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PROGRESSION OF RENAL DISEASE

High salt intake blunts the benefit of ACE inhibitors and accelerates renal function decline

High dietary salt intake seems to reduce the renoprotective effects of angiotensin-converting-enzyme (ACE) inhibitors and may increase the risk of progression to end-stage renal disease (ESRD), say investigators of a study recently published in the *Journal of the American Society of Nephrology*.

Inhibitors of the renin–angiotensin system effectively control high blood pressure and reduce proteinuria in patients with chronic kidney disease (CKD), but experimental data have shown that increased salt intake blunts the beneficial effects of this therapy. In addition, evidence from studies in humans suggests that high salt intake contributes to proteinuria and renal disease progression. "We designed this study to assess whether ACE inhibitors are effective in patients who eat large amounts of salt despite dietary recommendations to restrict salt intake, and whether the benefits of therapy are blunted by excessive salt intake," explains investigator Piero Ruggenenti. To evaluate the association between salt intake, proteinuria and renal disease progression, 500 patients with CKD who received 5 mg ramipril daily in the Ramipril Efficacy in Nephropathy (REIN) and REIN-2 trials were included in this *post hoc* analysis.

Creatinine clearance, 24 h urinary protein, and sodium and urea excretion were measured at randomization, at 3 and 6 months, and every 6 months thereafter. Blood pressure was also monitored at 3-month intervals. Based on average urinary sodium/creatinine excretion during the follow-up period of >4 years, patients were categorized into three groups: low sodium diet ($n = 111$; <100 mEq/g), medium sodium diet ($n = 336$; 100–200 mEq/g) and high sodium diet ($n = 53$; >200 mEq/g).

The incidence of ESRD per 100 patient-years was three times higher in the high sodium diet group than in the low sodium diet group (18.2 versus 6.1, respectively).

Patients in the high sodium diet group had a 3.3-fold and 2.4-fold increased risk of progressing to ESRD compared with patients in the low sodium diet and medium sodium diet, respectively. "After 4 years, only 20% of patients with low salt intake needed dialysis, whereas 60% of patients in the high sodium diet group needed dialysis," comments Ruggenenti.

Proteinuria reduction was significantly higher in the low sodium diet group as, after 3 months of treatment, urinary protein/creatinine excretion decreased by 31%, 25% and 20% versus baseline in the low, medium and high sodium diet groups, respectively. This effect was sustained throughout the whole observation period in the low sodium diet and medium sodium diet groups, whereas proteinuria increased towards baseline values in patients in the high sodium diet group, despite similar blood pressure control between the three groups. Using a time-dependent Cox model, the researchers found that a 100 mEq/g increase in urinary sodium excretion was associated with a hazard ratio of 1.67 for risk of progression to ESRD. This association was independent of changes in blood pressure and antihypertensive co-medication on follow-up. However, the association was lost when the analyses were adjusted for baseline proteinuria and changes in proteinuria during follow-up.

Urinary sodium excretion was significantly and positively correlated with proteinuria, which in turn predicted ESRD progression, independent of sex, age, creatinine clearance and blood pressure. "The major implication of these results for patient care is that avoiding too much salt is important not only when treating high blood pressure and to prevent cardiovascular disease, but also to preserve renal function," says Ruggenenti. "Hopefully, awareness that these benefits largely offset the small inconveniences of minimal dietary restrictions will increase patient compliance to dietary counseling. With relatively simple lifestyle measures, it is possible for patients with kidney disease to potentially achieve considerable health benefits."

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