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You are what you Eat: Dietary Salt Intake and Renin Angiotensin Blockade in Diabetic Nephropathy

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Abstract

Interactions between sodium intake, the renin angiotensin system and renal and cardiovascular outcomes are incompletely understood. Lambers Heerspink *et al's* analysis shows that angiotensin receptor blockade (ARB) improves diabetic nephropathy and cardiovascular disease more when dietary sodium intake is low and suggests possible harm when sodium intake is high. These findings highlight dietary salt as a modifiable cardiovascular and renal risk factor and emphasize the need for need for detailed mechanistic studies.

Angiotensin II (Ang II) contributes to the pathophysiology of diabetic nephropathy and other forms of progressive renal disease¹, and the benefits of antagonizing Ang II activity in the treatment of nephropathy due to type 2 diabetes has been established for more than a decade²⁻⁴. The renin-angiotensin system (RAS) plays a similarly important role in the pathophysiology of cardiovascular disease⁵.

Although dietary sodium loading suppresses the systemic RAS, resulting in lower plasma renin, Ang II, and aldosterone levels, a high sodium diet is also associated with an increased risk of cardiovascular disease⁶. This apparent paradoxical effect of sodium (suppression of the systemic RAS but exacerbation of cardiovascular risk) may be explained, in part, by the muted effects of sodium loading in some individuals, like those with hypertension and type 2 diabetes⁷. Such patients have RAS activation, both systemically and at the tissue level (eg, heart, kidney), that does not suppress normally on a high sodium diet. Moreover, short-term studies in both experimental animals and humans demonstrate that a high sodium diet blunts the beneficial effects of therapy with angiotensin converting enzyme (ACE) inhibitors on proteinuria and left ventricular hypertrophy⁸. It was therefore unsurprising that a high sodium diet was associated with greater proteinuria and faster progression to end-stage renal disease (ESRD) in hypertensive patients with proteinuria, as was recently shown in patients treated with an ACE inhibitor in the Ramipril Efficacy in Nephropathy trial⁹. These data suggest that both inhibition of Ang II and control of dietary sodium intake are important factors in the treatment of CKD (Figure 1).

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Nevertheless, the long-term effects of dietary sodium on the effects of angiotensin inhibition remain poorly studied. In this context, the study by Lambers Heerspink *et al.* in this issue¹⁰ provides intriguing new data. The authors conducted a post-hoc analysis of 1177 (36% of those enrolled) patients with type 2 diabetic nephropathy in the RENAAL⁴ and IDNT³ trials who had available measurements of 24 hour urinary sodium excretion. They found that the effect of angiotensin receptor blocker (ARB) therapy on renal and cardiovascular outcomes varied according to sodium intake. Both blood pressure and albuminuria were decreased by the ARB to a greater extent in those with lower compared with higher sodium intake. More importantly, the benefits of ARB therapy on renal outcomes (defined as a doubling of serum creatinine or progression to ESRD) and cardiovascular outcomes (defined as cardiovascular death, myocardial infarction stroke, or hospitalization for heart failure or coronary revascularization) were significantly greater in those at the lowest compared with highest tertile of sodium intake. Specifically, the ARB was associated with significantly reduced risks of renal and cardiovascular events, 43% and 37% respectively, if sodium intake was low. In contrast, ARB therapy was associated with nonsignificantly higher risks when sodium intake was high. These data support the idea that renal and cardiovascular protection is maximized when both salt restriction and renin angiotensin blockade are combined.

The author's findings are intuitively compelling, and the analysis has several strengths, including the use of high-quality, randomized trial data with sufficient numbers of patients and outcomes to assess meaningful clinical endpoints. Furthermore, the collection of urine every 6 months allowed for the analysis of mean sodium intake throughout the trial rather than at baseline (or a single time point) as in most other studies of sodium intake.

However, a number of issues with the study methodology merit consideration. Although the authors analyzed data from two randomized trials, only the assignment to ARB vs. control was randomized. Sodium intake was not randomized, and there were many significant and clinically important differences in baseline characteristics at the extremes of intake. Compared with the lowest tertile of intake, for example, patients in the highest tertile were more likely to be female (46.9% vs. 20.9%), white (54.6% vs. 42.8%), and have a lower estimated GFR (42.2 vs. 45.6 ml/min/1.73m²), a lower body weight (85.4 vs 91.9 kg), and a higher urinary albumin to creatinine ratio (1905 vs. 1173 mg/g). The greater distribution of important risk factors in those with higher salt intakes suggests that the sickest patients—i.e. possibly those least able to respond to intervention—were most likely to have a high salt intake. This could be one critical factor underlying the greater benefits of ARB therapy observed in those with lower salt intakes. In fact, careful scrutiny of Lambers Heerspink's Kaplan-Meier curves raise that possibility: in ARB treated patients, the major differences in cardiovascular and renal event rates among the different sodium intake groups occur during the first year, with relatively equal event rates during subsequent years. In addition, the authors did not control for most of the potential confounding factors. Although adjusting for one factor (specifically, baseline estimated GFR or urea excretion) did not change the interpretation of the main findings, fully-adjusted multivariable models (controlling for age, sex, race, weight, baseline estimated GFR, blood pressure, urinary protein excretion and whether patients came from IDNT or RENAAL) should have been performed. Such data

would have provided greater confidence that the results are valid and do not simply reflect confounding by an asymmetric distribution of comorbidity.

An additional concern is that the significant differences in benefit derived from ARB therapy observed at different levels of sodium intake was largely driven by a higher risk of cardiovascular (hazard ratio 1.25, 95% CI: 0.89-1.75) and renal events (hazard ratio 1.37, 95% CI: 0.96-1.96) associated with ARBs compared with control therapy in those in the highest tertile of sodium intake. As above, these findings could simply reflect confounding due to baseline imbalances. For example, the well known hemodynamic effect of ARB initiation (resulting in a decline in GFR) may have been more clinically dramatic in patients with a lower baseline eGFR, resulting in a greater frequency of renal events. However, if the apparent adverse effects of ARB therapy in patients consuming a high sodium diet are not spurious observations resulting from uncontrolled confounding, then this finding suggests the intriguing possibility that ARBs are helpful in individuals with a low sodium intake, but potentially harmful when sodium intake is high. The mechanism for such an effect is uncertain. Although the authors provide rationale for a blunted effect of ARBs in patients who consume a high sodium diet, they do not provide an explanation for the worse outcomes, albeit not statistically significant, that were observed.

Although flawed, the study by Lambers Heerspink and colleagues confirms prior work suggesting that both sodium restriction and blockade of the renin angiotensin system are beneficial, and it should serve as a reminder to clinicians not to ignore diet as a modifiable cardiovascular and renal risk factor. In the context of decades of research into the important roles that sodium intake and Ang II play in pathogenesis of renal and cardiovascular disease, this study should increase clinician's comfort in recommending dietary sodium restriction for their patients with diabetic nephropathy on ARB, lest a high sodium intake abrogate the protective effects. The study also raises intriguing new questions about the mechanisms of the interaction between sodium intake and ARB, and raises some concern that ARB may be harmful in some patients. Additional mechanistic studies and randomized trials are clearly warranted. In short, this study reminds us of how much further there is to go in understanding the full potential of our therapeutic armamentarium in diabetic kidney disease.

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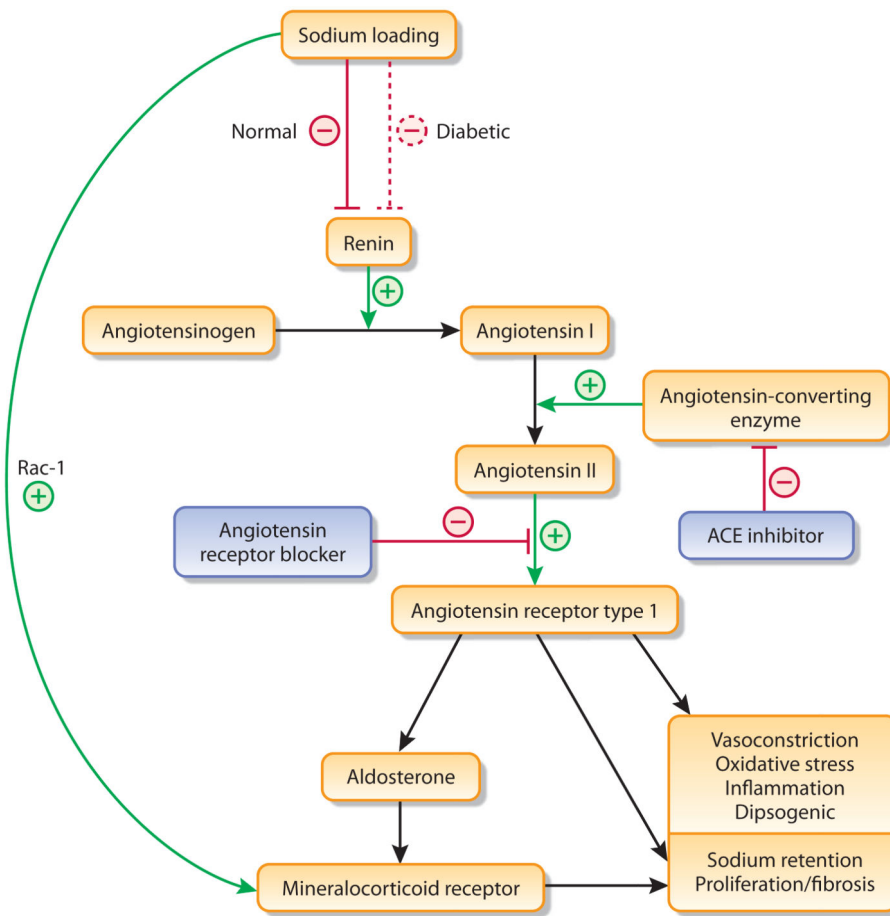


Figure 1. Multifactorial role of sodium in the renin angiotensin system—Sodium loading typically suppresses renin synthesis, but this response may be attenuated in diabetes. Conversely, sodium loading can directly activate the mineralocorticoid receptor activity via up-regulation of Rac-1 signaling or via increases in angiotensin converting enzyme (ACE) activity.