What Level of Sodium Intake Worsens Renal Outcomes?

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Sodium consumption in the United States is approximately 3,500 mg/day as estimated from urinary sodium collections. Although there is consensus that this is too much sodium, there remains lively debate as to what reduction in sodium is beneficial and safe. This is reflected in differences of opinion of knowledgeable consensus panels, such as those from the American Heart Association, which recommends restricting sodium to <1,500 mg/day in many cases, and the Institute of Medicine, which concluded that there is not enough evidence to support this low goal. The Institute of Medicine recommendations take into account some studies that suggest that targeting 1,500 mg/day can be harmful, at least in selected populations. Critiques of these studies have suggested that there is stratification within the studies, with the sickest patients having the lowest sodium intake. In many of the studies, the estimation of sodium intake was not ideal. However, there are short-term meta-analysis data indicating that low-salt diets increase plasma renin, plasma aldosterone, plasma catecholamines, cholesterol, and triglycerides. The long-term effects of these changes could potentially be harmful.

In this issue of the Journal, Smyth et al. have reviewed published data in an attempt to determine whether it is possible to define a level of sodium intake that slows the progression of kidney disease. The strict criteria used for this article, which required robust evidence for sodium intake, allowed inclusion of only 7 studies, 4 in chronic kidney disease (CKD) and 3 in normal populations. Heterogeneity in study design prohibited a meta-analysis. Review of the data shows that high sodium intake (>4,600 mg/day) is deleterious compared with low intake (<2,300 mg/day), but no conclusion could be drawn about whether moderate sodium intake (2,300–4,600 mg/day) was harmful compared with low sodium intake. The strengths of this review are that it uses data from prospective studies with a renal outcome and that 5 of the 7 studies had multiple urinary sodium collections, 1 had multiple food frequency questionnaires, and only 1 relied on a single sodium collection. The weaknesses are that few studies were included and study design was heterogeneous. In the end, it was not possible to define an ideal level of daily sodium intake to limit CKD progression.

There are data from other studies that suggest that sodium intake plays a role in progression of CKD. There are important epidemiologic data that relate incidence of cardiovascular disease and end-stage renal disease to levels of blood pressure: for every increment in blood pressure there is an increase in risk, without an apparent threshold. Because there are data that salt restriction can reduce blood pressure, as best shown in the Dietary Approaches to Stop Hypertension study, this has led to the call to reduce dietary sodium intake to decrease the incidence of cardiovascular and renal disease. There are also additional prospective studies that did not meet the criteria for the Smyth study that show a link between sodium intake and CKD progression. For example, in the African American Study of Kidney Disease and Hypertension, there was a significant association of increased sodium intake with renal events (halving of glomerular filtration rate, or end-stage renal disease, or death) in unadjusted analyses. However, this effect was lost after adjustment for proteinuria, which could be interpreted to indicate that higher sodium intake causes increased proteinuria.

Animal studies also provide evidence that high salt intake promotes renal disease and provide information as to mechanism. Many of these effects are not blood pressure dependent. For example, salt loading can diminish glomerular filtration rate, increase proteinuria, and cause renal hemodynamic changes independent of blood pressure in spontaneously hypertensive rats. Animal models that are commonly used to study CKD, including, for example, reduced renal mass and deoxycorticosterone acetate–salt require high salt intake to promote renal disease. These models have shown that high salt increases production of oxygen free radicals in the kidney, increases expression of enzymes that are pro-oxidant, and decreases antioxidant pathways. High salt also diminishes renal nitric oxide production. Nitric oxide donors and antioxidants can slow the progression of renal disease in this setting. An additional effect of high-salt diet is that despite the salt surfeit and increases in blood pressure, it may increase renal angiotensinogen production, which is an index

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of intrarenal angiotensin II concentration. This suggests that the salt load may paradoxically stimulate the renal renin-angiotensin system and limit salt excretion. It has also been shown that angiotensin II increases oxidative stress in the kidney, resulting in renal damage. Sodium loading impairs microvascular function independent of blood pressure in humans, also likely by increasing oxidative stress. Finally, it has been shown that transient pretreatment with angiotensin II predisposes to hypertension and kidney damage when followed by a high-salt diet in the absence of exogenous angiotensin II, suggesting that prior exposure to angiotensin II can condition the kidney to respond adversely to salt.

The data presented herein and cogent arguments of others provide evidence that salt intake should be reduced in most populations to prevent cardiovascular disease and CKD progression. However, there are not enough data to determine the optimal target sodium consumption. There are very few studies that provide any data about sodium intake and CKD progression, and some studies, although criticized for potential methodological flaws, suggest harmful effects of very low sodium targets in selected populations. Furthermore, many of the arguments for sodium reduction are based on the resultant blood pressure reduction, regardless of the baseline blood pressure. However, several major treatment studies have not shown significant benefit of blood pressure targets <140/90 in hypertensive populations. This finding, in conjunction with the lack of good prospective studies, argues that appropriate outcome-based clinical trials should be planned to assess current sodium consumption goals for benefits and risks in broad-based populations, across a wide range of age, renal function, racial/ethnic, and comorbidity groups, as being done for hypertension therapy (Systolic Blood Pressure Intervention Trial; https://www.sprinttrial.org/public/dspSprintScience.cfm). At the same time, public health efforts to reduce sodium content, particularly in prepared foods, should continue because the ubiquitous presence of high salt content in foods makes achieving even moderate levels of sodium consumption a challenge.

**DISCLOSURE**

The author declared no conflict of interest.

**REFERENCES**