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Challenges in Treating Cardiovascular Disease: Restricting Sodium and Managing Hyperkalemia

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Abstract

High sodium intake, whether via diet or drugs, augments cardiorenal risk. Regardless of its source, high sodium intake can both lead to hypertension and reduce the efficacy of renin-angiotensin-aldosterone system inhibitors, which are currently guideline-recommended treatments for hypertension, chronic kidney disease, and heart failure. Reducing sodium intake is therefore recommended to reduce the risk of adverse cardiorenal outcomes. An inverse relationship exists between sodium and potassium, with foods high in sodium being lower in potassium. Diets high in potassium have been associated with reducing hypertension and heart failure; however, optimal renin-angiotensin-aldosterone system inhibitor dosing is often limited by hyperkalemia, which can lead to life-threatening cardiac arrhythmias and increased mortality. Potassium binders are effective at reducing potassium levels. Although some use sodium as the potassium exchange ion, thus increasing sodium intake, a new potassium binder uses another exchange ion and therefore does not increase sodium intake. When treatment options require agents that may precipitate hyperkalemia, particularly in patients at high cardiorenal risk, drugs that do not add to the sodium load may be preferred. A literature search was conducted using PubMed; search terms included *potassium, sodium, hyperkalemia, potassium binders,* and the literature search focused on manuscripts published more recently since 2000.

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High sodium intake is associated with adverse cardiorenal outcomes, including oxidative stress, arteriolar damage, interstitial fibrosis, glomerular hyalinization, glomerular fibrosis, increased glomerular hydrostatic pressure in the kidneys, and ventricular hypertrophy, myocardial fibrosis, and diastolic dysfunction in the heart.[1] To reduce cardiovascular risk, the US Department of Agriculture dietary guidelines emphasize reducing sodium intake to less than 2.3 g/d as part of a healthy eating pattern.[2] For patients with prehypertension and hypertension, the US Department of Agriculture guidelines recommend targeting 1.5 g/d to achieve blood pressure (BP) reductions. Similarly, treatment guidelines for patients with hypertension, chronic kidney disease (CKD), and heart failure (HF) recommend reducing dietary sodium intake to less than 2.0 g/d to less than 2.4 g/d.[3-5] The American Heart Association (AHA) recommends an even more stringent target of less than 1.5 g/d.[1]

Diets low in sodium are often rich in potassium, which may also contribute to clinical benefits inasmuch as increased dietary potassium reduces BP and lowers risk of stroke and renal calculus disease.[6-8] Conversely, underconsumption of potassium, particularly when combined with high sodium intake, has been associated with a variety of chronic disorders, including hypertension, diabetes, obesity, and renal calculi.[8] However, in patients with impaired renal function, potassium-enriched diets and renin-angiotensin-aldosterone system (RAAS) inhibitors can cause hyperkalemia, which in turn is associated with adverse outcomes.[8-11] The benefits associated with low-sodium diets have come into question because recent data indicate an adverse effect on cardiovascular risk.[12-14] Despite paradoxical data, the benefits of low-sodium diets remain a primary intervention for improving cardiorenal outcomes.[15]

In this article, we review the impact of high sodium intake on cardiorenal outcomes and its impact on RAAS inhibitor activity. We then describe the catch-22 that patients with CKD often face while balancing the risks

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of hyperkalemia with the benefits of RAAS inhibition. Recognizing that diet may not be the only important sodium source, we describe how drugs containing sodium may contribute to adverse outcomes and how available potassium binders, and those in development, treat hyperkalemia but differ as sources of sodium, which may be an important consideration when prescribing these agents.

COMPLIANCE WITH LOW-SODIUM DIETS

Data from the National Health and Nutrition Examination Survey 2009-2010 revealed that most Americans exceed dietary sodium recommendations, with 52% reporting sodium intake exceeding 3 g/d and 15% exceeding 5 g/d.[16] Even patients with CKD have higher than recommended sodium intake. Using 24-hour urinary sodium excretion data from more than 10,000 patients with CKD and renal transplant recipients, sodium intake averaged 3.8 g/d,[17] almost double the recommended level of less than 2.0 g/d for patients with CKD in the Kidney Disease: Improving Global Outcomes guidelines[4] and substantially above the 1.5 g/d limit recommended for adults by the AHA.[1] Importantly, however, 24-hour urinary sodium excretion may not fully reflect daily sodium intake in light of recent data indicating that sodium stores are important in maintaining sodium balance.[18] These sodium stores may fluctuate independently of sodium intake or body weight, exhibit weekly to monthly rhythms, and are larger in hypertensive compared with normotensive individuals. Functionally, sodium stores may reflect differences in hemodynamic responses between salt-sensitive and salt-resistant individuals.[19] Additionally, it has been suggested that sodium stores may be mobilized to regulate a hypertonic interface in the skin that may serve a protective barrier function.[18]

Given the prevalence of sodium in our food choices, fewer than half of patients prescribed dietary sodium restriction successfully follow the recommendations.[20] Numerous reasons contribute to patients' failure to follow a low-sodium diet, including more expensive and limited food choices, perceived loss of taste without added salt, inherent difficulty when eating at restaurants or places away from home, family or friends who do not follow the same diet, and lack of adequate dietary instructions.[20] Patients with additional comorbidities, such as diabetes, may experience confusion when asked to follow more than one type of diet.

ARTICLE HIGHLIGHTS

- Many drugs contain sodium, including some used to treat hyperkalemia, and therefore have the potential to substantially increase sodium levels and influence outcomes.
- Low-sodium diets and renin-angiotensin-aldosterone system inhibitor therapy are recommended for patients with hypertension, chronic kidney disease, and heart failure to improve cardiorenal outcomes.
- High sodium intake reduces the efficacy of renin-angiotensin-aldosterone system inhibitor therapy, and continued treatment with these agents at recommended doses is often limited by the development of hyperkalemia.
- Both dietary and medication-based sodium intake should be considered when treating hyperkalemia.
- Unlike potassium binders that use sodium as the exchange ion for potassium, a new potassium binder that uses another ion for exchange does not increase sodium intake.

EFFECTS OF EXCESS DIETARY SODIUM INTAKE ON OUTCOMES

Excess dietary sodium worsens hypertension, CKD, and HF. The LowSALT CKD study, a double-blind, placebo-controlled, randomized crossover study, evaluated sodium restriction in 20 patients with hypertension and stage 3 to 4 CKD.[21] Patients received individualized counseling on following a low-sodium diet and were then randomized to high or low sodium intake for 2-week periods (1380-1840 mg/d plus either 2760 mg/d or placebo tablet; to convert to mmol, divide by 23). Compared with the high sodium intake period, 24-hour systolic BP (SBP)/diastolic BP (DBP) was significantly reduced by a mean of 9.7/3.9 mm Hg with low sodium intake ($P \leq .01$). Proteinuria and albuminuria were also significantly reduced with low sodium intake ($P \leq .01$).

In the Trials of Hypertension Prevention I and II, 3126 individuals with prehypertension (defined as DBP of 80-89 mm Hg and SBP/DBP of <140/83-89 mm Hg, respectively) were randomized to a sodium reduction