

# Approaches to and Clinical Benefits of Reducing Dietary K in CKD

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Hyperkalemia is a common electrolyte abnormality in patients with CKD. The incidence of hyperkalemia increases as GFR declines and has been found to be as high as 31% among patients with an eGFR <20 ml/min per 1.73 m<sup>2</sup> in cross-sectional studies (1). Patients with CKD are predisposed to hyperkalemia for a number of reasons, but serum potassium levels are usually maintained in the normal range as long as aldosterone secretion and delivery of sodium to the distal nephron are maintained. Thus, hyperkalemia develops in patients with concomitant high potassium intake, decreased distal delivery of sodium, or hypoaldosteronism. Patients with diabetes mellitus often may develop hyperkalemia at earlier stages of CKD from hyporeninemic hypoaldosteronism and/or insulin deficiency. Medications used to treat CKD, primarily inhibitors of the renin-angiotensin-aldosterone system, may exacerbate hyperkalemia, and the development of hyperkalemia frequently limits their use at doses optimal for cardiorenal protection. There is no question of the need to keep potassium levels below critical levels, but what are the consequences of moderately high potassium in patients with CKD?

Serum potassium is a critical determinant of the resting cell membrane potential of muscle and nerve fibers. Thus, hyperkalemia is associated with a variety of cardiac and neuromuscular complications. Rises in extracellular potassium concentration render the resting cardiac membrane potential more negative and predispose to cardiac arrhythmias, which can be fatal. Increases in both short- and long-term mortality have been found in patients irrespective of eGFR and potassium levels >5.5 mEq/L. In patients on incident dialysis, initial serum potassium levels >5.5 mEq/L were the strongest predictor of mortality over a 15-year follow-up period (2). Hyperkalemia in patients with predialysis CKD is also associated with adverse outcomes, but the data are conflicting. In an analysis of 36,000 patients with stages 3 and 4 CKD, a U-shaped relationship was found with both higher (>5.0 mEq/L) and lower (<3.5 mEq/L) potassium levels associated with increased risk of death (3). A secondary analysis of patients with stages 3–5 CKD from the Renal Research Institute CKD Study found increased risks of a composite outcome of cardiovascular events and death when potassium levels were >5.5 mEq/L; however, there was no significant association with overall

mortality (4). Interestingly, a recent study of 840 patients from the Modification of Diet in Renal Disease Study with a mean eGFR of 33 ± 12 ml/min per 1.73 m<sup>2</sup> found that higher urine potassium excretion (a proxy for higher dietary intake) was associated with lower risk for all-cause mortality (5). Others have found that, although higher serum potassium levels predict death, the association declines as CKD stage progresses, with patients with stage 5 CKD having a lower relative risk of death compared with patients without CKD (6). These studies suggest that perhaps chronic hyperkalemia is better tolerated than acute hyperkalemia, resulting in reduced sensitivity to cardiac complications.

The dangers of hyperkalemia are not limited to the heart. Several observational studies have shown that hyperkalemia is associated with uremic neuropathy. It has been hypothesized that chronic hyperkalemia leads to neurotoxicity through a depolarizing mechanism. Peripheral nerves in patients on dialysis have been found to be chronically depolarized compared with in the non-CKD population (7). In the acute setting, a single dialysis session to correct hyperkalemia improves neurophysiologic abnormalities (7). Hence, normalizing potassium levels in patients with CKD may be a treatment option for neuropathy.

Patients with CKD are advised to follow low-potassium diets to reduce the risk of adverse outcomes. However, there are very limited data to support that dietary potassium restriction improves outcomes, and most of the recommendations are opinion based. In this issue of the *Clinical Journal of the American Society of Nephrology*, Arnold *et al.* (8) present the results of a randomized, single-blind study examining the effect of dietary potassium restriction on neuropathy in patients with stages 3 and 4 CKD. Arnold *et al.* (8) randomized 47 patients with CKD to either dietary potassium restriction to meet a monthly serum potassium level of ≤4.5 mEq/L or control. Patients in the intervention arm received regular dietician consultation with strategies to reduce potassium intake. If the target serum potassium was not achieved with dietary intervention alone, the patients received sodium polystyrene sulfonate daily until the potassium level was at goal. Total neuropathy score and physical function were assessed at baseline and 6-month intervals for 24 months. Compared with control, the intervention significantly

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reduced mean serum potassium levels, although the effect was very modest ( $4.6 \pm 0.5$  versus  $4.8 \pm 0.4$  mEq/L;  $P=0.03$ ). The intervention significantly reduced neuropathy progression compared with in the control group ( $P<0.01$ ) and increased gait speed ( $P=0.01$ ). The results of this study are encouraging and suggest that dietary potassium restriction may have long-term benefits on neuromuscular outcomes, but it is important to consider some limitations of this study.

Dietary intervention alone only achieved goal serum potassium levels in 53% of the patients, and the difference between the groups was very small (0.2 mEq/L). The remainder of the patients required sodium polystyrene sulfonate to achieve the goal potassium. This could indicate that dietary potassium does not have a large effect on serum potassium. In patients on dialysis, dietary potassium is weakly, if at all, associated with serum potassium levels (9). However, given that dietary potassium intake is measured with error, the lack of an association between potassium intake and serum potassium does not exclude the possibility that high potassium intake affects hyperkalemia risk in patients with CKD. For this reason, 24-hour urinary potassium excretion may be a better proxy for dietary potassium intake than dietary recall in patients with well preserved eGFR. However, because there is upregulation of colonic potassium secretion as eGFR decreases (10), even 24-hour urine potassium assessment may be an inaccurate marker of dietary potassium intake in advanced CKD. Some studies have found no correlation between serum potassium concentration and urinary potassium excretion in patients with CKD, whereas others have found a positive one. The conflicting data highlight the need for randomized, controlled trials in patients with CKD. In this study, there was no significant difference in change in 24-hour urinary potassium excretion between the two groups, despite a significant change in serum potassium.

Although this study is not advocating for the use of medications to augment the gastrointestinal elimination of potassium, nearly one half of the patients in the intervention group required daily sodium polystyrene sulfate to achieve the goal potassium level. These medications may have additional risks and side effects. Sodium polystyrene sulfate use has been linked to intestinal necrosis. Even the newer agents, including sodium cyclosilicate and patiomer, which have both been shown to effectively reduce serum potassium levels in patients with CKD, have adverse side effects, including hypomagnesemia and hypercalcuria, and the long-term effects of these medications are unknown. Furthermore, it is possible that changes in potassium intake affect various patient populations differently. For example, patients with diabetes may be more sensitive to changes in dietary potassium given their predisposition to hyperkalemia much earlier in the course of CKD. Although nearly one half of the patients had diabetes in this study, the small sample size did not allow for subgroup analysis to determine the effect of diabetic status on outcomes.

Despite these limitations, the authors should be commended for their work. There is a significant paucity of randomized trials evaluating the effect of potassium reduction in patients with CKD. There is no clinical trial evidence to provide guidelines on ideal dietary intake or serum potassium in CKD. This study marks an important first step and paves the way for a larger clinical trial. Although high

potassium intake may be an important factor in the development of adverse outcomes, it is important to note that diets high in potassium may also be high in fruits and vegetables. Diets high in fruits and vegetables have been shown to reduce dietary acid load in CKD and thus, may be beneficial. Hence, potassium may simply be an indicator of an overall healthier diet. Until further data are available, we recommend that practitioners continue to restrict dietary potassium intake in CKD when the serum potassium level is elevated  $>5.0$  mEq/L. Future trials will need to rigorously monitor potassium intake and avoid the use of surrogates to answer these critical questions to determine if modifications to dietary guidelines in patients with CKD will improve outcomes.

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#### Disclosures

S.L. reports serving on an advisory board for ZS Pharma.

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See related article, "Randomized, Controlled Trial of the Effect of Dietary Potassium Restriction on Nerve Function in CKD," on pages 1569–1577.