REFERENCES


See related article, “Elevated Soluble Flt1 Inhibits Endothelial Repair in PR3-ANCA–Associated Vasculitis,” on pages 155–164.

Sodium Intake, ACE Inhibition, and Progression to ESRD

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Renin-angiotensin-aldosterone system (RAAS) blockade is the most effective and widely used treatment for attenuating CKD. Enthusiasm must be tempered, however, by recognition that CKD progresses in many patients despite this blockade, and therapeutic trials with alternative agents have proven ineffective thus far. Identification, therefore, of modifiable risk factors for treatment resistance could lead to more effective interventions that eventually might reduce the burden of ESRD.

Intake of dietary salt (sodium chloride) may just be one of the low-hanging fruits. Patients with CKD are particularly salt-sensitive because of the inability to excrete a sodium load, diminished sodium buffering capacity, and increased incidence of hypertension, and efforts to reduce dietary sodium could be particularly effective in this population. Experimental studies demonstrate that sodium chloride accelerates and may even be particularly effective in this population. Experimental studies demonstrate that sodium chloride accelerates and may even be essential for development of end-organ damage during exogenous angiotensin II or mineralocorticoid administration. One can reason that limiting dietary sodium intake should reduce the incidence of renal failure. However, studies that address the association between sodium and development of ESRD are notably absent from the literature.

By conventional thinking, a randomized, controlled dietary intervention trial with anything more than a surrogate end point would likely be cost-prohibitive. Consequently, observational studies and small interventional trials have used the intermediate end points of systemic BP and proteinuria. In general, these studies demonstrate a beneficial effect of sodium restriction, which is additive to RAAS blockade. This effect is probably not specific to the RAAS, because similar results have been observed with other antihypertensive drugs such as calcium channel blockers.

In the current issue of JASN, Vegter et al. provide important post hoc epidemiologic evidence that urinary sodium excretion is positively associated with development of ESRD in nondiabetic kidney disease studied in the Ramipril Efficacy in Nephropathy (REIN) trials and may modify the protective effect of RAAS blockade. Although the study is observational, it provides firm evidence extending beyond surrogate end points for the first time. This study should be put into context with additional renal outcome studies that addressed similar questions. Supporting the current findings, in patients with polycystic kidney disease, urinary sodium excretion correlates with an increase in kidney volume and rate of decline of GFR when followed over 6 years, but not in the fully adjusted model. However, contrary data have also been reported. In the Finnish Diabetic Nephropathy (FinnDiane) Study of patients with type 1 diabetes, the highest risk of all-cause mortality and ESRD occurred in the lowest 10th percentile of urinary sodium excretion, demonstrating a J-curve effect. Conflicting data regarding the effect of sodium intake on mortality have similarly been reported in the general population and in patients with heart failure. This discrepancy could be explained by malnutrition in the self-selected low sodium groups, which is adjusted incompletely by statistical modeling. However, the concern remains that overly restricting sodium intake during RAAS blockade could be potentially harmful. The question remains, how much sodium restriction is enough?

The study by Vegter et al. will not likely provide a definitive answer, but will inform future studies. The largest effect appears to be between the high (243 mmol/d) and moderate (185 mmol/d) sodium groups, with minimal further benefit in the lowest sodium intake. Importantly, there was no apparent J-curve during very low sodium intake (121 mmol/d), suggesting there was also no harm. A similar analysis using sodium as a continuous variable also failed to define a harmful effect during low sodium intake. This could be due to lack of power given the small sample size or lack of a full range of low sodium intake; alternatively, this could reflect the selection of relatively healthy individuals into the REIN studies compared with a relatively unselected population in the FinnDiane study.

J-shaped mortality curves have also been observed in association studies with BP, despite beneficial effects of BP lowering in interventional trials. Would it be feasible to conduct such an interventional study with hard outcomes to identify the optimal sodium intake in CKD patients? The ability of the investigators to demonstrate such an association in such a small sample size is encouraging, and hopefully other observational studies will refine our estimates of this sodium effect. However, this view could be overly optimistic. Large-scale trials have struggled to provide a clear answer regarding sodium restriction and cardiovascular outcomes in the prehypertensive population, possibly because of low incidence or lack of long-term compliance. Progression to ESRD could in fact prove to be a more powerful salt-sensitive end point in the CKD population due to its high incidence in selected populations (18.2 versus 7.9 per 100 patient years in high versus moderate sodium groups in the REIN trials). The effectiveness of sodium reduction appears to be additive to ACE inhibition in small studies, making this complementary approach very attractive.

Opinion regarding sodium intake has already been translated into clinical guidelines to direct clinical care, so do we need more evidence? According to current opinion-based National Kidney Foundation guidelines, patients with CKD should limit sodium intake to <2400 mg (104 mmol)/d. However, urinary sodium excretion was above recommended goals in both the REIN I and REIN II trials (170–200 mmol/d) and was no different than what is typically observed in the general population. Although data in the US CKD population are lacking, a similar trend is likely. Why is there such a failure to achieve these goals, and how can this be improved? Achieving compliance with sodium restriction is difficult with a Western diet, where ~70–80% of sodium comes from processed foods. A large proportion of the American CKD/ESRD population live in poverty or in areas that are food deserts, defined by overexposure to fructose and limited access to healthy foods; canned or fast foods present the most convenient and affordable option, but they are invariably high in sodium. An important first step in reducing sodium is identification of potential treatment barriers and
patient education, optimally by a renal dietician. Even if access to a dietitian is unavailable, other resources are available for patients, including the American Association for Kidney Patients Nutrition Counter (http://www.aakp.org/brochures/nutrition-counter/), which provides the sodium content of common foods. Broader population-based initiatives to reduce sodium added to processed foods are also underway, but do not seem likely to have immediate effects.

Unmeasured confounding variables and practical matters often thwart translating observational findings into success in clinical trials and then clinical practice. Work in both translational arenas is needed to better define dietary sodium goals and to improve dietary counseling in CKD clinics. The present study suggests that sodium reduction to at least 200 mmol/d could significantly reduce the incidence of ESRD, although no clear level of sodium intake has been defined. How much is enough? Until further studies are done, we are left with observational data and opinion to guide us. Regardless, one thing seems apparent: we aren’t doing enough.

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DISCLOSURES

None.

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