Aldosterone, Dietary Salt, and Renal Disease

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Increased urinary albumin excretion (UAE) is an early indicator of glomerular damage and of increased cardiovascular risk. Systemic endothelial dysfunction, for which albuminuria is presumed to be a sensitive biomarker, likely underlies, at least in part, these combined cardio renal effects. A large body of experimental data implicates the independent roles of aldosterone and high dietary salt ingestion in contributing to the development of kidney disease separate from the effects of high blood pressure. Less well documented is the degree to which aldosterone and dietary salt contribute to renal disease in humans and, in particular, how these factors interact to effect renal function.

In this issue of Hypertension, Rossi et al report that patients with newly diagnosed hypertension who were confirmed to have primary aldosteronism had greater UAE than newly diagnosed hypertensive patients without primary aldosteronism. In all of the patients, urinary sodium excretion independently predicted UAE. These results both compare and contrast with recent results from Framingham investigators who found that in a cohort of normotensive and hypertensive subjects, urinary sodium excretion was positively associated in a continuous fashion with urinary sodium excretion. No such association was seen with serum aldosterone, although UAE was higher in subjects in the highest quintile of serum aldosterone levels. These 2 studies emphasize the importance of the combined roles of aldosterone and dietary salt ingestion in the progression of kidney disease while also generating important research questions to further explore the clinical ramifications of this interaction.

A large number of animal studies have confirmed the inflammatory, fibrotic, and thrombotic effects of hyperaldosteronism on target organs, including the heart, brain, and kidney. These studies have also been extremely consistent in demonstrating that concomitant high dietary salt intake is an obligatory component of this process. That is, aldosterone alone, without excess dietary salt ingestion, has little or no deleterious effects on target organs. Although the mechanisms of aldosterone-induced inflammation and fibrosis have been widely studied and increasingly defined, the role of salt in this process has not been extensively studied and remains poorly understood. This is especially true of humans in whom the independent and interactive roles of aldosterone and dietary salt remain poorly elucidated. Although clinical studies suggest that hyperaldosteronism does increase the risk of cardiovascular disease, it is not known to what degree, if at all, excessive dietary salt ingestion is necessary for these effects to manifest.

As part of a larger prospective assessment of the relative prevalence of aldosterone-producing adenomas (APAs) versus idiopathic hyperaldosteronism (IHA), Rossi et al measured UAE by 24-hour urine collection in 490 subjects with newly diagnosed hypertension. Of these 490 subjects, 31 subjects with APA and 33 with IHA were distinguished from one another by evidence of lateralization of aldosterone excretion during adrenal vein sampling or adrenocortical scintigraphy and with confirmation of APA by adrenalectomy. Having distinguished APA from IHA, the investigators were able for the first time to rigorously compare renal function and UAE in subjects with the 2 subtypes of primary aldosteronism who were otherwise similar, particularly in terms of the duration and severity of hypertension.

Plasma aldosterone levels were slightly higher and serum potassium levels slightly lower in subjects with APA versus IHA, as would be anticipated. The estimated glomerular filtration rate was normal for all of the subjects per study entry criteria. In the entire cohort comprised of hypertensive subjects with primary aldosteronism and subjects without primary aldosteronism, that is, presumed primary hypertension, UAE was related to body mass index, age, serum potassium, mean blood pressure, and urinary sodium excretion. In contrast, UAE was not predicted by plasma aldosterone or plasma renin activity. When compared by subgroup, UAE was significantly higher in subjects with primary aldosteronism compared with subjects with primary hypertension. The degree of UAE, however, was not different in subjects with APA versus IHA.

These results confirm that hyperaldosteronism is associated with early kidney disease as indicated by increased UAE. Not surprisingly, with only a small difference in plasma aldosterone levels, the degree of UAE was not different in subjects with APA versus IHA, suggesting that the mechanism of aldosterone-induced renal disease is the same regardless of subtype of primary aldosteronism. Equally relevant, but not elaborated on, was that dietary salt ingestion, as indexed by 24-hour urinary sodium excretion, positively predicted UAE across the entire cohort. With a relatively small number of subjects with primary aldosteronism, the authors were likely not able to explore the potential interaction between high endogenous aldosterone and various levels of dietary salt intake.

In a cross-sectional analysis, Fox et al evaluated 2700 participants from the Framingham Offspring Study by measurement of serum aldosterone and estimates of urinary sodium and albumin excretion based on spot urine collections. In all of the subjects, urinary sodium excretion was a very strong positive predictor of UAE. UAE was 24% higher and 2-fold higher in the fourth and fifth quintiles of the urinary sodium index, respec-
tively. In contrast, in multivariable models, serum aldosterone was not related to UAE, although the top quintile of serum aldosterone levels was associated with a 21% higher UAE level relative to the lowest quintile. However, when subjects with cardiovascular disease, hypertension, or chronic kidney disease were excluded from the analysis, this difference in UAE between quintiles of aldosterone levels was absent. The Framingham investigators looked for but did not find any interaction between the top quintile of serum aldosterone and the top quintile of urinary sodium index with regard to their combined effects on UAE.

The studies of Rossi et al⁴ and Fox et al⁵ provide considerable insight into our understanding of the role of aldosterone and dietary salt on the development of kidney disease. Both studies are limited in their cross-sectional design, so neither can infer causality; however, they are consistent with a large body of in vitro and animal data demonstrating the direct nephrotoxic effects of aldosterone. Beyond this design limitation, the results of these 2 studies are reassuringly similar. Both studies demonstrate the independent roles of dietary sodium and aldosterone on the progression of renal disease. Dietary sodium, in both analyses, seemed to be a continuous risk, whereas the effects of aldosterone seem to be limited to patients with high aldosterone levels. These results have important clinical implications in terms of developing strategies to preserve kidney function through the restriction of dietary salt and potentially through the prophylactic use of mineralocorticoid receptor antagonists. The potential benefit of the latter approach is supported by recent but scanty reported evidence. Aldosterone-dietary salt interaction, including identification of a potential threshold effect whereby the tissue effects of aldosterone-diuretic use of mineralocorticoid receptor antagonists are minimized or even avoided, it may be that dietary salt recommendations can be revised for maximal end-organ preservation.

**Disclosures**

D.A.C. is on the advisory board of Pfizer and AstraZeneca. E.P. reported no conflicts.

**References**

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