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REVIEW

Current Management of Hyperkalemia in Patients on Dialysis

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Patients with end-stage renal disease (ESRD) on maintenance dialysis have a high risk of developing hyperkalemia, generally defined as serum potassium (K^+) concentrations of >5.0 mmol/l, particularly those undergoing maintenance hemodialysis. Currently, the key approaches to the management of hyperkalemia in patients with ESRD are dialysis, dietary K^+ restriction, and avoidance of medications that increase hyperkalemia risk. In this review, we highlight the issues and challenges associated with effective management of hyperkalemia in patients undergoing maintenance dialysis using an illustrative case presentation. In addition, we examine the potential nondialysis options for the management of these patients, including use of the newer K^+ binder agents patiromer and sodium zirconium cyclosilicate, which may reduce the need for the highly restrictive dialysis diet, with its own implication on nutritional status in patients with ESRD, as well as reducing the risk of potentially life-threatening hyperkalemia.

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The overall prevalence of ESRD in the United States is increasing, with >725,000 cases in 2016.[1] Hemodialysis (HD) was used as renal replacement therapy in 63% of these prevalent patients, and peritoneal dialysis (PD) in 7%; the remaining 30% of patients underwent kidney transplantation.[1] Most patients (98%) undergoing HD were on in-center HD, with only 2% on home HD.[1]

Patients undergoing maintenance HD have a high risk of hyperkalemia, generally defined as serum potassium (K^+) concentrations of >5.0 mmol/l, even when receiving adequate treatment with 3-times-weekly HD (Figure 1).[2,3] Hyperkalemia is a potentially life-threatening disorder that can cause arrhythmias and sudden cardiac arrest.[3,4] In a US cohort study of patients undergoing HD between 2007 and 2010, the rate of hyperkalemia (K^+ ≥5.5 mmol/l) was 16.3 to 16.8 per 100 patient-months.[3] More recently, the PORTEND (POtassium and Cardiac Rhythm Trends in MaintE-Nance HemoDialysis) observational study of US patients on maintenance HD showed that the incidence of predialysis hyperkalemia (K^+ >5.0 mmol/l) after the long interdialytic interval was 37% and 21% among patients on dialysate K^+ concentrations of ≤2 and ≥3 mmol/l, respectively (Singh B, Block G, Lerma EV, et al. Hyperkalemia and serum potassium variability in patients on hemodialysis [abstract]. *Am J Kidney Dis*. 2017;69:A3. Late-breaking abstract 6). Patients undergoing PD have a lower risk of developing hyperkalemia than those on HD because of the continuous nature of PD treatment[5] and the fact that many patients on PD retain residual kidney function for longer than those on HD and receive high-dose diuretics, which increases the urinary excretion of K^+[6]; however, the risk of hypokalemia is increased in these patients, with a prevalence of between 10% and 36%.[7–9] In a meta-analysis of observational studies, the risk of cardiovascular mortality in patients on dialysis was increased by 1.4-fold with hyperkalemia and by 1.1-fold with hypokalemia.[4] Taken together, these studies emphasize the importance of maintaining serum K^+ concentrations within the normal range in patients on dialysis. Furthermore, hyperkalemia is associated with an increased health care burden in patients with chronic kidney disease.[10]

The goals of HD in patients with ESRD include the removal of excess K^+ that accumulates between dialysis sessions to avoid potentially serious predialysis hyperkalemia, while at the same time preventing

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A 58-year-old female patient with ESRD due to diabetic nephropathy who had emigrated from Mexico at 35 years of age was evaluated for recurrent predialysis hyperkalemia. For the past 3 years, she had undergone HD using a left brachiocephalic arteriovenous fistula with three 4-hour sessions a week with a dialysate K^+ bath concentration of 2 mmol/l. She also had a history of hypertension, peripheral arterial disease, atrial fibrillation, chronic depression, and a remote history of smoking. She was compliant with her dialysis treatment and medications, which included epoetin alfa, paricalcitol, warfarin, short- and long-acting insulin, carvedilol, atorvastatin, losartan, sevelamer carbonate, a renal vitamin, a sleeping aid pill, and an anxiolytic. Over the past 3 months, her predialysis serum K^+ concentrations had ranged from 5.5 to 6.5 mmol/l and were frequently >6.0 mmol/l. Physical examination was generally normal and laboratory tests ruled out hemolysis, rhabdomyolysis, and inadequate dialysis as potential causes. Dialysis access recirculation was ruled out and arteriovenous fistula angiogram did not show clinically significant outflow occlusion or inflow problems.

Figure 1. Case presentation. ESRD, end-stage renal disease; HD, hemodialysis.

equally serious intradialytic and postdialysis hypokalemia.[11] Currently, the key approaches to the management of hyperkalemia in patients with ESRD are decreasing the dialysate K^+ concentration, additional dialysis sessions, dietary restriction of K^+, and avoidance of medications that increase serum K^+; however, there are several issues and challenges associated with effective hyperkalemia management in these patients.

This review describes the current management of hyperkalemia in patients undergoing dialysis, including discussion of the factors that determine serum K^+ concentrations, the role of dialysis in maintaining physiologic K^+ concentrations, and the potential nondialysis options for the management of these patients.

Dialysis Kinetics: Maintaining Physiologic K^+ Concentrations

Physiology of Normal K^+ Homeostasis

The multiple mechanisms involved in maintaining normal K^+ homeostasis have been reviewed in detail previously (Figure 2).[12–14] Following administration or ingestion of K^+, extracellular K^+ concentrations are maintained within a physiologic range by a shift of K^+ into the intracellular space of skeletal muscle, liver, and red blood cells.[12,13] This internal K^+ homeostasis is primarily regulated by insulin and catecholamines.

Total body K^+ content is regulated primarily by the kidneys through changes in K^+ excretion that take place over several hours.[12] Most of the K^+ filtered through the glomerulus is reabsorbed in the proximal tubule and thick ascending limb of the loop of Henle, and the proportion of K^+ delivered to the distal nephron, the main site for fine tuning of K^+ balance, is consistently small ($\sim$10%).[12,13] The main determinants of K^+ secretion from the distal nephron include aldosterone activity and delivery of sodium and water at the distal nephron.[12] Approximately 90% of the ingested K^+ load is excreted in the urine, with the remaining 10% eliminated in the feces.[13]

Physiology of K^+ Removal During Dialysis

Each session of HD typically removes 70 to 100 mmol K^+, so in patients on a 3-times-weekly schedule, the total weekly K^+ removal is 210 to 300 mmol.[11] During HD, K^+ is removed from the extracellular fluid, which contains only 2% of total body K^+ (the remaining 98% is intracellular) (Figure 3). Diffusion is responsible for 85% of K^+ dialytic clearance, with the serum–dialysate K^+ gradient being the main determinant of K^+ removal; a small amount (15%) is removed by convection.[11,15] Therefore, the dialysate bath K^+ concentration largely determines the rate of K^+ removal. A rapid decrease in K^+ (typically 1 mmol/l) occurs in the first hour of dialysis, when the difference between serum and dialysate K^+ concentrations is the largest.[11] This is followed by a gradual decrease of a further 1 mmol/l over the next 2 hours as this gradient is reduced. Serum K^+ concentrations remain stable over the final hour of dialysis as an equilibrium is reached between the rate of K^+ dialytic removal and the shift of K^+ from the intracellular space.[11] This implies that if the burden of total body K^+ is high and removal is needed, the dialysis session needs to be extended to be effective.

Because of the intermittent schedule of HD, patients often experience fluctuations in serum K^+, from high predialysis concentrations to low intradialysis or postdialysis concentrations.[15] After HD, the ongoing shift of intracellular K^+ to the extracellular space results in a rebound of serum K^+ concentrations.[11,15] A more rapid postdialysis rebound of serum K^+ concentrations may occur with a greater serum–dialysate K^+ gradient (discussed later in this article).[11] This fluctuation in serum K^+ concentrations may increase intradialytic cell membrane polarization and potentially cause cardiac arrhythmia.[15]

In comparison with HD, the rate of K^+ removal with PD is much slower, but equally or more effective due to the continuous nature of treatment.[7] The average K^+ clearance is approximately 17 ml/min in patients on intermittent PD and approximately 7 ml/min in those on continuous ambulatory PD (CAPD). During intermittent PD, there is a rapid decrease in serum K^+ concentrations in the first 1 to 2 hours, mainly caused by a shift of K^+ into the intracellular space related to glucose absorption from the dialysate and a resulting increase in insulin release.[7] K^+ equilibration between plasma and dialysate reaches approximately 55% after a 30-minute cycle and approximately 70% after a 60-minute cycle. With CAPD, a K^+ equilibration of 83% to 88% may be achieved over >4 hours. Assuming 4-times-daily CAPD exchange with K^+-free dialysate

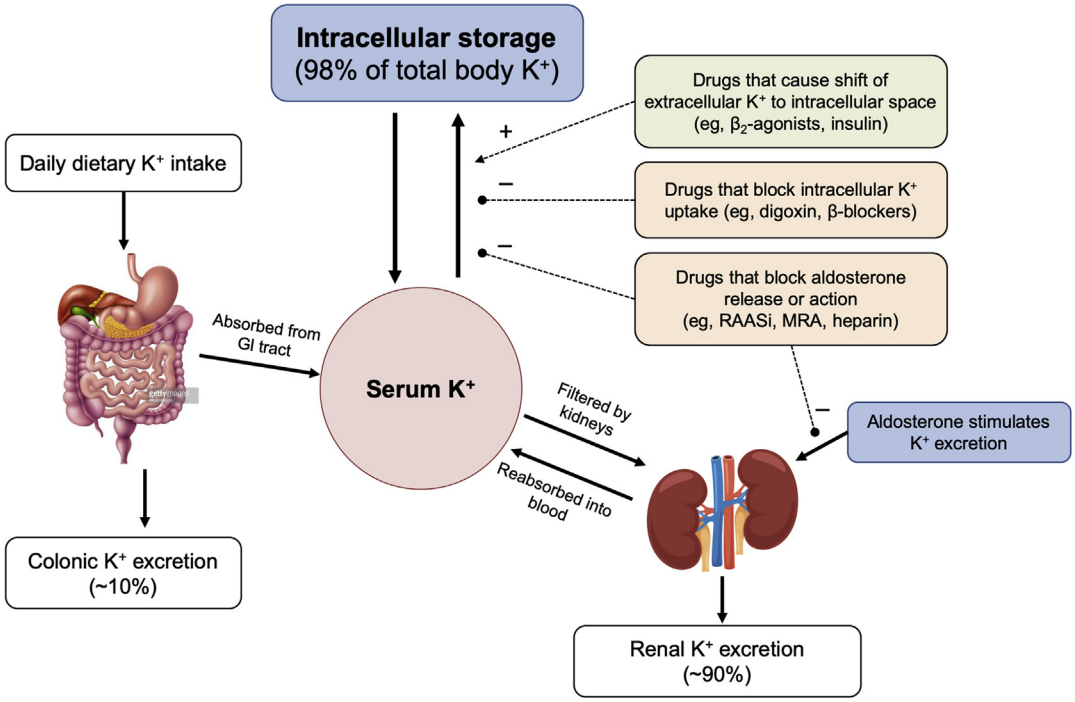

Figure 2. Overview of mechanisms controlling serum potassium (K^+) concentrations. Serum K^+ is lowered by drugs that promote intracellular uptake of K^+ and increased by drugs that block intracellular uptake through inhibition of sodium (Na^+)/K^+-ATPase transporters. K^+ excretion is stimulated by aldosterone, which increases delivery of sodium and water to the renal distal tubule. Inhibition of aldosterone secretion or its action will therefore lead to elevated serum K^+. GI, gastrointestinal; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor.

and steady-state K^+ concentrations of 5 mmol/l, it is estimated that a relatively small amount of K^+ removed is 33 to 35 mmol/d compared with normal intake (70–80 mmol/d).[7,9] Ultrafiltration may remove a further 8 to 9 mmol/d of total K^+, assuming fluid removal of 2 l/d.[7]

Patients undergoing CAPD may be prescribed loop diuretics more often than HD patients to improve urine output; however, diuretics increase urinary K^+ excretion and may potentially increase the risk of hypokalemia in these patients.[16,17]

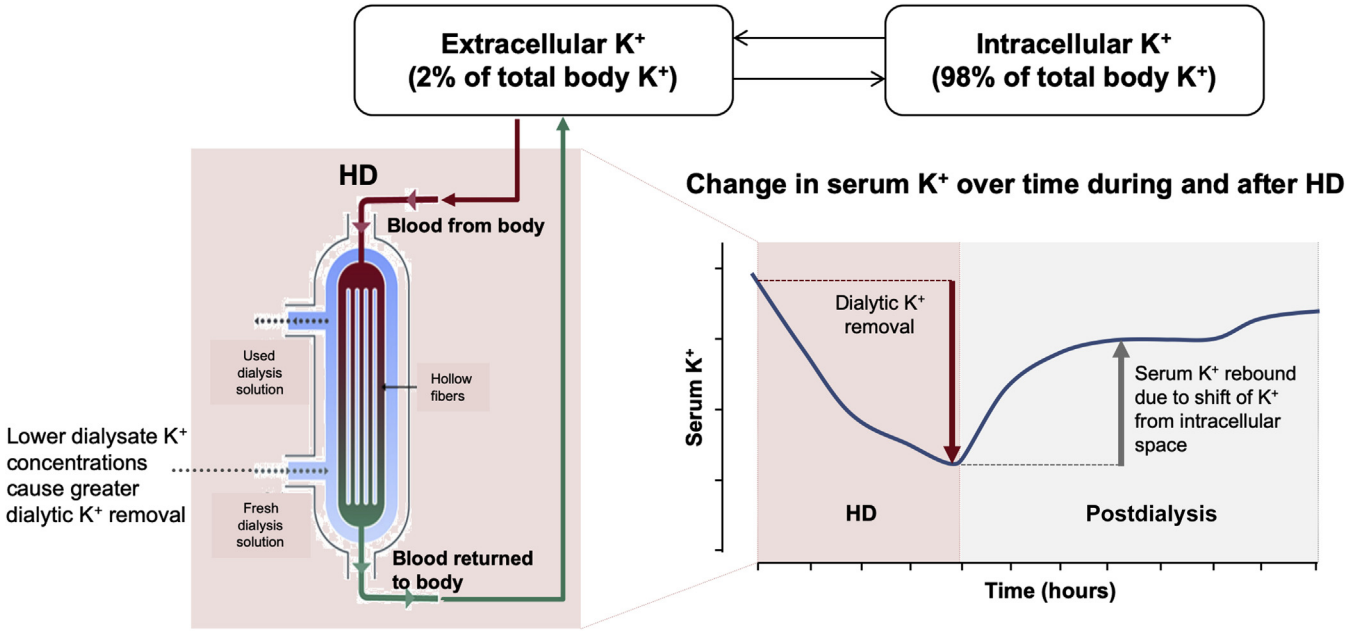

Figure 3. Physiology of potassium (K^+) removal during HD. K^+ is removed from the extracellular space by diffusion and convection during hemodialysis (HD). Lower dialysate K^+ concentrations (<2 mmol/l) create a higher serum-dialysate gradient, causing greater dialytic K^+ removal and more rapid serum K^+ rebound postdialysis than higher dialysate K^+ concentrations (≥2 mmol/l). Serum K^+ concentrations rebound after the end of hemodialysis because K^+ continues to shift from the intracellular to extracellular space.

Table 1. Summary of factors contributing to high serum K^+ concentrations in patients undergoing dialysis

Parameter	Determinants of high K^+
Dietary K^+ intake	High intake of fruits (including fruit juices) and vegetables (e.g., melons, apricots, bananas, potatoes, sweet potatoes, avocadoes) Intake of other rare food and beverages with high K^+ content (e.g., raw tamarind, prickly pear, noni juice) Increased intake of food additives and potassium chloride–containing salt substitutes
Dialysis parameters	Dialysate K^+ concentration of <2 mmol/l can increase serum K^+ fluctuations pre- vs. postdialysis Dialysate bicarbonate concentration Dialysate glucose content Dialysis session duration
Medications	Amino acids (e.g., ε-aminocaproic acid) β-blockers Digoxin PPIs Heparin RAASis (ACEis, ARBs, MRAs, direct renin inhibitors) NSAIDs K^+-sparing diuretics
Other conditions	Insulin deficiency Acidosis Hemolysis Hyperosmolality (due to glucose, contrast agents, mannitol) Rhabdomyolysis Insufficient K^+ removal by dialysis

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; K^+, potassium; MRA, mineralocorticoid receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton-pump inhibitor; RAASi, renin–angiotensin–aldosterone system inhibitor.

Based on multiple dietary inquiries, the patient profiled in Figure 1 completed a dietary intake that did not reveal high K^+-containing food at first (e.g., Mexican-made Sprite, which contains potassium citrate). Losartan was discontinued, and fludrocortisone was started; however, her predialysis hyperkalemia did not improve. Dialysate K^+ concentration was not lowered to 1 mmol/l because of concern for rapid shifts in serum K^+ concentrations. Finally, she was instructed to record everything ingested in a food diary, which revealed consumption of raw tamarind, a product known to be rich in K^+. After stopping this food, her predialysis K^+ concentrations improved, but still remained in the 5.0 to 5.8 mmol/l range after both the short and long interdialytic interval.

Causes of Hyperkalemia in ESRD

Multiple factors are responsible for determining serum K^+ concentrations in patients with ESRD, including the individual patient's diet, the dialysis prescription, medications, and other conditions or comorbidities (Table 1).[15,18–20] Management of these modifiable factors plays a crucial role in preventing hyperkalemia in patients undergoing dialysis, because as noted, the removal of K^+ by dialysis is somewhat fixed unless the dialysis prescription is modified by increasing the duration of dialysis, the frequency of treatments, or lowering the dialysate K^+ concentration in the case of HD.

Dietary Intake

According to the US National Academy of Sciences, the recommended daily adequate intake of K^+ for healthy adults is 3400 mg (87 mmol; convert mg to mmol dividing by 39) in men and 2600 mg (67 mmol) in women.[21] Among US adults, the K^+ content of a typical diet is 2323 mg/d in women and 2967 mg in men.[22]

For most people, intake of fruits and vegetables supplies most of dietary K^+.[18] The Dietary Approaches to Stop Hypertension diet, which is rich in fruits and vegetables, low in fat, and has a target K^+ intake of ≥2238 mg/1000 kcal,[23] has been shown to favorably effect blood pressure, and may reduce the risk of chronic kidney disease progression.[23,24] A plant-based diet also supplies a high fiber content, antioxidants, and trace elements,[18] and has acid-neutralization properties that may prevent further kidney damage in patients with a reduced glomerular filtration rate.[25] Furthermore, studies in patients on HD suggest that increased fruit and vegetable intake is associated with a lower risk of all-cause mortality over 12 months (Diaz-Martinez J, Martinez-Motta P, Delgado-Enciso I, et al. Diet and all-cause mortality in hemodialysis patients [abstract]. *Curr Dev Nutr*. 2019;3[suppl 1]:1550. Abstract P18–010–19), and a lower risk of noncardiovascular and all-cause mortality over 3 years.[26]

In patients undergoing maintenance HD, high dietary K^+ intake has been associated with increased 5-year mortality rates.[27] The National Kidney Foundation recommends restriction of dietary K^+ intake to approximately 2000 mg/d in patients with chronic kidney disease.[28] In patients with ESRD, restricted dietary K^+ intake also must be balanced against other nutritional recommendations, including a protein intake of 1.2 g/kg per day,[29] high fiber content, reduction of net acid load, and consumption of a heart-healthy diet consisting of fruits and vegetables.[18]

The restrictive dialysis diet is complicated and often challenging to adhere to, and may lead to deterioration in nutritional status and health-related quality of life.[30] Limiting K^+-rich foods, including fruits and vegetables, legumes, and grains, may increase the risk of cardiovascular disease in patients with chronic kidney disease.[31] Recent Kidney Disease Improving Global Outcomes guidelines recommend the development of educational materials regarding the K^+ content of foods that promote a low-K^+ plant-based diet, to be used at the clinician's discretion in patients in whom a reduction in high-K^+ foods is clinically indicated.[32] Physicians and patients should be aware that increased intake of rare foods and beverages may also contribute to elevated predialysis serum K^+ concentrations. As highlighted in the case presentation (Figure 1), besides commonly consumed high-K^+ foods

Table 2. Summary of studies investigating dialytic K^+ removal in patients on maintenance HD

Study, yr (*n*)	Dialysate K^+ concentration, mmol/l	Dialysate duration, h	Other dialysis parameters	Outcomes
Allon *et al.*, 1995 (7)[34]	2.0	4	Pretreatment with albuterol 20 mg vs. control; dialysis flow rate = 500 ml/min	Total K^+ removal: With albuterol: 37.6 mmol Control: 58.8 mmol Correlation between predialysis plasma K^+ and dialytic K^+ removal ($r = 0.69$, $P < 0.001$)
Blumberg *et al.*, 1997 (14)[35]	1.0	4	High-flux dialyzer; dialysis flow rate = 500 ml/min	Dialytic K^+ removal: 107 mmol (42% from ECF, 58% from ICS) 6-hour postdialysis rise in plasma K^+ (from 3.6 to 5.0 mmol/l), with 6-h postdialysis plasma K^+ correlated with predialysis plasma K^+ ($r = 0.78$, $P < 0.01$)
Feig *et al.*, 1981 (7)[36]	0	3	Dialysis flow rate = 500 ml/min	Dialytic K^+ removal (1.22 mmol/kg) correlated with predialysis plasma K^+ ($r = 0.75$; $P = 0.0001$)
Sherman *et al.*, 1986 (8)[37]	2.0	4	Dialysis flow rate = 500 ml/min	Dialytic K^+ removal (0.36–1.07 mmol/kg) correlated with predialysis plasma K^+ ($P = 0.03$)
Ward *et al.*, 1987 (12)[38]	2.0–3.0[a]	4.5	Dialysate contained acetate 35 mmol/l or bicarbonate 35 mmol/l (± glucose 11.1 mmol/l)	Dialytic K^+ removal: Acetate: 79.7 mmol Acetate + glucose: 62.2 mmol Bicarbonate: 72.0 mmol Bicarbonate + glucose: 54.5 mmol

ECF, extracellular fluid; ICS, intracellular space; K^+, potassium.
[a]According to patient needs.

(e.g., bananas, potatoes, melons, and avocadoes), some rare foods and beverages are rich in K^+, such as raw tamarind (K^+ content 628 mg/100 g), prickly pear (220 mg/100 g), raw hearts of palm (1806 mg/100 g), and Mexican-made Sprite (contains potassium citrate). The nutritional supplement noni juice also has high K^+ content (estimated K^+ concentration 218 mg/100 ml [56 mmol/l]).[33] Patients should be aware of the K^+ content of food additives, low-sodium salt substitutes,[18] and in rare cases, water softened with potassium chloride instead of sodium chloride. Furthermore, the recommended increased protein intake in patients with ESRD can lead to higher intake of K^+ and phosphorus, an increased risk of metabolic acidosis, and a greater need for increased fluid intake.[31] Patients should be educated and receive routine counseling regarding different sources of K^+ and the use of different cooking procedures to minimize K^+ content.[18]

In the case presentation described in Figure 1, routine counseling and education may have identified the sources of K^+ in the patient's diet and allowed for reduction in dietary K^+ content sooner. If possible, dietary regimens should be individualized by a registered dietitian.

Dialysis Parameters

As the risk of hyperkalemia in patients on HD is much higher than that in those undergoing PD, this section focuses on HD parameters that may influence K^+ concentrations.

Given the dependence of dialytic removal of K^+ on the serum–dialysate K^+ gradient, the selection of an appropriate dialysate K^+ concentration is essential for maintaining K^+ homeostasis in patients undergoing HD.[15] In a Dialysis Outcomes and Practice Patterns Study analysis, dialysate K^+ concentrations of 3 mmol/l versus 2 mmol/l showed no difference in the risk of all-cause mortality or an arrhythmia composite outcome (including sudden cardiac death and arrhythmia-related hospitalization), and had minimal effect on predialysis serum K^+ concentrations.[19] However, dialysate K^+ concentrations of <2 mmol/l may lead to a rapid reduction in serum K^+ concentrations and should be avoided, especially in patients with high predialysis serum K^+.[19] Across studies investigating the dialytic removal of K^+ in patients on maintenance HD, lower dialysate K^+ concentrations (≤1.0 mmol/l) were associated with greater dialytic K^+ removal than higher K^+ concentrations (2.0–3.0 mmol/l) (Table 2).[34–38] Three of these studies reported a significant correlation between predialysis plasma K^+ concentrations and dialytic K^+ removal,[34,36,37] and in one study that used high-flux dialysis, predialysis K^+ was correlated with 6-hour postdialysis increases in plasma K^+.[35] More recently, the PORTEND study of patients on maintenance HD demonstrated a higher incidence of predialysis hyperkalemia after the long (2-day) interdialytic interval among patients on dialysate K^+ concentrations of ≤2 mmol/l versus ≥3 mmol/l (Singh B, Block G, Lerma EV, et al. Hyperkalemia and serum potassium variability in patients on hemodialysis [abstract]. *Am J Kidney Dis*. 2017;69:A3. Late-breaking abstract 6).

The time between HD sessions also can affect serum K^+ fluctuations and clinical outcomes. Patients on 3-times-weekly HD may be exposed to excess volume and metabolic fluctuations during the long interdialytic interval that increase the risk of cardiovascular morbidity and mortality.[39] In a US Renal Data System study of cardiac and noncardiac deaths among patients

undergoing dialysis, those on HD showed a higher frequency of cardiac deaths at the end of the long interdialytic interval than on any other day of the week, whereas noncardiac deaths were evenly distributed throughout the week.[40] In contrast, patients on CAPD showed an even distribution of both cardiac and noncardiac deaths throughout the week.[40] Furthermore, a study of patients with ESRD from Australia and New Zealand showed that this pattern of increased cardiac mortality after the long interdialytic interval in patients on 3-times-weekly HD was not apparent in patients on PD, in-home HD, or receiving more than 3 sessions of in-center HD per week.[41] Similarly, data from the ESRD Clinical Performance Measures Project in US patients on 3-times-weekly HD showed that the day after the long interdialytic interval had higher rates of mortality and cardiovascular hospitalizations than any other day.[42] This included higher rates of all-cause mortality, mortality from cardiac causes, cardiac arrest, or myocardial infarction, infection-related mortality, and admission for myocardial infarction, congestive heart failure, stroke, arrhythmia, and any cardiovascular event.[42] It has been suggested that the accumulation of toxins, electrolytes, and fluid during the long interdialytic interval may lead to these adverse outcomes when combined with underlying cardiovascular morbidity.[40]

Other HD parameters can affect serum K^+ concentrations.[11] High dialysate bicarbonate concentrations are associated with a more rapid decrease in serum K^+ than lower bicarbonate concentrations, although this is most likely due to increased movement of K^+ into the intracellular space rather than an increased total body removal of K^+.[43]

In our case presentation (Figure 1), HD was conducted using dialysate K^+ concentrations of 2 mmol/l. Although the patient was experiencing repeated intermittent episodes of predialysis hyperkalemia, a lower dialysate K^+ concentration was not used because of the known risks of rapid serum K^+ fluctuations, particularly in patients with high predialysis serum K^+ concentrations and her underlying cardiac arrhythmia. The use of an oral K^+-binder (discussed in the next section) in patients on dialysis may allow for prevention of persistent predialysis hyperkalemia without the need for reducing the dialysate K^+ concentration.

Medications

Various medications may influence serum K^+ concentrations in patients undergoing dialysis, including those that promote the transfer of K^+ from the intracellular to the extracellular space.[20] For example, use of the lysine analog ε-aminocaproic acid has been associated with persistent hyperkalemia in a dialysis patient undergoing cardiopulmonary bypass,[44] and β-blockers may increase serum K^+ concentrations by ≥1 mmol/l in patients with ESRD.[45] Digoxin, which is known to block intracellular storage of K^+ through Na^+/K^+-ATPase transporters, also has been associated with refractory hyperkalemia in patients with kidney failure.[46,47] The use of unfractionated heparin during HD may lead to hyperkalemia by suppression of aldosterone release.[48] Some medications, such as insulin and the β_2-agonist salbutamol, can cause low predialysis serum K^+ concentrations by increasing intracellular K^+ uptake; however, this can result in reduced dialytic K^+ removal and exacerbate rebound hyperkalemia postdialysis.[7] Thus, use of insulin and inhaled β_2-agonists needs to be carefully taken into consideration in patients on HD who present to the emergency department with hyperkalemia and no cardiac arrhythmia and are scheduled to receive dialysis.

In patients with residual kidney function, renin–angiotensin–aldosterone system inhibitors are known to cause hyperkalemia by blocking aldosterone secretion and impairing renal excretion of K^+[20]; however, renin–angiotensin–aldosterone system inhibitor therapy is recommended in patients undergoing dialysis to manage cardiovascular disease.[49] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers do not appear to increase the risk of hyperkalemia among patients undergoing stable PD, regardless of residual kidney function.[50] The addition of the mineralocorticoid receptor antagonist spironolactone to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy in patients on PD has been shown to decrease the rate of change in left ventricular mass index and prevent left ventricular hypertrophy without increasing the risk of severe hyperkalemia (K^+ >6.0 mmol/l).[51] Similarly, in patients on HD, careful use of spironolactone is not associated with an increased risk of hyperkalemia,[52] and may reduce the risk of cardiovascular and cerebrovascular morbidity and mortality.[53] The use of eplerenone has been observed to increase the risk of hyperkalemia among patients on HD; however, its use may be safe with careful monitoring of predialysis K^+ concentrations over the first 4 weeks of therapy.[54]

Other Conditions

In patients with diabetes, insulin deficiency can lead to impaired intracellular storage of K^+, thereby increasing the risk of hyperkalemia.[55–57] Hyperglycemia and osmotic agents, such as mannitol and contrast media, can induce a transient increase in plasma osmolality that may result in the osmotic shift of water and K^+ out of cells.[55,58] This may cause extracellular fluid volume expansion, hyponatremia, metabolic acidosis, and hyperkalemia.

Therefore, the use of high-glucose solutions (D50W) without adequate doses of insulin for the treatment of hyperkalemia in patients on dialysis should be discouraged, in particular if the patient already presents with hyperglycemia. This increased shift of K^+ from the intracellular to extracellular space also can be caused by acidosis, with K^+ concentrations increasing by approximately 0.4 mmol/l with each 0.1 decrease in pH.[59] Sodium bicarbonate administration for the treatment of hyperkalemia is common in the emergency department, but its use needs to be considered carefully in patients who present with concurrent volume overload. Plasma K^+ concentrations are also increased when intracellular K^+ stores are released by conditions associated with cell lysis (e.g., hemolysis, rhabdomyolysis).[59] The breakdown of skeletal muscle cells during rhabdomyolysis leads to the release of intracellular proteins and electrolytes, including large amounts of K^+, into the blood.[60] Among patients undergoing dialysis, insufficient K^+ removal, for example, due to noncompliance with treatment (frequency, duration, or both) or access malfunction also may increase the risk of hyperkalemia.

Nondialysis Options for Managing Hyperkalemia

The Role of the Gastrointestinal Tract in K^+ Removal

In healthy individuals, a small percentage (~10%) of the daily K^+ intake is excreted by the gastrointestinal tract.[14,61] K^+ transport varies in different segments of the colon, with net secretion being observed in the proximal colon and net absorption occurring in the distal colon.[61] There is evidence, albeit conflicting, that suggests colonic K^+ secretion is increased in patients undergoing maintenance dialysis.[61,62] Therefore, the gastrointestinal tract represents a potentially important additional pathway for K^+ excretion, particularly if long-term treatment with agents that enhance intestinal K^+ removal is used to prevent predialysis hyperkalemia.[61]

K^+ secretion from the colon is mediated by large-conductance K^+ (BK) channels on the apical surface of colonic epithelial cells.[62,63] In patients with ESRD, expression of BK channels is increased compared with individuals with normal kidney function.[64] Animal studies have demonstrated that colonic secretion of K^+ is stimulated by aldosterone, most likely through increased expression of luminal BK channels in colonic crypt cells.[65] Therefore, aldosterone release plays an important role in colonic K^+ excretion in patients undergoing maintenance dialysis.

In addition to colonic excretion, enteric sensing of K^+ intake can stimulate renal secretion of K^+, even before serum K^+ concentrations increase, potentially through deactivation of sodium-chloride cotransporters in the early distal convoluted tubule and increased sodium delivery to the distal nephron.[14] Treatment with the synthetic mineralocorticoid fludrocortisone has been shown to be minimally effective for reducing serum K^+ concentrations in patients undergoing HD with hyperkalemia.[66,67]

K^+-Binder Therapy

As noted in the case presentation (Figure 1), patients on HD can experience persistent hyperkalemia, even after optimization of 3-times weekly dialysis treatment. The use of dialysate K^+ concentrations of $<$2.0 mmol/l is not recommended because of the risk of serum K^+ fluctuations, but persistent hyperkalemia is associated with significant risks, as discussed earlier. Thus, there is a potential role for oral K^+ binders in the management of patients on maintenance dialysis.

Until relatively recently, the only K^+-binders available for managing hyperkalemia were sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate. SPS, a cation-exchange resin, acts by nonspecifically binding K^+ ions in exchange for sodium ions in a K^+ concentration-dependent manner in the colon.[68,69] Although small amounts of SPS may be used to manage hyperkalemia in patients on maintenance HD,[70] its efficacy has not been proven in large prospective studies, and long-term evidence for positive outcomes is lacking. Furthermore, this K^+-binding agent has been associated with gastrointestinal intolerance and serious gastrointestinal complications.[71–73] The US Food and Drug Administration warns against using SPS with sorbitol because of cases of intestinal necrosis and other serious gastrointestinal events (e.g., bleeding, ischemic colitis, and perforation).[74] They also recommend separating the administration of SPS from other oral medicines by $\geq$3 hours because of the nonspecific binding properties of SPS.[75] Other laxatives also should be used with caution in combination with SPS. In addition, the Food and Drug Administration advises caution when administering SPS to patients who may not tolerate an increase in sodium load, as a typical 30-g dose contains approximately 120 mmol of sodium.[76]

Two other K^+-binders are now approved for the treatment of hyperkalemia: patiromer[77] and sodium zirconium cyclosilicate (SZC).[78] Similar to SPS, patiromer nonspecifically binds K^+ ions in the colon where K^+ concentrations are the highest,[79] whereas SZC exhibits non–pH-dependent binding of K^+ with high specificity throughout the gastrointestinal tract, including the small intestine (duodenum and jejunum).[80] In randomized, placebo-controlled studies of patients with hyperkalemia, serum K^+ concentrations were significantly reduced over 4 weeks with twice-daily patiromer[81–83] and were maintained within the normal range for a further 8 weeks[83] or

Table 3. Summary of studies investigating patiromer and SZC in patients on hemodialysis

Study, yr (*n*)	Study design	Treatment	Key outcomes
Bushinsky *et al.*, 2016 (6)[89]	Non-R	Patiromer 4.2 g TID for 1 wk vs. 1 wk pretreatment	Mean ± SE serum K^+ difference on patiromer day 7 vs. corresponding pretreatment day: −0.6 ± 0.2 mmol/l ($P = 0.009$) Percent of daily serum K^+ values ≥5.5 mmol/l: 38% on patiromer vs. 69% pretreatment ($P = 0.008$) Fecal K^+ excretion increased by 58% on patiromer vs. pretreatment ($P = 0.02$)
Kovesdy *et al.*, 2019 (10,126)[2]	RW	Patiromer OD ($n = 527$) SPS ($n = 852$) No K^+-binder ($n = 8747$); median follow-up 141 d	Mean change in serum K^+ before vs. after patiromer initiation: 30 d: −0.47 mmol/l ($P < 0.001$) 60 d: −0.49 mmol/l ($P < 0.001$) 90 d: −0.50 mmol/l ($P < 0.001$) Percent of patients with serum K^+ ≥6.0 mmol/l before vs. after patiromer: 30 d: 49% vs. 24% ($P < 0.001$) 60 d: 48% vs. 20% ($P < 0.001$) 90 d: 48% vs. 22% ($P < 0.001$)
DIALIZE, 2019 (196)[90]	R, DB, PC	SZC 5–15 g ($n = 97$) vs. PBO ($n = 99$) OD on nondialysis days for 4 wk	Patients maintaining predialysis serum K^+ 4.0–5.0 mmol/l after long IDI during ≥3 of 4 HD sessions[a] on SZC vs. PBO: 41% vs 1% ($P < 0.001$) Intradialytic K^+ shifts[b] on SZC vs. PBO: At randomization: 2.0 vs. 2.1 mmol/l Wk 3–9: 1.4–1.5 mmol/l vs. 1.9–2.0 mmol/l

DB, double-blind; IDI, interdialytic interval; K^+, potassium; OD, once daily; PBO, placebo; PC, placebo-controlled; R, randomized; RW, real-world; SPS, sodium polystyrene sulfonate; SZC, sodium zirconium cyclosilicate; TID, 3 times daily.
[a]Without the need for rescue therapy.
[b]Difference between pre- and postdialysis serum K^+.

for up to 52 weeks[81] with ongoing treatment. In randomized studies of SZC in patients with hyperkalemia, serum K^+ concentrations were significantly reduced within 48 hours with 3-times-daily administration of SZC,[84–87] and normokalemia was effectively maintained for 12 to 28 days with once-daily SZC.[85–87] The long-term efficacy and safety of SZC as maintenance therapy for up to 12 months also has been shown in an open-label study of outpatients with hyperkalemia.[88]

Studies in patients undergoing maintenance HD have indicated that these new K^+-binders may have a potential role in the management of these patients, including 2 studies with patiromer (an observational study and a retrospective cohort study)[2,89] and 1 randomized, double-blind, placebo-controlled study with SZC (Table 3).[2,89,90] Patiromer 3 times daily was shown to decrease serum K^+ concentrations and increase fecal excretion of K^+ in a small study of patients on HD.[89] Similarly, a real-world study of patients on HD showed an approximately 50% relative reduction in the incidence of severe hyperkalemia (K^+ ≥6.0 mmol/l) following initiation of once-daily patiromer therapy.[2] In a randomized, double-blind, placebo-controlled study of SZC in patients undergoing HD with predialysis hyperkalemia (DIALIZE), significantly more patients maintained predialysis serum K^+ concentrations of 4.0 to 5.0 mmol/l after the long interdialytic interval during at least 3 of 4 HD sessions with SZC administered on nondialysis days versus placebo ($P < 0.001$).[90] In addition, SZC was associated with less intradialytic change in serum K^+ concentrations compared with placebo.[90] These findings suggest that SZC may normalize serum K^+ concentrations between HD sessions.[90] Although both drugs effectively reduce serum K^+ concentrations, patiromer functions optimally in the colon where pH conditions allow K^+ binding after dissociation of its carboxylic acid group,[79] whereas K^+-binding with SZC may start in low pH conditions (e.g., the stomach) and is expected to continue throughout the rest of the gastrointestinal tract.[91]

Long-term treatment with new K^+-binder therapy may allow for a less-restrictive diet and optimization of renin–angiotensin–aldosterone system inhibitor therapy, as well as reducing the risk of hyperkalemia and cardiovascular events after the long interdialytic interval in patients on HD.

Conclusions

There are several issues and challenges associated with effective management of hyperkalemia in patients with ESRD undergoing dialysis. The key approaches to managing hyperkalemia in these patients are monitoring and restricting dietary intake of K^+, optimization of the dialysis prescription, and modification of medications that increase serum K^+ concentrations. Management of these modifiable factors plays a crucial role in preventing hyperkalemia in patients undergoing dialysis. The availability of new oral K^+-binders may potentially reduce the need for a highly restricted diet in patients with ESRD, and reduce the risk of potentially life-threatening hyperkalemia and the cardiovascular complications associated with rapid shifts in serum K^+ concentrations that can occur with HD. Long-term studies evaluating the safety and efficacy of the new

oral K^+-binders for the management of serum K^+ in patients undergoing dialysis are warranted.

DISCLOSURE

SB declared no competing interests. PEP has received personal fees and/or honoraria for serving on advisory boards and as a consultant for AbbVie, Akebia, AstraZeneca, Bayer, Gilead, and Reata. As principal investigator for many pharmaceutical companies, his institution has received research support. The development of this manuscript was supported by AstraZeneca.

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