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REVIEW

Hyperkalemia in patients undergoing hemodialysis: Its pathophysiology and management

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Abstract

Potassium is a major intracellular cation in the body, regulating membrane potential of excitable cells, such as cardiomyocytes and skeletal muscle cells. Because the kidney plays a critical role in controlling potassium balance, the elevation in serum potassium levels is one of the most common complications in patients with maintenance hemodialysis (MHD). In addition to reduced renal potassium excretion, the alteration in body potassium distribution owing to comorbid conditions may also contribute to dyskalemia. Besides potassium elimination through hemodialysis in MHD patients, accumulating data indicate the potential importance of extra-renal elimination involving the gastrointestinal system, which can be affected by the inhibitors of the renin-angiotensin-aldosterone system. In this article, the literature on potassium physiology in MHD patients is reviewed with an emphasis on the changes from individuals with normal kidney function. This article also summarizes the findings of recent studies on dietary control, dialysate prescription, and pharmacological therapy.

KEYWORDS

electrolyte homeostasis, extra-renal potassium secretion, hemodialysis, plant-based diet, renin-angiotensin-aldosterone system inhibitors

1 | INTRODUCTION

Potassium is the most abundant cation within cells, amounting to 3000–4000 mmol in the human adult body. Among its diverse roles, the ratio of extracellular to intracellular potassium concentration determines the resting membrane potential, regulating the function of excitable cells, such as cardiomyocytes and skeletal muscles. Because the dysregulation of extracellular potassium levels can potentially result in fatal outcomes by affecting the contractility of these cells, serum potassium concentration is strictly controlled in a very narrow range of 3.5–5 mmol/L.

The kidney plays a critical role in regulating serum potassium levels, and hyperkalemia is one of the most common complications in patients with CKD and end-stage kidney disease (ESKD) [1–3]. In addition to the reduced renal elimination of potassium, patients with kidney diseases often have multiple comorbidities that affect potassium homeostasis, including DM, metabolic acidosis, and cardiovascular diseases [4, 5]. Medications such as renin-angiotensin-aldosterone system (RAAS) inhibitors (especially mineralocorticoid receptor [MR] antagonists) and non-steroidal anti-inflammatory drugs further increase the risk of hyperkalemia [3, 6, 7]. As a result, the prevalence of hyperkalemia (serum potassium levels of 5.1 mmol/L or higher) is reported to be 25%–30% in CKD patients and in maintenance hemodialysis (MHD) patients [3, 4, 7]. In this article, we discuss physiological changes in potassium

TABLE 1 Changes in potassium balance in MHD patients

	Healthy subject	MHD patients
Potassium intake	50–100 mmol per day	Decreased
Extracellular potassium levels	2% of total body potassium	Increased or unchanged
Intracellular potassium levels	98% of total body potassium	Unchanged or decreased
Renal potassium excretion	80%–90% of daily potassium intake	Decreased or none
Fecal potassium excretion	~10% of daily potassium intake	Increased
Potassium removal by hemodialysis	None	70–100 mmol per session

Abbreviation: MHD, maintenance hemodialysis.

homeostasis in ESKD patients compared with healthy individuals, as well as recent advances in potassium management in MHD.

2 | OVERVIEW OF POTASSIUM HOMEOSTASIS IN HEALTHY INDIVIDUALS

Most of the potassium in the body is distributed within cells, such as skeletal muscle and liver, whereas only 2% is present in the extracellular fluid (Table 1). Body distribution (intracellular vs. extracellular) and the rate of excretion are the key factors that determine serum potassium levels. In the former process, the sodium-potassium-adenosine-triphosphatase (Na/K-ATPase) at the cell surface is responsible for the intracellular uptake of potassium in exchange for sodium. Several hormones, such as insulin, thyroid hormone, and epinephrine, facilitate potassium uptake into cells by stimulating the activity of Na/K-ATPase. In the latter process, the kidney excretes 80%–90% of the daily potassium intake, and the remainder is excreted through the gastrointestinal system. Recent studies have elucidated that the appropriate responses of the kidney to varied potassium intake are achieved through the coordinated action of distal convoluted tubule cells, collecting duct principal cells, intercalated cells, and the steroid hormone aldosterone. The current model indicates that aldosterone-mediated stimulation of the epithelial sodium channel in principal cells, along with the inactivation of the sodium chloride cotransporter (NCC) in the distal convoluted tubules and pendrin in intercalated cells, maximizes potassium secretion through renal outer medullary potassium (ROMK) channel [8, 9] and flow-induced potassium secretion through high conductance potassium (BK) channel [10]. In addition, as-yet-to-be-identified gut factors can also play important roles in renal adaptation to potassium [11].

Epidemiological studies have demonstrated that a high potassium intake in subjects with normal renal function is associated with favorable effects, such as reduction in salt sensitivity, blood pressure lowering, and prevention of cerebrovascular diseases [12–14]. These observations are explained by the renal and extra-renal effects of potassium, including suppression of NaCl reabsorption and modulation of sympathetic nerve activity and vascular function [15–17].

3 | CHANGES IN POTASSIUM REGULATION IN MHD PATIENTS

3.1 | Potassium removal during hemodialysis

One of the essential roles of hemodialysis is to maintain body potassium balance in ESKD patients. Sodium, which is mostly present in the extracellular fluid, is mainly removed via convection during hemodialysis, whereas approximately 85% of intradialytic potassium removal is achieved by diffusion [18], which is highly influenced by the serum-to-dialysate potassium gradient [19]. During the dialysis treatment, serum potassium levels typically decrease by 1 mmol/L in the first hour, followed by an additional decline of 1 mmol/L in the next 2 h, and a gradual decline toward a dialysate potassium concentration in the final hours [18, 20]. Given the intermittent nature of dialysis therapy, post-dialysis rebound of serum potassium levels occurs, caused by the shift of potassium from intracellular to extracellular compartments after the treatment. The decrease in serum potassium levels is attenuated by approximately 70% within the following 6 h after dialysis therapy [20, 21]. Considerable efforts have been made to elucidate the optimum dialysate potassium prescription, which will be discussed later.

3.2 | Extra-renal potassium secretion through the gastrointestinal system

Potassium removal in dialysis is typically approximately 70–100 mmol per session (210–300 mmol/week for

typical three times weekly hemodialysis) [18]. Therefore, extra-renal elimination is considered to be necessary to achieve potassium balance in MHD patients who have a potassium intake that exceeds this level (Figure 1). Several studies have shown that potassium excretion through the gastrointestinal tract is increased in ESKD patients [22, 23] (Table 1). For example, Hayes et al. conducted a metabolic balance study in 21 patients with CKD, including patients undergoing hemodialysis and found that creatinine clearance below 5 ml/min is associated with a marked increase in fecal potassium excretion, with the total amount exceeding 30% of the daily potassium intake [22, 23]. This increase in fecal potassium excretion is likely due to enhanced potassium secretion from the colon [24]. Experimental studies using animal models of CKD have shown that potassium secretion is increased in the colon but not in the small intestine [25]. Rectal dialysis has consistently shown that rectal potassium secretion is increased in patients with ESKD [26, 27]. Of importance, the clinical significance of gastrointestinal potassium secretion in advanced CKD has been highlighted by a recent study showing that time-varying laxative use was associated with lower risk of hyperkalemia in advanced CKD [28]. The role of colonic potassium secretion in ESKD has also been illustrated through a case of an MHD patient with treatment-resistant hyperkalemia associated with colon diversion surgery [29].

As for the mechanism of colonic potassium excretion, BK channel at the apical membrane [30–32], along with Na-K-2Cl cotransporter 1 (NKCC1) and Na/K-ATPase at the basolateral membrane [33–35], is considered to play a major role. In particular, mice-lacking BK channel has reduced potassium content in their feces [31], and this channel is shown to be increased in colonocytes and crypt cells in ESKD patients compared to individuals with normal renal function [36].

The upstream signaling that increases BK channel in the colon is not entirely clear. Changes in serum potassium levels have been suggested as a potential mechanism [37], and it is also possible that MR in the distal colon, which mediates a part of the electrolyte action of

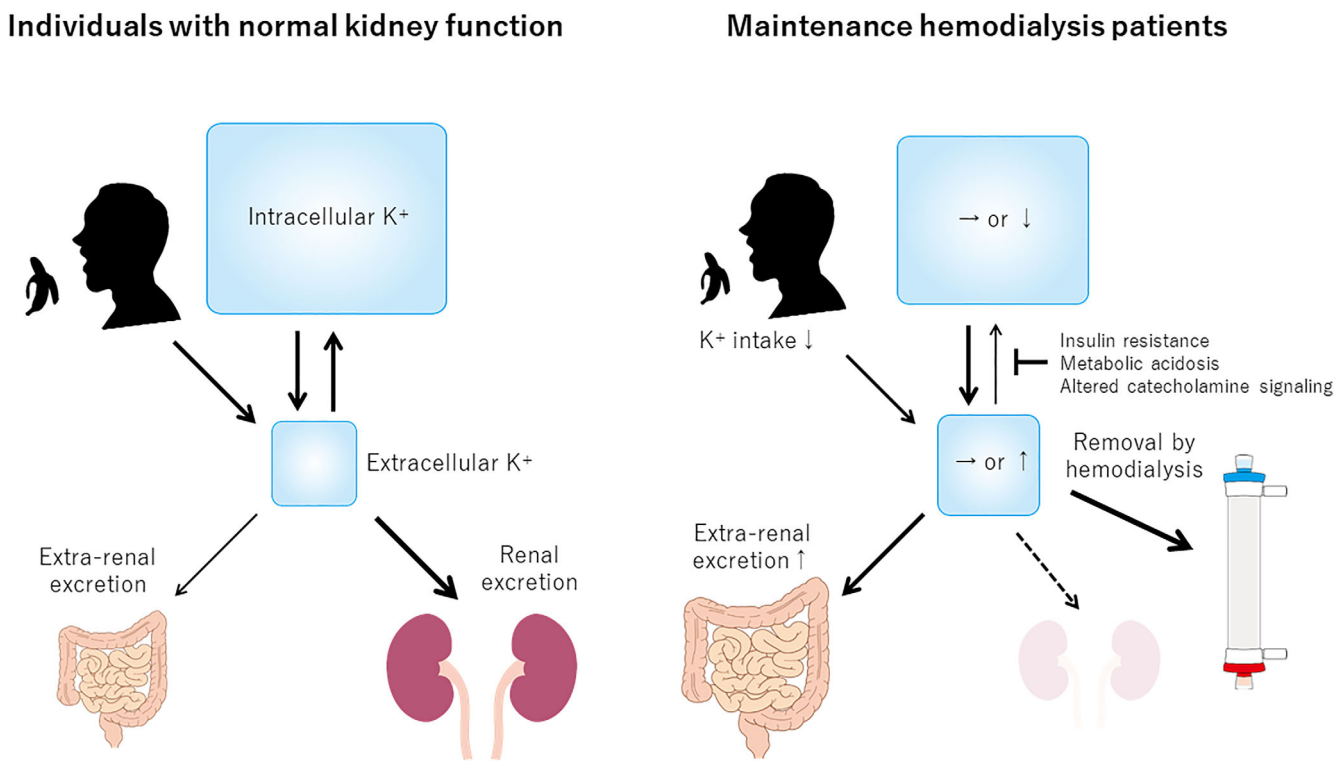

FIGURE 1 Changes in potassium homeostasis in hemodialysis patients. In subjects with normal kidney function, 98% of potassium (K^+) is present in intracellular compartment of the body. About 80%–90% of the daily potassium intake is excreted from the kidney, and the rest is excreted from the extra-renal route, including the gastrointestinal system. In maintenance hemodialysis patients, potassium is removed by hemodialysis and also by the increased excretion from the gastrointestinal tract. Although potassium intake is generally reduced, extracellular potassium levels can increase due to reduced renal potassium excretion. Impaired cellular potassium uptake owing to comorbid conditions such as reduced muscle mass, metabolic acidosis, altered catecholamine signaling, and insulin resistance can also contribute to increased serum potassium levels; in these cases, total body potassium amount can either be unchanged or reduced despite hyperkalemia

aldosterone [38, 39], is involved. Previous studies have shown that aldosterone promotes potassium secretion that is inhibited by iberiotoxin, a BK channel blocker, in rodent colonic mucosa [32]. In addition, it has been recently shown that an MR antagonist spironolactone increases serum potassium levels in MHD patients [40], a finding consistent with the role of MR in regulating colonic potassium secretion in ESKD patients.

Besides the kidney and the gastrointestinal system, excretion of electrolytes can occur from the skin. Several lines of evidence indicate the role of the skin in body sodium handling in hypertensive and ESKD patients [41, 42]. Multiple ion channels and transporters are present in the eccrine sweat glands, and a few studies have suggested that the sweat electrolyte composition, including potassium concentration, can be altered in advanced CKD patients [43, 44]. The potential benefit of exercised-induced diaphoresis in ESKD patients as an adjunct treatment has also been discussed [45, 46].

3.3 | Total body potassium content

Because only a limited portion of potassium is present in extracellular fluid, frequent observation of hyperkalemia in MHD patients does not necessarily mean that the total body potassium content is increased in these patients. In a previous study that determined the total mineral content in the body, Bilbrey et al. reported that total sodium content in the skeletal muscle of ESKD patients increased, whereas the total potassium content decreased compared with that in healthy individuals [47]. Similarly, in an autopsy study involving 24 patients undergoing hemodialysis, Butkus et al. reported that both skeletal muscle and myocardium had lower potassium content than the control group with no history of kidney disease [48]. Many other studies have evaluated body potassium levels in ESKD patients using the naturally occurring isotope ^{40}K, or by an isotope dilution technique using ^{42}K; these studies, overall, demonstrated either a decrease or no change in total potassium levels [49]. These studies suggest that hyperkalemia and intracellular potassium deficiency can coexist in a subpopulation of MHD patients. Factors that influence intracellular potassium storage, such as DM, acid/base disorders, and reduced muscle mass, may contribute to the disturbance [5, 46, 50].

3.4 | Changes in body potassium distribution

Comorbid conditions such as DM can significantly alter potassium distribution in the body. Clinical studies have shown that DM is associated with hyperkalemia both in patients with non-dialysis-dependent CKD and in MHD patients [5], which can be explained by the reduced tissue sensitivity to insulin and impaired cellular glucose uptake. Uremia in ESKD patients can also impair intracellular potassium shift through several mechanisms, such as altered responses to insulin and to catecholamine. Indeed, several studies demonstrated that uremia causes insulin resistance in advanced CKD patients [51, 52]. In addition, there are several studies suggesting that β-adrenergic receptor responsiveness is attenuated in uremic states [53]. In MHD patients, the response to isoprenaline, a non-selective β-adrenergic receptor agonist, is significantly reduced compared with healthy volunteers [54]. Experimental studies showed a selective reduction in β-adrenergic receptor-mediated adenylyl cyclase in the rat remnant model, indicating that the receptor is uncoupled from the downstream signaling mechanism in renal dysfunction [54, 55].

Metabolic acidosis frequently accompanies ESKD, which also contributes to the occurrence of hyperkalemia by preventing intracellular potassium shift. Previous studies have shown that the low serum bicarbonate levels were associated with increased serum potassium levels in non-dialysis-dependent CKD patients [5]. The significance in MHD patients seems less clear, given that no association was found between serum potassium and serum bicarbonate levels in MHD patients [5].

4 | ASSOCIATION BETWEEN SERUM POTASSIUM LEVELS AND MORTALITY IN MHD PATIENTS

Abnormal serum potassium levels are associated with all-cause mortality. Goyal et al. conducted a retrospective study of 38 689 patients with acute myocardial infarction and reported a U-shaped relationship between serum potassium levels and in-hospital deaths [56]. In this study, the odds ratio for mortality was lowest in patients with the serum potassium levels of 3.5–4.5 mmol/L, and it was significantly higher in those with serum potassium levels either ≥4.5 mmol/L or < 3.5 mmol/L [56]. In CKD patients, Luo et al. analyzed 55 266 subjects with estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 and found that the adjusted mortality incidence rate ratios in CKD patients with serum potassium levels <3.5 mmol/L and those with levels ≥6 mmol/L were more than three times higher than the reference group (4.5–4.9 mmol/L) [57]. Kashihara et al. analyzed the association between serum potassium levels and prognosis using a 10-year Japanese hospital claims database [3]. In this analysis, three-year mortality was lowest at 4.0 mmol/L, with a U-shaped association between serum

potassium concentration and mortality. Moreover, the association between hyperkalemia and increased mortality was also found in CKD population [3].

In MHD patients, Kovesdy et al. analyzed a database of 74 219 MHD patients in the United States [58]. In this study, patients with the pre-dialysis serum potassium levels of 4.6–5.3 mmol/L had the best prognosis, and the hazard ratio of all-cause mortality was significantly higher in patients with a serum potassium level of ≥ 5.6 mmol/L. An increase in the hazard ratio for all-cause mortality was also observed with the serum levels of <4.0 mmol/L. However, the estimated protein intake in these patients was also low, and the association between hypokalemia and all-cause mortality was attenuated after adjustment with nutritional status. In other studies, serum potassium levels ≥5.6 and < 3.5 mmol/L were associated with increased mortality in MHD patients [59, 60]. Recent studies also suggest that serum potassium variability prior to the initiation of dialysis therapy is associated with a higher risk of post-dialysis mortality [61].

Because of the intermittent nature of hemodialysis therapy, the timing of blood sampling is an important factor in evaluating the prognostic significance of serum potassium levels. Brunelli et al. examined serum potassium at the beginning of the week (Monday), mid-week (Wednesday), and weekend (Friday) and addressed the association with the risk of hospitalization within 96 h [62]. In this study, the serum potassium levels of 5.5 to <6 mmol/L, compared with 4.0 to <4.5 mmol/L, were associated with increased risk of hospitalization on Fridays (adjusted odds ratio, 1.68; 95% CI 1.22–2.30). However, the odds ratio for hospitalization at the same potassium levels on Mondays was moderate (adjusted odds ratio, 1.12; 95% CI 1.00–1.24) and was not increased on Wednesdays (adjusted odds ratio, 1.04; 95% CI 0.94–1.16). Using 3967 subjects of the Dialysis Outcome and Practice Patterns Study (DOPPS) in Japan, Ohnishi et al. analyzed the significance of post-dialysis serum potassium levels. The authors reported that the post-dialysis serum potassium levels of <3.0 mmol/L compared with 3.0–3.5 mmol/L were associated with increased mortality. That finding was largely attenuated by the adjustment of pre-dialysis serum potassium levels [63]. They also found that the combination of pre- and post-dialysis hypokalemia was associated with the highest risk of mortality [63].

In addition to pre- and post-dialysis potassium levels, acute changes in serum potassium levels during hemodialysis treatment can affect mortality in MHD patients. Arrhythmic risk of increased serum-to-dialysate potassium gradient has been highlighted by an early study that described the clinical characteristics of patients who had cardiac arrest while in the dialysis center [64]. In this study, a low (1 or 0 mEq/L) potassium dialysate was prescribed for 17.1% of case patients, compared with only 8.8% in controls [64]. A recent study has also shown that a high serum-to-dialysate potassium gradient is associated with electrocardiography changes, such as ST changes, QT interval dispersion, and ventricular events during 12-h post hemodialysis [65].

5 | POTASSIUM MANAGEMENT IN MHD PATIENTS

5.1 | Dietary potassium intake

Given the previous studies showing that that the majority of hyperkalemic episodes were temporally related to excessive potassium intake [66], and that the magnitude of serum potassium elevation in response to acute potassium loading was higher in ESKD patients than in healthy individuals [67], an increase in potassium intake that surpasses the output increases the risk of hyperkalemia, especially during the long dialysis interval. However, previous studies have shown a modest or no correlation between average dietary potassium intake and pre-dialysis serum potassium levels, suggesting that there is considerable inter-individual variation [5, 68]. In the study by Noori et al., potassium intake was evaluated using the food frequency questionnaire (FFQ), and there was a weak correlation ($r = 0.14$) between dietary potassium and serum potassium concentrations (which was a mean value of routine laboratory measurements for 3 months) [68]. Ramos et al. measured fasting serum potassium levels and average three-day potassium intake in 95 non-dialysis-dependent CKD patients and 117 MHD patients [5]. The study did not find a significant association between dietary potassium levels (g/1000 kcal/day) and serum potassium levels in either hemodialysis or non-dialysis-dependent CKD patients. In a multivariable analysis, factors associated with hyperkalemia in non-dialysis-dependent CKD patients were DM and metabolic acidosis whereas those in MHD patients were DM and serum creatinine levels [5]. Similarly, the three-day mean potassium intake (mg/kcal) and serum potassium levels had no significant correlation in MHD patients in the BalanceWise study [69].

It remains inconclusive how the variation in dietary potassium intake affects mortality in ESKD patients. In a retrospective analysis by Noori et al. involving 224 MHD patients, high dietary potassium intake was associated with an increased hazard ratio of death in the adjusted model [68]. In a recent prospective cohort of 415 MHD patients, however, Narasaki et al. found that the subjects

with the lowest tertile of potassium intake had higher mortality than those with the highest tertile even after adjustment for laboratory and nutritional covariates (adjusted hazard ratio of 2.65) [70]. Several studies have also addressed the significance of plant-based diet (such as fruits, vegetables, nuts, and beans) in MHD patients. Gonzalez-Ortiz et al. evaluated whether a plant-based diet was associated with serum potassium levels and nutritional status in 150 HD patients [71]. They used a healthy plant-based diet score (HPDS), which evaluates plant-derived foods positively and animal-derived foods and sugar negatively. In this study, high HPDS levels were not associated with elevated serum potassium levels, nor were there significant differences in dietary potassium density. HPDS was associated with low protein intake and a reduction in the malnutrition inflammatory score [71]. In another study, Saglimbene et al. examined the association between fruit and vegetable intake and mortality in 8078 participants of the dietary intake, death, and hospitalization in adults with ESKD treated with hemodialysis (DIET-HD) study, which is a prospective cohort study [72]. They found no difference in baseline serum potassium levels among the three groups divided according to fruit and vegetable intake, and that the hazard ratio of all-cause mortality in the highest and middle tertiles, of serving per week, was 0.80 (95% CI, 0.71–0.91) and 0.90 (95% CI, 0.81–1.00), respectively, compared with the lowest tertile group. Therefore, in this study, high fruit and vegetable intake was associated with lower mortality rates.

Although plant-based diets are often restricted in hyperkalemic ESKD patients, other dietary sources of potassium also need to be considered. For example, in the abovementioned study by Noori et al., the top five sources of dietary potassium were beef, chicken, Mexican food (such as burritos and enchiladas), hamburgers, and legumes [68]. In addition, dietary potassium content can be influenced by food additives [73, 74], and elderly MHD patients are shown to consume more processed food than non-CKD elderly individuals of the same age [75]. Another point that must be considered is that the plant-based diet is rich in dietary fiber, which positively influences microbiota and intestinal function, and bicarbonate precursors, such as citrate and acetate. In addition, excessive potassium restriction may paradoxically increase potassium absorption in the intestinal tract [76]. Thus, although dietary potassium restriction is generally recommended in CKD patients with hyperkalemia and in MHD patients, the target dietary potassium levels may need to be adjusted on a case-by-case basis according to the patients' medical conditions, nutritional status, and serum potassium levels [77, 78].

5.2 | Pharmacological treatment of hyperkalemia

Potassium-binding resins are commonly used for the management of hyperkalemia in MHD patients, and the prescription rate across countries is reported to be 20% in international studies [79]. However, the rate varies in different countries, ranging from 5% to 60% [1, 79]. ESKD patients have a compensatory increase in colonic potassium secretion, and the use of potassium binders seems to be a rational approach. Sodium polystyrene sulfonate (SPS) (and calcium polystyrene sulfonate in a few countries) has mainly been used as a potassium binder for the past 60 years. Polystyrene sulfonate, administered as a sodium salt or calcium salt, adsorbs potassium in exchange for sodium or calcium in the intestinal tract. In a study of 32 patients with acute or chronic renal failure, the average decrease in serum potassium levels 24 h after oral SPS administration was 1.0 mmol/L [80]. A recent retrospective study also confirmed that SPS reduces serum potassium levels by 0.9 mmol/L [81]. Nonetheless, the use of SPS is associated with gastrointestinal adverse events [82, 83]. In recent years, two new potassium binders, such as patiromer and sodium zirconium cyclosilicate (SZC), have been developed, and accumulating clinical evidence suggests their use as a therapeutic option in hyperkalemic MHD patients.

Patiromer is a non-absorbable potassium-exchange resin that contains a calcium-sorbitol counterion [84]. Patiromer binds potassium in the colon and reduces serum potassium levels within 7 h [85]. Patiromer does not contain sodium, and calcium is released in exchange for potassium. Clinical evidence indicates that patiromer is effective in controlling hyperkalemia in patients with heart failure and non-dialysis-dependent CKD patients for up to 8 or 52 weeks, and its use is associated with a higher proportion of patients on RAAS inhibitors [86–89]. In the Spironolactone With Patiromer in the Treatment of Resistant Hypertension in CKD (AMBER) study, the use of patiromer enabled continued use of spironolactone in CKD patients (eGFR 25–45 ml/min per 1.73 m^2) with uncontrolled resistant hypertension [90].

Several clinical studies have tested the efficacy of patiromer in MHD patients [91, 92]. In a study by Bushinsky et al., 12.6 g of patiromer per day (4.2 g three times daily) for a week decreased serum potassium levels by up to 0.6 mmol/L in six MHD patients [91]. Kovesdy et al. performed a retrospective analysis using electronic health record data from MHD patients and reported a decrease in a serum potassium concentration of 0.5 mmol/L after the use of patiromer [93]. Amdur et al. evaluated serum and fecal potassium levels in 27 anuric MHD patients

with hyperkalemia [92]. In this study, participants received patiromer (16.8 g daily) for 12 weeks after 2 weeks without treatment, followed by 6 weeks of no treatment. Patiromer reduced serum potassium levels from 5.7 to 5.1 mmol/L, and serum potassium levels rebounded to 5.4 mmol/L post-treatment. Stool potassium significantly increased during the treatment phase and decreased significantly after the end of treatment, confirming that patiromer promotes intestinal excretion of potassium [92].

The observed adverse effects of patiromer include reduced serum magnesium levels and gastrointestinal symptoms (such as constipation, nausea, and diarrhea). The occurrence of hypomagnesemia (3%–7%) [86, 87] may be due to the adsorption of cations, such as magnesium in addition to potassium. The decrease in serum magnesium levels was also observed in MHD patients, and the monitoring of serum magnesium levels is recommended especially in cases with an increased risk of arrhythmia [92].

Calcium released from patiromer can in theory bind phosphorus, reducing its absorption in the intestine. Bushinsky et al. found that patiromer reduced serum phosphorus levels from 7.0 to 6.2 mg/dl, supporting this possibility [91]. On the other hand, no obvious changes in serum phosphorus levels were observed in another study [92]. Although the reason for this difference is unclear, it may be related to the difference in the administration regimen of patiromer and the concomitant use of phosphate binders.

Another new potassium binder, SZC, is a non-absorbable inorganic crystal that selectively adsorbs potassium ions in exchange for hydrogen or sodium ions. Several clinical trials to date have shown that SZC is effective in controlling hyperkalemia. In a phase-III study involving hyperkalemic patients (serum potassium levels of 5.0–6.0 mmol/L), SZC dose dependently reduced serum potassium at the initial phase (up to 0.7 mmol/L at 48 h) [94]. In the 12-day maintenance phase, serum potassium levels were maintained at 4.7 and 4.5 mmol/L in the SZC 5 g per day group and 10 g per day group, respectively, compared with >5.0 mmol/L in the placebo group [94]. Similarly, in the Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) trial, SZC reduced serum potassium levels to normal levels within 48 h in outpatients with hyperkalemia, and a higher proportion of patients remained in the state of normokalemia in SZC groups compared with placebo group [95]. The long-term efficacy of SZC was confirmed in a 12-month phase-III study, and normokalemia was maintained in the majority of patients without dose adjustment of RAAS inhibitors [94]. Adverse events related to SZC included edema and hypokalemia in the HARMONIZE study [95].

The efficacy of SZC in MHD patients was evaluated in the phase-IIIb, multicenter, prospective, randomized, double blind, placebo-controlled study to reduce incidence of pre-dialysis hyperkalemia With SZC (DIALIZE) trial [96]. This study included 196 MHD patients with hyperkalemia (pre-dialysis serum potassium levels of >5.4 mmol/L), who received 5 g of placebo or SZC daily on non-dialysis days, which was adjusted (maximum 15 g) to achieve normokalemia. In this study, the proportion of patients who maintained pre-dialysis serum potassium of 4.0–5.0 mmol/L was 41% (40 of 97) in the SZC group, compared with 1% (1 of 99) in the placebo group. The proportion of patients requiring rescue therapy to lower potassium was 5.1% (5 of 99) in the placebo group and 2.1% (2 of 97) in the SZC group. Intradialytic weight gain and rates of serious adverse events were similar between the two groups. The results of these interventional studies (summarized in Table 2) indicate that new potassium binders are effective in controlling pre-dialysis potassium levels, and may allow fewer restrictions on dietary potassium intake in MHD patients.

5.3 | Dialysate potassium concentrations

Another important option for optimal potassium management is to modify the dialysate potassium concentration. Whereas excess potassium that accumulated in the body needs to be efficiently removed, acute changes in serum potassium levels and severe post-dialysis hypokalemia can adversely affect mortality [63, 64]. Evidence suggests that a high serum-to-dialysate potassium gradient is associated with short-term hospitalization [97]. In the phase-5 DOPPS study (2012–2015), the most common prescription was 2.0–2.5 mmol/L of dialysate potassium, although the concentrations of prescribed dialysate potassium considerably vary per country [98]. For example, a dialysate potassium concentration of ≥ 3.0 mmol/L was used in 75% of patients in Germany, whereas a concentration of 2.0 mmol/L was uniformly used in Japan. The concentrations of 1.0–1.5 mmol/L were used in 62% of patients in Spain [98].

Several studies have evaluated the optimal dialysate potassium concentration. In one study, the use of dialysate with ≥3 mmol/L of potassium in patients with hyperkalemia (≥5 mmol/L) was associated with increased mortality after full multivariable adjustment [58]. In another study, the use of low potassium dialysate (<2 mmol/L) was associated with sudden cardiac arrest within dialysis facilities [99]. In this case–control study, the probability of sudden cardiac arrest with the use of dialysate potassium <2 mmol/L was higher when pre-dialysis potassium levels were lower [99]. Using the DOPPS data of 37 765

TABLE 2 Interventional studies that evaluated the effects of patiromer and SZC in MHD patients

Study (year)	*N*	Patient characteristics	Medication (dose)	Study design	Outcome
Bushinsky et al. (2016)	6	MHD patients with the serum potassium levels of 5.5 mmol/L or higher	Patiromer (12.6 g/day)	Pretreatment period for 1 week and patiromer treatment period for 1 week	Maximal decrease of serum potassium was 0.6 mmol/L and fecal potassium excretion increased by 58% in the treatment period
Amdur et al. (2020)	27	Anuric MHD patients with the predialysis serum potassium levels of 5.1 mmol/L or higher on more than two occasions	Patiromer (16.8 g/day)	Two weeks of no intervention, 12 weeks of patiromer treatment, and 6 weeks of no treatment	Mean potassium levels decreased by 0.6 mmol/L during treatment period and rebounded post-treatment; stool potassium levels significantly increased during the treatment period
Fishbane et al. (2019)	196	MHD patients with the predialysis serum potassium levels of >5.4 mmol/L after the long interdialytic interval and > 5.0 mmol/L after one short interdialytic interval	SZC (5–15 g/day)	A randomized, double blind, placebo-controlled study consisting of eight-week treatment period and two-week follow-up period	41.2% in SZC group maintained the predialysis serum potassium levels of 4.0–5.0 mmol/L during four-week stable-dose evaluation period, as compared with 1.0% in placebo group

Abbreviations: MHD, maintenance hemodialysis; SZC, sodium zirconium cyclosilicate.

participants in 12 countries, Jadoul et al. analyzed the association between several clinical practices with sudden death and reported that the sudden death rate was higher for dialysis potassium ≤1.5 or 2–2.5 mmol/L compared with ≥3 mmol/L (hazard ratio, 1.39 for ≤1.5 mmol/L and 1.17 for 2–2.5 mmol/L) [100]. However, in a study that compared all-cause mortality and arrhythmia composite outcomes between the two most commonly used dialysate potassium prescriptions (2 vs. 3 mmol/L), the differences in the outcomes between the two dialysate potassium prescriptions were not significant [98]. Hazard ratios for all-cause mortality were in the range of 0.94–1.03 across four subgroups with the pre-dialysis serum levels of <4.0, 4.0–5.0, 6.1–6.0, and > 6.0 mmol/L [98].

In a recent report by Mercadal et al., the relationship between dialysate potassium prescription and prognosis was examined using 25 629 French Renal Epidemiology and Information Network (REIN) registry data [101]. More than 90% of the institutions used two or more potassium concentration dialysates, and the combination of 2 and 3 mmol/L was the most common (40%), followed by that of three dialysate prescriptions (<2, 2, and 3 mmol/L; 37%). The dialysis units that used the two and three dialysate formula had adjusted mortality hazard ratios of 0.91 (95% CI 0.82–1.01) and 0.84 (95% CI 0.75–0.93), respectively, compared with those using a single dialysate formula [101]; this result indicates the potential benefit of increased diversity in the dialysate potassium prescriptions.

5.4 | Other factors

Other modifiable factors that can influence serum potassium levels in MHD patients include the gastrointestinal function, acid/base balance, glycemic control, and medications that alter serum potassium levels. The use of RAAS inhibitors is associated with changes in serum potassium levels even in MHD patients especially at a higher dose [40, 102, 103], likely through attenuating extra-renal potassium excretion. A recent study demonstrated that the laxative use was associated with the reduced risk of hyperkalemia in advanced CKD [28], underscoring the importance for the control of constipation.

6 | FUTURE PERSPECTIVE

This article reviewed the literature on the factors affecting potassium homeostasis and summarized the current evidence on the management of potassium in MHD patients. Regarding the modalities to maintain potassium balance in MHD patients, we consider there are several important areas that need further evaluation. First, it remains to be determined whether strict potassium restriction (such as 1500–2000 mg of daily potassium intake) should be applied, or whether more liberalized diet with an aid of potassium binders is favorable in MHD patients. In the management of phosphate balance, studies have shown that prescribed phosphate restriction was associated

with poorer indices on nutritional status and did not improve survival in MHD patients [104]. It has also been reported that treatment with a phosphate binder was associated with a better nutritional status and improved survival [105]. Although studies, indicate that the serum potassium levels of 5.6 mmol/L or higher are associated with increased mortality in MHD patients, there has been a weak or no correlation between average pre-dialysis serum potassium concentrations and mean dietary potassium levels [5, 58, 68]. A plant-based diet has also been shown to be associated with reduced malnutrition score and all-cause mortality [72]. Given the advent of new potassium binding agents, future studies that determine the optimal amounts and sources of dietary potassium, as well as the role of adjunctive use of potassium binders (on-demand use, every other day dosing, etc.), would be helpful.

Second, there still seems to be room for improvement in potassium control during hemodialysis treatment. Although there are no randomized controlled data that show the best dialysate prescription, recent studies indicate a potential benefit of adjusting dialysate potassium prescription depending on patients' conditions [98]. The optimized approaches to safely and effectively remove potassium during hemodialysis, as well as the risk and benefit of personalized interventions, need to be evaluated in future studies.

Finally, it is unclear whether hyperkalemic HD patients would benefit from continued use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Several recent studies have shown that discontinued ACE inhibitor or ARBs therapy was associated with a higher risk of mortality and cardiovascular events in advanced CKD patients (eGFR < 30 ml/min per 1.73 m^2) [106, 107]. Interestingly, a recent case–control study involving 8229 MHD patients has shown that the use of ARBs, but not of ACE inhibitors, was associated with lower all-cause mortality rate [108]. Thus, although the use of RAAS inhibitors can increase the risk of hyperkalemia even in anuric MHD patients [40, 102], the benefit of stopping ACE inhibitors and ARBs in controlling serum potassium levels needs to be balanced against the risk of cardiovascular diseases in MHD patients. Similarly, previous studies have addressed the possible cardiovascular protective effects of MR antagonists in CKD requiring dialysis, and a very recent meta-analysis concluded that MR antagonists probably reduces the risk of all-cause and cardiovascular death in this population [109]. Large ongoing clinical trials [110, 111] will hopefully provide solid evidence on the protective effects, as well as the effects on serum potassium levels, of MR antagonists in ESKD patients.

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CONFLICT OF INTEREST

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