Review Article

Kidney360

Potassium Homeostasis, Chronic Kidney Disease, and the Plant-Enriched Diets

Biff F. Palmer,[1] Gates Colbert,[2] and Deborah J. Clegg[3]

Abstract

There are data demonstrating that ingestion of potassium-rich foods reduces the incidence of stroke, hypertension, nephrolithiasis, and osteoporosis. Dietary-consumption data indicate Westernized diets are high in processed foods, high in sodium content, and low in potassium. In fact, there are data suggesting individuals are not consuming enough potassium in their diet. Although consumption of diets high in plant proteins, fruits, and vegetables—which are excellent sources of potassium—is recognized as healthy and beneficial, individuals with decrements in their kidney function have been advised to avoid these foods. In reviewing the literature that provides the rationale for potassium restriction in patients with reductions in kidney function, it appears there is little direct evidence to support the levels of restriction which are now prescribed. Additionally, there are two new potassium-binding agents which are well tolerated and have been documented to be effective in controlling serum potassium. Therefore, with the new binding agents and the lack of empirical evidence supporting the stringent dietary potassium restrictions, the authors conclude by indicating the pressing need for further research focusing on dietary liberalization of potassium in patients with reductions in kidney function to enhance overall health and well being, to provide them cardiovascular benefits, and to reduce overall risk of mortality through the incorporation of potassium-enriched foods.

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Introduction

Potassium (K^+), the most abundant intracellular cation, is located in the intracellular space (98%) and in the extracellular space (2%). K^+ homeostasis is achieved by matching intake with excretion and by ensuring proper distribution between extra- and intracellular fluid compartments. The kidney, and to a much lesser extent the colon, are responsible for maintaining total body K^+ content (1–3) (Figure 1). Normal blood K^+ levels range from 3.5 to 5.0 mEq/L, although there is variability in these levels between individuals depending on the presence of comorbidities such as CKD, diabetes, and heart failure (HF); as well as muscle mass; and/or differences in insulin sensitivity.

Elevated blood K^+, or hyperkalemia, can be lethal. Risk factors include advanced age, CKD, diabetes mellitus, HF, and use of drugs that block the renin-angiotensin-aldosterone system (RAAS) (4–6). Hyperkalemia is also associated with an increased risk of hospitalization, longer length of stay once admitted, and greater use of health care resources (6–8). Therefore, it is important to implement measures to minimize the occurrence of this disorder.

This review discusses the most common practice used by clinicians when patients present with hyperkalemia, which is to reduce dietary intake of K^+. We discuss the relationship between dietary K^+ and serum K^+ (which is not as straightforward as many believe), the rationale for dietary restriction of K^+, and focus on the fact that this rationale is derived from observational studies demonstrating only weak associations between dietary intake and K^+ levels. We conclude by recommending dietary K^+ restriction should not be a "one-size-fits-all" approach but should be individualized. We discuss new strategies that may allow patients at risk for hyperkalemia to liberalize their diet and receive the health benefits associated with consumption of foods high in K^+.

Health Benefits of Dietary K^+ Intake

There is a prodigious capacity for the healthy/normal kidney to excrete K^+, especially when following diets that are high in K^+. This ability may have evolved from prehistoric man who consumed diets containing approximately 15,000 mg/d of K^+, which is nearly fourfold higher than current nutritional recommendations for K^+ (4700 mg/d) (9). Diets in industrial societies are not only lower in K^+ compared to our prehistoric ancestors, but are currently lower in dietary K^+ than recommended guidelines. In addition, industrial-society diets exceed sodium (Na^+) chloride recommendations and are approximately three times higher in Na^+ than the daily intake of K^+ on a molar basis (10). It has been hypothesized that the relative lack of K^+ combined with excess consumption of Na^+ may be etiologically linked to the increased risk of

[1]Division of Nephrology, Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; [2]Division of Nephrology, Department of Medicine, Texas A&M Health Science Center College of Medicine, Baylor University Medical Center, Dallas, Texas; and [3]College of Nursing and Health Professions, Drexel University, Philadelphia, Pennsylvania

Correspondence: Dr. Biff F. Palmer, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390. Email: biff.palmer@utsouthwestern.edu

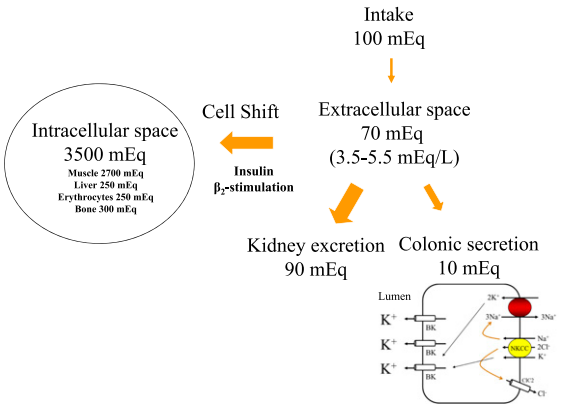

Figure 1. | Overview of potassium homeostasis. In a typical 70-kg man, there is approximately 3500 mEq of total body potassium (K^+), 98% of which is located in the intracellular space and 2% is in the extracellular space. The kidney is the primary organ responsible for maintenance of total body K^+ content and the gastrointestinal tract, primarily the colon, is responsible for 10% of K^+ secretion. Colonic K^+ secretion significantly increases with advancing CKD. The most important determinants of K^+ distribution between the intracellular and extracellular space are insulin and β-adrenergic–receptor stimulation. Cl^-, chloride; Na^+, sodium; NKCC, Na-K-Cl cotransporter.

diseases such as obesity, cardiovascular disease, stroke, and CKD (11).

Health benefits associated with foods enriched in K^+ can be traced to their alkalinity, fiber, micronutrient (vitamin and mineral, including K^+), and phytochemical content (12,13). Consumption of foods high in K^+ reduce the risk of cardiovascular disease, stroke, kidney stone formation, and improve acid-base balance, all of which will be discussed in greater detail below (14,15) (Table 1). Conversely, insufficient intake of K^+ increases the risk of cardiovascular disease and stroke (16).

Table 1. Benefits of increased dietary potassium intake

Benefit
BP-lowering effect
Magnified under conditions of high sodium intake and in black subjects
Mechanism
Natriuretic effect
Adrenergic outflow decreased
Vascular tone favorably affected
Beneficial effect in reducing stroke
Decrease in BP
Effects independent of BP lowering
Bone homeostasis benefited
Foods enriched in potassium provide a base load
High potassium may have a direct effect on bone metabolism that is favorable
Kidney stone risk is decreased
Base load afforded by potassium-enriched foods
Decreased urinary calcium excretion due to direct effects on transport in distal nephron
Decreased progression of CKD
Bioavailability of phosphate is decreased with plant protein compared with animal protein
Base load ameliorates metabolic acidosis

Cardiorenal Benefits and Reduction in BP

In a study of 17,000 adults who participated in the NHANES III survey, dietary K^+ intake was associated with lower BP (17). Similar findings were reported in the Dietary Approaches to Stop Hypertension (DASH) trial, which compared diets consisting of 3.5 servings per day of fruit and vegetables and containing 1700 mg/d of K^+ with the DASH diet that included 8.5 servings per day of fruit and vegetables and contained 4100 mg/d of K^+ (18). The high K^+ diet was associated with lower BP by an average of 2.8/1.1 mm Hg in all subjects and by an average of 7.2/2.8 mm Hg in those with hypertension. In an additional meta-analysis of 33 randomized controlled trials including 2609 individuals, increased K^+ intake (2300–3900 mg/d) significantly reduced BP by an average of 1.8/1.0 mm Hg in normotensive subjects, whereas BP fell by 4.4/2.5 mm Hg in those with hypertension (19). The BP-lowering effects of high-K^+ diets are influenced by race, because the effect is more pronounced in black individuals, particularly those ingesting higher amounts of Na^+.

Reduction in Stroke Risk

Several large epidemiologic studies indicate an inverse relationship between dietary K^+ intake and stroke risk. Specifically, in one study, 43,000 men were followed for 8 years and those who had the highest intake of dietary K^+ (median intake, 4300 mg/d) had a reduced risk (62%) of stroke when compared with subjects with the lowest K^+ intake (median intake, 2400 mg/d) (20). Additionally, there was an analysis of 11 cohort studies of 127,038 participants where K^+ intake was again the focus. In this report, those with the highest K^+ intake (90–120 mmol/d) again had the lowest relative risk of stroke (relative risk, 0.79; 95% CI, 0.68 to 0.93) (20,21). In contrast, individuals ingesting diets low in K^+ (<34.6 mmol/d) suffered a 28% higher relative risk of stroke (22). Lastly, in a study specifically focused on postmenopausal women aged 50–79, the authors found higher K^+ intake was associated with a lower risk for ischemic stroke (23). In summary, these epidemiologic data indicate diets enriched in K^+ decrease stroke risk, especially in those with hypertension and/or in those who eat diets that have less K^+. The benefits of K^+ in the diet have been shown to reduce formation of atherosclerotic lesions, reduce free-radical formation and platelet aggregation, and decrease vascular smooth muscle cell proliferation and migration (24).

Reduction in Risk of Nephrolithiasis and Favorable Effects on Acid-Base Balance

K^+-rich foods contain precursors to bicarbonate which buffer acids in the body. The modern Western diet is relatively low in sources of alkali (high K^+ foods such as fruit and vegetables), whereas it is high in sources of acid (fish, meats, and cheeses). When the quantity of base is insufficient to maintain normal pH, the body mobilizes alkaline calcium salts from the bone to neutralize acids consumed in the diet and generated by metabolism. High dietary-acid loads can contribute to metabolic acidosis and cause detrimental effects including bone demineralization, protein degradation, and kidney stone formation (25,26). Increased

consumption of fruit and vegetables reduces the net acid content of the diet and may preserve calcium in bones, which might otherwise be mobilized to maintain normal acid-base balance (27–29). Additionally, diets rich in fruits and vegetables increase urinary citrate levels and lower urinary calcium excretion, both of which reduce the risk of calcium oxalate stone formation (28).

The alkaline content of diets enriched in K^+ may be of particular benefit to patients with CKD because they have a decreased capacity for net acid excretion and are prone to development of metabolic acidosis. Current guidelines suggest metabolic acidosis should be treated and the most common therapy used is oral sodium bicarbonate ($NaHCO_3$). A potential drawback of this treatment is the Na^+ load that can lead to volume overload and hypertension. An alternative approach is to provide alkali derived from increased ingestion of fruits and vegetables. In one trial, 71 patients with stage 4 CKD and a serum bicarbonate <22 mEq/L were randomized to 1 year of sodium bicarbonate at 1.0 mEq/kg per day or a diet enriched in fruits and vegetables in an attempt to reduce the dietary acid load by half (29). These interventions were compared with standard therapy. The diet intervention was found to be equivalent to oral $NaHCO_3$ in terms of maintaining the serum bicarbonate concentration in the normal range as well as in slowing the progression of CKD when compared with standard therapy. However, the dietary intervention avoided the obligatory salt load and volume overload associated with $NaHCO_3$ therapy. Importantly, despite encouraging patients with stage 4 CKD to consume more fruits and vegetables, there were no complications from hyperkalemia; however, only patients with plasma K^+ ≤4.6 mEq/L were enrolled in the study.

Improvement in Phosphorus Homeostasis

Certain K^+-containing foods—including nuts, legumes, beans, and dairy products—also contain phosphorus. Phosphorus occurs in two forms: organic (as phosphates) and inorganic (as salts). Organic phosphorus is naturally found in food whereas inorganic phosphorus salts are added to foods for the purposes of moisture retention, longer shelf life, and enhanced flavor (30–32). Organic phosphorus in plant-based foods mostly occurs in the storage form of phytates or phytic acid, and humans do not have the enzyme required to degrade phytates or phytic acid. Thus, the bioavailability of phosphorus from plant-based sources is <50% due to the phytic acid content, whereas the absorption of phosphorus from inorganic sources is considerably higher (31). Therefore, plant-based foods have a lower effect on increasing the phosphorus load when compared with animal protein.

Phosphate homeostasis was examined in a crossover trial of nine patients with CKD by comparing a diet enriched with animal or vegetable protein for 7 days (33). Despite an equivalent amount of protein and phosphorus content in the diet, urinary phosphorus excretion was lower on the vegetarian diet when compared with a diet higher in meat, which is consistent with reduced gastrointestinal absorption of phosphate. This difference is particularly relevant to the patient with CKD because a diet enriched in fruits and vegetables can provide adequate protein intake and yet avoid the phosphorus load that can adversely affect the cardiovascular system. Importantly, despite patients with CKD consuming more K^+, there were no instances of hyperkalemia in this study.

Slows the Progression of CKD

Several studies suggest the risk of CKD and rate of decline in kidney function is lower when ingesting plant-rich diets. Adherence to a Mediterranean-style diet (high in legumes, fruits, vegetables, cereals, and fish) or a diet used in the DASH study can lead to a lower risk of incident CKD (34,35). A similar benefit of a plant-rich diet on CKD risk was recently demonstrated in a community-based cohort of adults in the United States, suggesting this benefit is generalizable to the population (36). Because plant-rich diets are enriched in K^+, studies have used the measurement of urinary K^+ excretion as a surrogate for ingestion of a plant-rich diet to overcome the limitations of dietary recall. Once again, higher urinary K^+ excretion is found to be associated with a slower cumulative incidence of CKD progression as well as a lower incidence of cardiovascular complications (37).

The mechanism by which plant-rich diets exert a beneficial effect on kidney disease and cardiovascular outcomes is multifactorial. Plant-rich diets are typically high in fiber and micronutrients and deliver a much lower acid load in comparison with diets higher in meat. In a 14 year follow-up of 1468 adult patients with CKD in the NHANES III study, higher dietary acid load was a strong predictor of ESKD (38). There is an inverse relationship between fiber intake and incident CKD suggesting the fiber content in plant-rich diets may contribute to protective effects on kidney function (39). High fiber intake is associated with improved glycemic control, beneficial effects on BP control, and body weight reduction. Micronutrients contained in plant-rich diets may be kidney protective by exerting favorable effects on endothelial function, reducing inflammation, and reducing oxidative stress.

Patients with CKD Are Typically Placed on K^+-Restricted Diets

For the general adult population, diets rich in fresh fruits and vegetables, whole grains, and plant-based protein is considered healthy as previously discussed (40). However, the typical diet recommended to patients with CKD is extremely restrictive and is low in fresh fruits and vegetables, and is very low in fiber. Dietary restrictions become even more stringent when patients develop ESKD requiring hemodialysis (HD) (41,42). The high K^+ content of a plant-rich diet in combination with the characteristic of impaired K^+ excretion in patients with CKD is fundamental to the recommendation of such diets. The rapid and severe elevation of serum K^+ after administration of K^+ chloride (KCl) salts to patients with CKD in older studies would seem to justify such recommendations (43,44). On the other hand, the association between dietary K^+ intake and risk of hyperkalemia as compared to administration of K^+ salts may not be as straightforward. In fact, there are studies demonstrating that consumption of high K^+ foods in patients with ESKD has only a modest, if any, effect of

increasing serum K^+ (45–47). For example, in a secondary analysis of 224 patients on HD in the Nutritional and Inflammatory Evaluation study, dietary K^+ intake was only weakly associated with pre-HD serum K^+ (45). As K^+ intake increased from 500 mg/d to 4500 mg/d (a ninefold increase), serum K^+ was only 0.4 mEq/L higher than baseline values. Similarly, in the Balance Wise study of 140 patients on HD, the association between reported K^+ intake (mg/d) and K^+ density (mg/1000 kcal) was examined and no correlation was found between serum levels and either absolute reported K^+ intake or K^+ density (48). Despite these data, patients on HD are typically advised to limit K^+ intake to <3 g/d, which is almost 40% less than the K^+ recommended for healthy adults (49).

Do these K^+ restrictions put patients with CKD at risk for lacking essential vitamins and minerals normally found in K^+-enriched food sources and deprive them from the cardiovascular benefits provided by such a diet? In a study of 9757 patients across European and South American countries in the Dietary Intake, Death and Hospitalization in Adults with ESKD Treated with HD study, the authors found higher intake of fruits and vegetables (17 servings each week or 2–3 per day) was associated with lower all-cause mortality and a reduction in death due to noncardiovascular causes (50). Given the paucity of evidence showing a direct relationship between dietary intake of K^+ and serum levels in the HD population, the usual dietary recommendations to restrict consumption of fruits and vegetables to prevent hyperkalemia may not be warranted and may in fact deprive this population of the potential health benefits afforded by consumption of K^+-enriched foods. Randomized trials evaluating the potential benefits and harms of increased intake of fruits and vegetables in the CKD population are needed to provide stronger evidence-based dietary recommendations.

Foods Enriched in K^+ Differ in Their Ability to Increase Serum K^+

Common foods high in K^+ include leafy greens (cabbage, kale, spinach), fruit of vine-based plants (cucumbers, eggplant, pumpkin, tomatoes, zucchini), root vegetables (carrots, onions, radishes), beans and peas (chickpeas, green beans, kidney beans, peas, soybeans), tree fruits (oranges, bananas, grapes, strawberries), tubers (potatoes, sweet potatoes, yams), and milk and yogurt. What is perhaps underappreciated is that animal proteins are also high in K^+, especially those from organ meats and cattle.

The bioavailability of dietary K^+ is influenced by the consumption of other nutrients and constituents in the foods (Table 2). For example, K^+-rich foods also high in carbohydrates may affect serum K^+ to a lesser degree than foods that are high in K^+ and low in carbohydrates. Carbohydrate-rich foods stimulate insulin release, which can mitigate the initial rise in serum K^+. For example, the increase in K^+ after ingestion of a banana is likely to cause less of an increase in serum K^+ as compared with an avocado, even though the latter has a higher K^+ content. In addition, the alkali content of K^+-enriched fruits and vegetables may also promote a greater proportion of dietary K^+ into cells as compared with effects of an acid load typical of a meat-base diet. The high fiber content of fruits and vegetables may serve to limit K^+ absorption by enhancing fecal excretion through increases in stool bulk. Cooking methods can also significantly affect the amount of K^+ in food products. Boiling fruits and vegetables for example, significantly reduces the K^+ load of foods, whereas drying enhances the K^+ content. Therefore, it is often best to encourage patients to consume fresh, minimally processed fruits and vegetables to obtain the potential vitamins and minerals found within these foods. Differences in muscle mass may also be a variable in determining serum K^+ after a meal. Increased muscle mass can provide a greater capacity for K^+ uptake (51). One can speculate that a potential benefit of exercise in patients on HD would be a lower frequency of predialysis hyperkalemia related to increased muscle mass.

Processed Foods Are a Hidden Source of K^+

The transition from raw to processed foods began approximately 10,000 years ago with the onset of agriculture. Processing foods has increased the amount of Na^+ and, in some cases, has reduced the amount of K^+ intake. As previously discussed, inadequate consumption of K^+ combined with excessive intake of Na^+ is thought to contribute to the pathophysiology of a variety of chronic diseases such as obesity, hypertension, diabetes, kidney stones, and bone disease. As consumers and health agencies have pushed to reduce the amount of Na^+ in processed foods, the food industry has begun to use food additives and preservatives, which are hidden sources of K^+. These additives can significantly contribute to the total daily K^+ content of foods because some preservatives in meat may add 300–575 mg of K^+ per 100 g of intake (52–55). Additionally, there are products used to enhance flavor which are KCl based and include salt substitutes where 20% of salt is replaced by KCl, which adds approximately 12 mmol/d (0.45 g/d) to the usual K^+ intake (56). In many cases, low K^+ products may be high in Na^+, making it difficult for patients with CKD to simultaneously adhere to low K^+ and low Na^+ food selections on a chronic basis (57).

Plant-based meat alternatives (PBMAs) are becoming increasingly available and popular in the food market. These foods contain no meat and claim to have similar health benefits to those of natural fruits and vegetables. Currently, precise health outcomes have not been well studied to determine if PBMAs are actually equivalent to eating fruits and vegetables, or even if they offer long-term health benefits when replacing meat intake. PBMAs are processed foods and do contain a Na^+ load inappropriate for patients on low-salt diets. The K^+ content has not been fully validated across all PBMAs, making official recommendations for consumption to patients with CKD premature (58).

It Is Time for a Paradigm Shift Concerning K^+-Restricted Diets in CKD

The restrictive nature of the current prescribed diet for patients with CKD and on dialysis is not ideal, difficult to maintain, and noncompliance in such patients is prevalent. When added to the fact that there is a lack of clarity and rationale for the severe K^+ restriction imposed on patients with CKD and those on dialysis, there is mounting data to

Table 2. Characteristics of a diet enriched in fruits and vegetables that minimize hyperkalemia

Characteristics
Carbohydrate load causing stimulation of insulin release and shift of potassium into cells
Increased alkali content
Shift of potassium into cells
Increased potassium secretion brought about by pH effect on renal outer medullary potassium channel (ROMK) in collecting duct
High fiber content
Increased stool bulk and less potassium absorption
Decreased constipation
Possibly increased kidney potassium secretion *via* gastric-kidney crosstalk
Possibly increased colonic potassium secretion
Lack of exogenous administration of potassium for flavoring, unlike meat products

suggest current dietary prescriptions have the potential to be harmful with regards to overall health and cardiovascular outcomes. It is plausible to suggest a more liberalized plant-rich diet will lead to better compliance and overall improved health (59,60).

One strategy to correct chronic hyperkalemia has been the use of K^+-binding agents (Table 3). For >50 years, clinicians were solely dependent on acute and chronic use of sodium polystyrene sulfonate as the only treatment of hyperkalemia. Sodium polystyrene sulfonate binds K^+ in the gastrointestinal tract and promotes immediate loose bowel movements with sorbitol. This therapy is poorly tolerated on a long-term basis and has been linked to gastrointestinal toxicity, including rare cases of intestinal necrosis.

There are new oral compounds, patiromer and sodium zirconium cyclosilicate (SZC), which are K^+-binding compounds shown to be effective in correcting hyperkalemia. Both drugs exhibit good gastrointestinal tolerability and are not associated with serious adverse effects. Patiromer is a calcium-based, nonabsorbed polymer that binds K^+ in the gastrointestinal tract, predominately in the colon. Patiromer effectively decreases serum K^+ concentrations in high-risk patients on RAAS blockers, including those with HF, CKD, and diabetic nephropathy (61). SZC binds K^+ in the gastrointestinal tract by virtue of its nonabsorbed, microporous structure. This compound has a pore size that allows it to be highly selective for the K^+ ion. SZC dose-dependently lowers plasma K^+ and is most efficacious in those with the highest serum K^+ levels (62,63). SZC can cause edema at higher doses in some individuals, although this effect is without alterations in BP.

Dietary K^+ intake was not controlled for in clinical trials. It is interesting to speculate if these new binding agents might allow patients at risk for hyperkalemia to enhance their consumption of K^+-containing fruits and vegetables without developing this complication. This benefit would in essence provide high-risk patients the health benefits afforded by diets rich in fruits and vegetables.

Summary and Conclusion

The restrictive nature of the current diet for patients with CKD and those on HD is not ideal and is difficult to maintain. Furthermore, there is a disconnect between the restrictive prescription of the CKD and HD diet and what patients actually consume. Additionally, plant-rich diets are recommended for their heart-healthy effects. We submit there is a lack of data to support the severity of the K^+ restriction currently used in many patients with CKD. The current dietary prescription may deprive or, yet worse, contribute to the development of cardiovascular disease in patients with CKD. In patients who are found to be hyperkalemic, one should not reflexively institute dietary restriction in fruits and vegetables. Rather, one should first consider nondietary factors such as metabolic acidosis, hypertonic states such as poorly controlled diabetes mellitus, increased catabolism, tissue breakdown, constipation, and medications. To be sure, dietary counseling is still required for individuals ingesting large quantities of food types enriched with K^+

Table 3. Approach to minimize risk of hyperkalemia when ingesting high potassium diet

Approach
Accurately assess level of kidney function to better define risk
Discontinue drugs that interfere in kidney potassium secretion, inquire about herbal preparations, and discontinue nonsteroidal anti-inflammatory drugs to include selective cyclooxygenase 2 inhibitors
Avoid potassium-containing salt substitutes
Thiazide or loop diuretics (loop diuretics necessary when eGFR <30 ml/min)
Sodium bicarbonate to correct metabolic acidosis in patients with CKD
Consider long-term use of binding drugs (patiromer or sodium zirconium cyclosilicate)
If patient is receiving or starting a RAAS inhibitor (ACEi, ARB, mineralocorticoid blocker)
Measure potassium 1 week after initiation of such therapy or after increasing dose of drug
For increases in potassium up to 5.5 mEq/L, decrease dose of drug; or if taking some combination of ACEi, ARB, or mineralocorticoid blocker, discontinue one and recheck potassium or consider long-term use of potassium-binding drug
The dose of spironolactone should not exceed 25 mg daily when used with an ACEi or ARB, this combination of drugs should be avoided with GFR <30 ml/min
For potassium ≥5.6 mEq/L despite above steps, consider long-term use of binding drugs to enable use of RAAS inhibitor if clinically indicated

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RAAS, renin-angiotensin-aldosterone system.

additives and/or those that provide high amounts of sodium.

Author Contributions

B. Palmer performed the formal analysis and wrote the original draft; B. Palmer, G. Colbert, and D. Clegg wrote the review and edited the manuscript.

Disclosures

G. Colbert reports personal fees from Astra Zeneca and personal fees from Relypsa outside the submitted work. D. Clegg and B. Palmer have nothing to disclose.

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