AJKD
In the Literature

Don't Pass the Salt: Evidence to Support Avoidance of High Salt Intake in CKD

Commentary on Mills KT, Chen J, Yang W, et al. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. JAMA. 2016;315(20):2200-2210.

Called a "divine substance" by Homer, salt has been an essential part of civilization for culinary, political, commercial, and scientific uses. The word "salary" is derived from the Latin word salarium, or salt-money, because salt was used as a form of payment in Ancient Rome. With global modernization, salt has shifted from monetary currency to food currency and is widely used as a food preservative and for food flavoring, particularly in commercially prepared or packaged foods.

Dietary sodium intake in the general population of the United States is high, with 89% of adults exceeding the current recommendation of <2,300 mg/d.[1] A recent evaluation of dietary trends from the National Health and Nutrition Examination Survey estimated that the average sodium intake has not changed between 1999 to 2000 and 2011 to 2012 despite widespread efforts to educate the public on the associations of high sodium intake with adverse health-related effects, including increased mortality and cardiovascular disease (CVD) events, and that reduction in sodium intake can lead to improvement in blood pressure and proteinuria.[2] Although precise guidelines from several health organizations are inconsistent regarding the exact target for sodium intake, each of these guidelines suggests a reduction in sodium intake for individuals who exceed the daily recommendation.[3-5]

Although the public health focus has been on avoiding high sodium intake, some evidence suggests that low levels of sodium intake may also be associated with adverse outcomes in the general population.[6] The mechanism behind this J-shaped curve has not been established, although several hypotheses have been proposed, including activation of the renin-angiotensin-aldosterone system or sympathetic nerve activation leading to endothelial dysfunction.[7,8] These studies have been subject to methodologic criticisms, including bias in assessment of sodium intake with use of either spot urinary sodium measurements or dietary recall; potential for reverse causality; insufficient adjustment for confounding variables, including caloric intake and other comorbid conditions; and small sample size for individuals with low sodium intake.[9,10] As such, current guidelines do not provide recommendations for a lower limit of sodium intake. Further complicating this literature is the paucity of evidence for individuals with chronic kidney disease (CKD), a group at very high risk for CVD events and progression of kidney disease.

WHAT DOES THIS IMPORTANT STUDY SHOW?

Using data from 3,757 participants in the observational CRIC (Chronic Renal Insufficiency Cohort) Study, Mills et al[11] evaluated the relationship between urinary sodium excretion, as a proxy for dietary sodium intake, and CVD outcomes among patients with CKD stages 2 to 4. The exposure variable was mean cumulative 24-hour urinary sodium excretion from 3 visits. Urinary sodium excretion was calibrated by multiplying the 24-hour urinary sodium-creatinine ratio by the study population's sex-specific mean urinary creatinine excretion to minimize measurement error from incomplete 24-hour urine collections. The primary outcome was a CVD composite, defined as the first episode of heart failure, myocardial infarction, and/or stroke; these were identified by interviews and adjudicated by medical record review and physician congruency. Mean 24-hour urinary sodium excretion was 3,701 (standard deviation, 1,443) mg. During a median 6.8 years of follow-up, the cumulative incidence of the composite CVD outcome was 18.4% in individuals in the lowest quartile of urinary sodium excretion, followed by 16.5%, 20.6%, and 29.8% in each subsequent higher quartile of urinary sodium excretion. After adjustment for modifiable CVD risk factors, blood pressure medications, and estimated glomerular filtration rate (GFR), there was a statistically significant increased risk in the highest quartile of urinary sodium excretion (≥4,548 mg) compared to the lowest quartile (hazard ratio, 1.36; 95% confidence interval, 1.09-1.70), but no differences in the lower 3 quartiles. These findings were primarily driven by heart failure outcomes rather than other components of the composite outcome. There was no evidence of nonlinearity (ie, a J-shaped relationship) for the composite CVD outcome, but for the heart failure outcome, there was a trend toward nonlinearity. Results were consistent after adjustment for baseline blood pressure, suggesting that the association of high urinary sodium excretion with CVD events was

Originally published online October 24, 2016.
Address correspondence to Amanda K. Leonberg-Yoo, MD, MS, 51 N 39th St, Philadelphia, PA 19104. E-mail: Amanda.Leonberg-Yoo@uphs.upenn.edu

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2016.09.008

independent of blood pressure. Results were also for the most part consistent in analyses that used uncalibrated mean 24-hour urine sodium excretion.

This study has several strengths, including use of a large cohort of individuals with CKD, adjudicated outcomes, and detailed ascertainment of covariates, including assessment of nutritional status, caloric intake, and severity of illness, all of which are key confounders when investigating the relationship between low urinary sodium excretion and outcomes. Importantly, accurate assessment of the exposure variable was performed using three 24-hour urinary sodium excretion measurements. Measurement of 24-hour urinary sodium excretion is considered the gold standard for assessment of dietary sodium exposure, and the CRIC Study demonstrated remarkable results in terms of accurate 24-hour urine collection, with only 4.8% of participants being excluded due to incomplete or missing urine collections (incomplete urine collections were defined as total urine volume $<$ 500 mL, collection duration $<$ 20 hours, total creatinine excretion $<$ 7 mg/kg of body weight, and mean urinary sodium excretion $<$ 20 mmol/24 h). Limitations of the study include the inability to evaluate the lower ranges of urinary sodium excretion, for example, $<$2 g/d of sodium, because there were too few individuals in this category. In addition, there is a lack of validated data that 24-hour urinary sodium excretion reflects dietary sodium intake, particularly in advanced stages of CKD. Last, the conclusion that the effect of high sodium was independent of blood pressure may be premature, especially given the potential for residual confounding. The analyses could have been strengthened through evaluation of blood pressure using time-dependent analyses, and adjustment for proteinuria at baseline and as a time-dependent variable may have provided additional insights into mechanisms.[12]

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

Many studies have evaluated the association between sodium intake and clinical outcomes in the general population, with several indicating increased risk for adverse outcomes at both high and low sodium intake. In general, these studies have not included individuals with CKD and have been subject to methodologic criticisms, as noted. That being said, the J-shaped relationship, whereby both low and higher sodium intake are associated with adverse outcomes, seems to exist in several carefully done epidemiologic studies, and some have suggested caution in being too aggressive with restriction of dietary sodium in certain populations.[6,13]

In a recent meta-analysis of 23 cohort studies and 2 randomized trials (n = 274,683), Graudal et al[8] evaluated the association of low sodium intake ($<$2,645 mg/d), usual sodium intake (2,645-4,945 mg/d), and high sodium intake ($>$4,945 mg/d) with all-cause mortality and CVD outcomes in the general population. Compared to usual sodium intake, both low and high sodium intake were associated with increased risk for all-cause mortality and CVD. Results did not differ in sensitivity analyses excluding high-risk groups such as those with hypertension, heart failure, diabetes mellitus, or CKD. Smyth et al[14] then performed a systematic review evaluating the relationship between sodium intake and kidney outcomes in individuals with and without CKD (n = 8,129). Their results showed that in individuals with CKD, there was an association between high sodium intake and decline in GFR, as well as an increase in proteinuria, whereas the association of low and usual sodium intake with outcomes did not differ. Among individuals without CKD, there was no consistent relationship between sodium intake and kidney disease progression. Due to heterogeneity of the studies, meta-analysis was not performed. In both these systematic reviews, individuals with CKD were under-represented, with only one study including individuals with estimated GFRs $<$ 60 mL/min/1.73 m^2 in the review by Graudal et al and 4 in the review by Smyth et al. Subsequent to these publications, additional studies have been published that investigated the association between sodium intake and adverse outcomes in populations with CKD (Table 1). These studies do not provide completely consistent evidence, but for the most part have suggested that high sodium intake is associated with adverse outcomes. In addition, they have not demonstrated the J-shaped relationship noted in several general population studies.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

Current dietary guidelines published by KDIGO (Kidney Disease: Improving Global Outcomes) and by the Canadian Society of Nephrology suggest an upper limit of sodium intake in individuals with CKD based on the available evidence.[15,16] KDIGO guidelines recommend sodium intake $<$ 2 g/d, unless contraindicated, citing that sodium restriction appears to be a promising method to reduce blood pressure and thereby progressive kidney disease and CVD events.[15] However, the guideline work group acknowledged that although there is robust evidence that sodium restriction can reduce blood pressure in the general population, there is limited evidence in a CKD population. Upon review of KDIGO guidelines, the Canadian Society of Nephrology provided a commentary suggesting that reduction in sodium intake should be recommended in patients whose

Table 1. Studies Investigating the Association Between Sodium and Adverse Clinical Outcomes in CKD Populations

Study	Participants and Selected Features	Study Design	Exposure Variable	Outcome Variable	Primary Conclusions
CRIC[11,17]	CKD cohort with 47% diabetic patients (n = 3,757); eGFR range, 20-70 mL/min/1.73 m^2; RAS inhibition, 68%; diuretic use, 59%	Prospective cohort study	Cumulative mean of 3 urinary Na measurements, calibrated to sex-specific mean 24-h urinary creatinine excretion; mean Na excretion: 3.70 ± 1.44 g/d	Composite CVD outcome including HF, MI, and stroke; composite kidney outcome of ESRD or halving of eGFR	Higher urinary Na is associated with increased risk for CVD; higher urinary Na is associated with increased risk for CKD progression
MDRD[18]	CKD clinical trial of predominantly nondiabetic white individuals (n = 840); mGFR range, 13-55 mL/min/1.73 m^2; RAS inhibition, 36%; diuretic use, 41%	Post hoc analysis using long-term follow-up	Mean baseline 24-h urinary Na excretion from 3-4 urine collections, with time-averaged data used for sensitivity analysis; mean Na excretion, 3.46 ± 1.13 g/d	Kidney outcome of progression to ESRD; composite of ESRD and all-cause mortality	No association between either high or low urine Na excretion with ESRD or composite of ESRD and all-cause mortality
IDNT & RENAAL[19]	CKD clinical trial of type 2 diabetic patients with proteinuria > 500 mg/d (n = 1,177); mean (SD) eGFR, 44 (16) mL/min/1.73 m^2; RAS inhibition (randomized), 42%; diuretic use, 61%	Post hoc analysis	Mean 24-h urine Na excretion, averaged from follow-up visits and normalized to urinary creatinine excretion; mean Na excretion, 4.16 ± 1.98 g/d	Composite CVD outcome of CVD death, MI, stroke, HF hospitalization, or revascularization procedure; composite kidney outcome of doubling of creatinine or ESRD	Reduction in CVD and kidney outcomes in patients using RAS inhibition compared to non-RAS inhibition was greater in patients with lower urinary Na as compared to higher urinary Na
REIN and REIN-2[12]	CKD clinical trial of proteinuric kidney disease (n = 500); CL_{cr} range, 20-70 mL/min/1.73 m^2; RAS inhibition (randomized), 100%[a]	Post hoc analysis using long-term follow-up	Baseline 24-h urinary Na excretion, normalized to urinary creatinine excretion; mean Na excretion, 4.08 ± 1.66 g/d	Kidney outcome of progression to ESRD	High urinary Na is associated with increased risk for ESRD, perhaps through a pathway of increasing proteinuria
AASK[20]	CKD clinical trial in African Americans with hypertension (n = 1,094); mGFR range, 20-65 mL/min/1.73 m^2	Post hoc analysis	Baseline 24-h urinary Na excretion; mean Na excretion, 3.68 ± 1.98 g/d	Composite outcome of CVD death, hospitalization for MI or CV event, revascularization procedure, stroke, HF	Higher urine Na-potassium ratio associated with increased risk for CVD

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; CKD, chronic kidney disease; CL_{cr}, creatinine clearance; CRIC, Chronic Renal Insufficiency Cohort Study; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated GFR; ESRD, end-stage renal disease; HF, heart failure; IDNT, Irbesartan Diabetic Nephropathy Trial; MDRD, Modification of Diet in Renal Disease; mGFR, measured GFR; MI, myocardial infarction; RAS, renin-aldosterone system; REIN, Ramipril Efficacy in Nephropathy Trial; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study; SD, standard deviation.

[a]All individuals in this post hoc analysis were part of the treatment arm, treated with ramipril.

estimated intake greatly exceeds a range of dietary sodium intake between 2.7 and 3.3 g/d.[16] Importantly, this guideline did not suggest a universal reduction to <2 g/d because of the absence of evidence for this threshold, as well as the possibility of harm at lower levels of sodium intake, thereby acknowledging the J-shaped observation noted in certain populations.

The recent article by Mills et al is a welcome addition to the literature, specifically focusing on sodium excretion and clinical outcomes in a CKD population. Not only does this raise awareness that certain dietary interventions affect clinically important outcomes in this high-risk population, but it also supports the concept stressed in current guideline recommendations

to reduce sodium intake in individuals with CKD, in particular those who are consuming high-sodium diets. Importantly, the risk of low sodium intake was not overtly evident in this study. Additional studies are now needed in populations with CKD to confirm these results, better define exact sodium dietary targets, and evaluate in clinical trials whether sodium reduction translates into reduced clinical outcomes.

Amanda K. Leonberg-Yoo, MD, MS
Penn Presbyterian Medical Center
Philadelphia, Pennsylvania

Mark J. Sarnak, MD, MS
Tufts Medical Center
Boston, Massachusetts

ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Evaluated by Deputy Editor Weiner and Editor-in-Chief Levey.

REFERENCES

1. Jackson SL, King SM, Zhao L, Cogswell ME. Prevalence of excess sodium intake in the United States - NHANES, 2009-2012. *MMWR Morbid Mortal Wkly Rep*. 2016;64(52):1393-1397.

2. Rehm CD, Penalvo JL, Afshin A, Mozaffarian D. Dietary intake among US adults, 1999-2012. *JAMA*. 2016;315(23):2542-2553.

3. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25)(suppl 2):S76-S99.

4. US Department of Health and Human Services. Dietary guidelines for Americans 2015-2020. 2015. http://health.gov/dietaryguidelines/2015/guidelines. Accessed July 5, 2016.

5. Strom BL, Yaktine AL, Oria M, eds. *Sodium Intake in Populations: Assessment of Evidence*. Washington, DC: The National Academies Press; 2013.

6. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371(7):612-623.

7. Graudal NA, Galloe AM, Garred P. Effects of sodium restriction on blood pressure, renin, aldosterone, catecholamines, cholesterols, and triglyceride: a meta-analysis. *JAMA*. 1998;279(17):1383-1391.

8. Graudal N, Jurgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. *Am J Hypertens*. 2014;27(9):1129-1137.

9. O'Donnell MJ, Yusuf S, Mente A, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA*. 2011;306(20):2229-2238.

10. Thomas MC, Moran J, Forsblom C, et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care*. 2011;34(4):861-866.

11. Mills KT, Chen J, Yang W, et al. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. *JAMA*. 2016;315(20):2200-2210.

12. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol*. 2012;23(1):165-173.

13. Kotchen TA, Cowley AW Jr, Frohlich ED. Salt in health and disease–a delicate balance. *N Engl J Med*. 2013;368(13):1229-1237.

14. Smyth A, O'Donnell MJ, Yusuf S, et al. Sodium intake and renal outcomes: a systematic review. *Am J Hypertens*. 2014;27(10):1277-1284.

15. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO Clinical Practice Guidelines for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl*. 2012;2(5):347-356.

16. Akbari A, Clase CM, Acott P, et al. Canadian Society of Nephrology commentary on the KDIGO clinical practice guideline for CKD evaluation and management. *Am J Kidney Dis*. 2015;65(2):177-205.

17. He J, Mills KT, Appel LJ, et al. Urinary sodium and potassium excretion and CKD progression. *J Am Soc Nephrol*. 2016;27(4):1202-1212.

18. Fan L, Tighiouart H, Levey AS, Beck GJ, Sarnak MJ. Urinary sodium excretion and kidney failure in nondiabetic chronic kidney disease. *Kidney Int*. 2014;86(3):582-588.

19. Lambers Heerspink HJ, Holtkamp FA, Parving HH, et al. Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. *Kidney Int*. 2012;82(3):330-337.

20. Norris K, Bourgoigne J, Gassman J, et al. Cardiovascular outcomes in the African American Study of Kidney Disease and Hypertension (AASK) Trial. *Am J Kidney Dis*. 2006;48(5):739-751.