The Highs and Lows of Potassium Intake in CKD—Does One Size Fit All?

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Electrolyte management is integral to the nephrological care of patients with CKD. Clinicians routinely face potassium derangements in settings of kidney dysfunction; hyperkalemia is of high concern given the potential for life-threatening cardiac arrhythmias. This concern drives recommendations of dietary potassium restriction, with diuretics and potassium-binding resins, to lower plasma potassium in these patients. Although effects of elevated plasma potassium on cardiac arrhythmias are well documented, multiple population studies have suggested a protective effect of potassium-rich diets on kidney function that might delay progression of CKD. In addition to these renoprotective effects, a host of studies have detailed beneficial effects of potassium-rich diets on cardiovascular health, including lower BP, incidence of stroke, and mortality (Figure 1).

Together, these reports suggest that potassium supplementation, up to a point, may blunt CKD progression, but prospective studies addressing this hypothesis have been lacking.

Recently, Hoorn and colleagues initiated a clinical trial (NCT03253172) to test the hypothesis that potassium supplementation slows rates of CKD progression on the basis of eGFR. In this issue of JASN, Gritter et al. report findings from the run-in phase of this clinical trial, “Effects of Short-Term Potassium Chloride Supplementation in Patients with Chronic Kidney Disease.” Specifically, the authors describe effects of treating 191 patients with CKD stage 3b–4 (mean eGFR 31 ml/min per 1.73 m²; 83% used renin-angiotensin inhibitors) with 40 mmol potassium chloride (KCl) daily (roughly equivalent to the potassium in four bananas) for 2 weeks. This dose was chosen to raise potassium intake to “recommended values of 90–120 mmol per day.” The investigators found that KCl supplementation raised plasma potassium, chloride, and aldosterone, along with urine potassium, but did not change urine sodium excretion or office BP. Hyperkalemia was reported for 11% of the participants (21 patients) for whom average plasma potassium increased to 5.9 mmol/L (range of 5.6–6.9 mmol/L; n = 5 had potassium levels >6 mmol/L). Hyperkalemia was more likely in older individuals and those with higher baseline potassium levels.

Although we anticipated the changes observed after potassium supplementation on the basis of our knowledge of renal physiology, this study highlights several, potentially paradigm-shifting, points. First, the authors demonstrate the feasibility of potassium supplementation in a patient population that is at high risk for hyperkalemia. Should this intervention prove to be beneficial, it is essential to determine if it can be implemented without harming patients. Second, the results demonstrate, on average, modest increases in plasma potassium (4.3 mM at baseline to 4.7 mM postsupplementation) and, third, identify patients with the greatest potential to develop hyperkalemia. Although supplementation was discontinued in these patients (several participants required additional treatment), no serious adverse effects were reported, indicating proper monitoring is sufficient to identify patients at risk of hyperkalemia and avoid poor outcomes.

Importantly, this study questions the current standard of care for patients with CKD. Whereas the 2-week duration of this run-in phase was too short to detect beneficial effects on kidney function, the longer randomized trial is designed to address this question by determining whether potassium supplementation slows rates of CKD progression. A demonstrated renal benefit of potassium supplementation would prompt further investigation into determining the optimal dietary potassium intake to achieve benefit, identifying the level of plasma potassium that is detrimental, and suggesting approaches to achieve these goals.
If potassium supplementation slows progression, even in just a subset of patients, then the question of who should, and who should not, be prescribed potassium restriction versus supplementation will become an important consideration. It is likely that a “one-size-fits-all” approach is not optimal for CKD treatment. We may learn that CKD progression adheres to a “U-shaped curve” in which a too high or too low potassium level confers risk. Positive outcomes in these trials support the liberalization of dietary potassium intake. Promotion of potassium-rich diets, such as the Dietary Approaches to Stop Hypertension and Mediterranean diets, are included in clinical guidelines for chronic disease prevention, with the exception of CKD due to concerns about hyperkalemia. In recent years, a model of distal nephron BP regulation has emerged on the basis of plasma potassium modulating sodium reabsorption through the sodium chloride cotransporter (NCC). According to this model, low plasma potassium is sensed in the distal convoluted tubule and stimulates sodium reabsorption via the NCC, which, in turn, increases BP. Higher potassium inhibits sodium reclamation via NCC (a thiazide diuretic-like effect), with subsequent BP reduction. The BP-lowering effects of higher potassium intake that underlie stroke protection may also offer kidney protection. Although Gritter et al. did not observe effects on BP over 2 weeks in this run-in phase, it will be important to determine if there are longer-term effects throughout the duration of their main trial. 

Acid-base balance and potassium homeostasis are intimately linked. The authors reflect on their use of KCI rather than an alkali-containing potassium supplement (e.g., potassium citrate or potassium bicarbonate) and mention their findings are “relevant because salt substitution is emerging as a public health intervention.” The authors mention another anion, such as citrate or bicarbonate, may be preferable, because their intervention did appear to slightly worsen metabolic acidosis in their patients with CKD. A more alkali supplement would likely prevent this effect. Beneficial Dietary Approaches to Stop Hypertension and Mediterranean diets, rich in fruits and vegetables, provide potassium predominantly in an alkaline form. Future investigation will need to determine which anion should accompany potassium to provide the full scale of beneficial effects.

Potassium-rich diets also benefit skeletal muscle, which contains >90% of the body’s potassium stores. Muscle sodium-potassium ATPases play a key role in maintaining potassium homeostasis by clearing potassium from extracellular fluid (ECF) to intracellular fluid (ICF) when plasma potassium is elevated, e.g., after meals or during exercise. This capacity is improved with potassium-rich diets and depressed with low potassium intake. Studies in rodents demonstrate reductions in sodium pump activity, along with muscle wasting and weight loss, in muscles of animals fed potassium-deficient diets to
the point that potassium shifts from ICF to ECF. Although not a focus of the Gritter et al. study,\textsuperscript{5,6} CKD is frequently associated with profound sarcopenia, which is an independent risk factor for poor outcomes.\textsuperscript{10} Inadequate nutrition, including low potassium intake, in patients with CKD has long been appreciated as a contributor to muscle wasting. The chronic disease process is likely a major cause, but dietary potassium restrictions present an additional barrier to achieving adequate nutrition. We postulate that maintaining potassium-rich diets in early CKD would maintain or amplify the capacity for extrarenal potassium shifts from ECF to muscle ICF and help maintain muscle mass, whereas restricting dietary potassium could reduce muscle sodium pump activity and muscle mass (as observed in rodents).\textsuperscript{4} Clinical trials, like those that Gritter et al.\textsuperscript{5,6} are conducting, motivate us to perform multisystem analyses to define the (patient-specific) sweet spot at the intersection of potassium intake and renal and muscle potassium handling during CKD.

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AUTHOR CONTRIBUTIONS

All authors wrote the original draft and reviewed and edited the manuscript.

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