: Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care* 34: 703–709, 2011
11. Tikellis C, Pickering RJ, Tsorotes D, Harjutsalo V, Thorn L, Ahola A, Wadén J, Tolonen N, Saraheimo M, Gordin D, Forsblom C, Groop PH, Cooper ME, Moran J, Thomas MC: Association of dietary sodium intake with atherogenesis in experimental diabetes and with cardiovascular disease in patients with Type 1 diabetes. *Clin Sci (Lond)* 124: 617–626, 2013
12. Miller JA: Renal responses to sodium restriction in patients with early diabetes mellitus. *J Am Soc Nephrol* 8: 749–755, 1997
13. Vallon V, Thomson SC: Renal function in diabetic disease models: The tubular system in the pathophysiology of the diabetic kidney. *Annu Rev Physiol* 74: 351–375, 2012

See related article, "A Randomized Trial of Dietary Sodium Restriction in CKD," on pages 2096–2103.