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CKJ REVIEW

Personalizing electrolytes in the dialysis prescription: what, why and how?

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ABSTRACT

Maintenance hemodialysis patients suffer from multiple comorbidities and treatment-related complications. A personalized approach to hemodialysis prescription could reduce some of these burdens by preventing complications such as excessive changes in blood pressure, arrhythmias, post-dialysis fatigue and decreased quality of life. A patient-centered approach to dialysate electrolyte concentrations represents one such opportunity. In addition to modifications in dialysate electrolyte concentrations, consideration of individual factors such as patients' serum concentrations, medication profiles, nutritional status and comorbidities is critical to tailoring hemodialysis prescriptions to optimize patient outcomes. The development of personalized dialysis treatment depends on the collection of comprehensive patient data, advances in technology, resource allocation and patient involvement in decision-making. This review discusses how the treatment of maintenance hemodialysis patients could benefit from individualized changes in certain dialysis fluid components.

Keywords: dialysate electrolytes, end-stage kidney disease, maintenance hemodialysis, personalized medicine

There are more than 2 million patients who receive maintenance dialysis therapies globally. While the incidence of chronic kidney disease (CKD) and progression to end-stage kidney disease (ESKD) have further declined due to recently approved medications such as sodium-glucose cotransporter 2 inhibitors, the total number of ESKD patients on maintenance dialysis therapy is projected to increase over the next decade. Combined with these projections, patients on maintenance dialysis therapy suffer from unacceptably high morbidity and mortality rates.

Despite the recent advances in science and technology, there has been minimal change in how maintenance dialysis is delivered in ESKD patients. Due to growing numbers and needs of ESKD patients, healthcare systems encourage nephrologists and dialysis providers to treat as many patients as possible, while at the same time being cost-effective, minimizing tests and costly treatments, and being practical. To achieve these goals, one needs to minimize variability, and potentially avoid innovative approaches that would require additional resources. Indeed, the current management of maintenance dialysis patients is all-inclusive, provides standardized prescription and is performed on an unyielding schedule. On the other hand, patients with ESKD live with a high symptom burden and suffer from high morbidity and mortality, and are likely to benefit from a more personalized approach [1]. Given the complexity and comorbidity burden of patients on maintenance dialysis, a multi-pronged approach to their care is necessary. Precision medicine is the evidence-based tailoring of prevention and treatment procedures that take into account individual characteristics to improve outcomes and reduce disease burden [2]. It provides a potential solution to improving the overall well-being of ESKD patients on maintenance dialysis. In this review, we will discuss certain components of hemodialysis (HD) fluid

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(i.e. dialysate) where improved outcomes can be achieved by a personalized approach.

WHY PERSONALIZE DIALYSATE PRESCRIPTION?

Despite its life-saving characteristic, the HD procedure is a metabolically very stressful event. The symptoms and clinical complications related to a single HD procedure are multiple and include, but are not limited to, intradialytic hypotension or hypertension, cramps, fatigue and dialysis-associated arrhythmias. Some of these acute complications also have medium- and long-term impacts, such as frailty and reduced quality of life, deterioration of the nutritional status, predisposition to infections and worsening cardiovascular disease profile [3]. In that respect, modifications in the dialysate composition can help reduce or even eliminate some of these problems. In doing so, we will primarily focus on several important outcomes such as arrhythmias, and intradialytic blood pressure changes and associated clinical symptoms.

Multiple studies suggest that cardiac arrhythmias are highly common in maintenance HD (MHD) patients. In a very detailed study using implanted loop recorders in 66 patients over a 6-month period, Roy-Chaudhury *et al*. found that 66% patients had a total of 1678 arrhythmia events [4]. Of these events, 1461 (87%) were bradycardias and 41% of the patients had atrial fibrillation, although it was not considered to be at a clinically significant threshold. In addition, there were 14 episodes of asystole and 1 sustained ventricular tachycardia during the study. The session following the longest interdialytic period was the one with the highest predisposition to the risk of arrhythmia. This study also showed that the current standard of care may have triggered a fatal arrhythmia and was a modifiable cause of sudden death. On the other hand, in a study by Jukema *et al*., the prophylactic use of intracardiac defibrillators (ICDs) did not reduce the risk of sudden cardiac death in dialysis patients [5], suggesting that additional data are required to assess the benefits and risks of prophylactic use of ICDs while simultaneously addressing the underlying cause and focusing on preventive strategies to reduce the development of cardiac arrhythmias. The composition of the dialysate, in particular sodium, potassium, calcium, bicarbonate and magnesium, which play critical roles in maintaining the stability of the cardiac rhythm and blood pressure during dialysis represent important variables to consider in minimizing the risk of arrhythmias and maintaining cardiovascular stability during dialysis [6, 7].

It should also be noted that a personalized approach to dialysate prescription may result in higher costs compared with conventional dialysate concentrations. These expenses may include additional laboratory testing, specialized equipment, increased staffing and training, complex formulations, advanced technology, monitoring visits, and research and development costs. These cost and feasibility issues need to be considered when applying individual changes in the dialysate prescription.

SPECIFIC ELECTROLYTES IN THE DIALYSATE

Table 1 summarizes the key studies that have examined the clinical outcomes of different serum electrolyte concentrations in patients with stage 3–5 CKD. Studies comparing different serum electrolyte concentrations with clinical outcomes suggest that both low and high serum electrolyte concentrations may have adverse effects on cardiovascular risk and mortality. This situation presents a great challenge and effort in adjusting serum and dialysate electrolyte concentrations in ESKD patients. Table 2 summarizes the studies that have investigated the clinical outcomes in association with different dialysate electrolyte concentrations utilized in MHD patients.

Potassium

Potassium is an essential electrolyte that is important for many bodily functions, such as maintaining proper nerve function, fluid balance and muscle contraction, including the contraction of the heart muscle. The most serious consequences of hyperkalemia are muscle weakness or paralysis, cardiac conduction abnormalities and cardiac arrhythmias [47]. Hypokalemia can also lead to a variety of arrhythmias and contribute to high blood pressure. Significant muscle weakness occurs at serum potassium concentrations below 2.5 mEq/L (or 2.5 mmol/L) as well as with overt hyperkalemia [48], so maintaining a proper serum concentration of potassium in the body is essential for overall health.

Hyperkalemia is highly common in ESKD patients on MHD. In a study using Dialysis Outcomes and Practice Patterns Study (DOPPS) data, it was shown that the prevalence of pre-dialysis potassium concentration above the upper limit of 5 mEq/L was approximately 74%. In the RE-UTILIZE study, more than 15% of patients had a pre-dialysis potassium concentration >6 mEq/L at least once a year [11]. In another study from DOPPS, Karaboyas *et al*. examined serum and dialysate potassium concentrations in 70 597 patients and showed noticeable variability in pre-dialysis serum potassium concentrations between countries [27]. Between 2012 and 2015, the most prescribed dialysate potassium concentrations in the world were 2.0–2.5 mEq/L (75% of patients in USA and >99% of patients in Japan). While Germany had the highest dialysate potassium concentration with 75% of patients with ≥3.0 mEq/L, Spain had the lowest concentrations of 1.0–1.5 mEq/L in most dialysis units. Comparing outcomes for 2 mEq/L versus 3 mEq/L dialysate potassium concentrations, there was no evidence of a difference in mortality risk. Another important finding in this study was that changes in dialysate potassium concentration had a minimal effect on pre-dialysis serum potassium concentrations. Overall, it was recommended that the difference between pre-dialysis serum potassium and dialysate potassium concentration should be minimized. In line with the observations above, Ferrey *et al*. showed that the risk for adverse outcomes are amplified when very low dialysate potassium concentrations (i.e. 1 mEq/L) are used in patients with pre-dialysis potassium concentrations >5 mEq/L as compared with dialysate potassium concentrations of 2 mEq/L or 3 mEq/L [28]. Finally, Pun *et al*. conducted a case–control study comparing sudden cardiac arrest (SCA) events in MHD patients and found that the highest risk of SCA due to low dialysate potassium was observed in patients with pre-dialysis serum potassium levels <5.1 mEq/L [24]. This study emphasizes the importance of regular monitoring of serum potassium levels and avoiding low potassium dialysate even in patients with normal-range pre-dialysis serum potassium levels.

Overall, these data suggest that selection of dialysate potassium concentration should consider pre-dialysis serum concentrations as well as assessment of total body potassium stores using several easy approaches such as obtaining medical and diet history, physical examination, reconciliation of current medications and symptom monitoring (Fig. 1). In a patient where pre-dialysis serum potassium is consistently below 4 mEq/L, a detailed assessment of their nutritional status, especially

Table 1: Studies about serum concentrations and their association with clinical outcomes.

	Authors	Study description	Number of patients	Outcomes and findings	Publication year
Potassium	Kovesdy *et al.* [8]	Retrospective cohort study	81 013 MHD patients	- The optimal survival was associated with serum potassium levels between 4.6 and 5.3 mEq/L (mmol/L), while lower or higher levels were linked to increased mortality - Hyperkalemic patients with elevated pre-dialysis serum potassium levels (≥5.0 mEq/L) had better survival when lower dialysate potassium concentrations were used	2007
	Korgaonkar *et al.* [9]	Prospective cohort study	820 patients with CKD stage 3–5	- Low serum potassium levels (≤4.0 mmol/L) were associated with increased mortality and risk for ESKD - Higher levels (≥5.5 mmol/L) were linked to the composite outcome of cardiovascular events or death	2010
	Luo *et al.* [10]	Retrospective cohort study	55 226 CKD patients with stage 3–5 without RRT	- Within specific categories or subgroups based on eGFR, serum potassium levels showed U-shaped associations with major adverse cardiovascular events, hospitalization and discontinuation of medications that block the RAAS	2016
	Agiro *et al.* [11]	Retrospective cohort study	9347 MHD patients	- 6910 hyperkalemia (potassium >5.0) events in a year - Increased prevalence of pre-dialysis hyperkalemia over time, including within 1 month, 3 months and 1 year - A significant proportion of patients on MHD experienced recurrent episodes of pre-dialysis hyperkalemia, even with long-term dialysis therapy	2022
Magnesium	Sakaguchi *et al.* [12]	Cohort study	142 555 MHD patients	- Total 11 454 deaths, 4774 (41.7%) were attributed to CVD and 6680 (58.3%) to non-CVD - A J-shaped curve suggesting that the 2–3 mg/dL range is the optimal range for the serum magnesium concentrations	2014
	de Roij van Zuijdewijn *et al.* [13]	*Post hoc* analysis	365 MHD patients	- Lower serum magnesium was associated with increased cardiovascular mortality and sudden death HRs per 0.1 mmol/L increase in serum magnesium were as follows: - 0.85 (95% CI 0.77–0.94) for all-cause mortality - 0.73 (95% CI 0.62–0.85) for cardiovascular mortality - 0.76 (95% CI 0.62–0.93) for sudden death	2015
Calcium	Foley *et al.* [14]	Prospective cohort study	256 MHD and 157 PD patients	- Chronic hypocalcemia[a] was associated with *de novo* ischemic heart disease (RR 5.23, $P < .001$), recurrent ischemic heart disease (RR 2.46, $P = .006$), *de novo* cardiac failure (RR 2.64, $P < .001$) and recurrent cardiac failure (RR 3.30, $P < .001$)	1996
	Wang *et al.* [15]	Prospective cohort study	35 144 MHD patients	- A total of 8102 (23%) patients died during the median follow-up of 1.3 years (interquartile range, 0.6–2.3 years) - Higher serum corrected total calcium and higher ALP concentrations consistently showed a higher risk of mortality P_{trend} (<.001 for both), independent of residual renal urea clearance strata ($P_{interaction} = .34$) and $P_{interaction} = .53$, respectively)	2017

Table 1: Continued

	Authors	Study description	Number of patients	Outcomes and findings	Publication year
Bicarbonate	Lowrie *et al.* [16]	Retrospective cohort study	12 099 MHD patients	- A U-shaped relationship exists between serum BIC concentrations and all-cause mortality, with increased risk observed for levels below 17.5 mEq/L or above 28 mEq/L	1990
	Bommer *et al.* [17]	Prospective cohort study	7140 MHD patients	- The lowest mortality rate was found in the quartile of patients with midweek pre-dialysis BIC concentrations of 19.1–21.0 mEq/L (mmol/L) - U-shaped relationship between serum BIC concentrations and mortality, indicating a higher risk for patients in a mid-week session with pre-dialysis serum BIC concentrations below 18 mEq/L or above 27 mEq/L	2004
	Wu *et al.* [18]	Retrospective cohort study	56 385 MHD patients	- Increased in mortality risk for patients with pre-dialysis serum BIC <19 mEq/L	2006
Sodium	Waikar *et al.* [19]	*Post hoc* analysis	1549 MHD patients	- Lower pre-dialysis serum sodium concentration is associated with an increased risk of death - Each 4-mEq/L increment in serum sodium concentration was associated with a HR for all-cause mortality of 0.84 (95% CI 0.78–0.90)	2011
	Hecking *et al.* [20]	Prospective cohort study	11 555 MHD patients	- Higher serum sodium concentrations were associated with lower adjusted all-cause mortality in a continuous model (HR 0.95 per 1 mEq/L higher; 95% CI 0.93–0.97)	2012
	Nigwekar *et al.* [21]	Prospective cohort study	6127 MHD patients	- Hyponatremia in incident HD patients is associated with hypercalcemia, elevated ALP concentrations, hypoparathyroidism and increased 1-year mortality - Hyponatremic patients had higher mortality rates compared with normonatremic patients (HR 1.59; 95% CI 1.34–1.87) and in multivariable analyses (HR 1.42; 95% CI 1.19–1.69)	2013
	Han *et al.* [22]	Data from two cohort studies	2182 CKD patients with stage 3–5, without RRT	- Mortality risk was significantly greater at $135 < Na \leq 140$ mEq/L (adjusted HR 1.68, $P = .02$) and Na ≥144 mEq/L (adjusted HR 2.01, $P = .01$)	2015
	Cole *et al.* [23]	Retrospective cohort study	326 CKD patients with stage 3–5, without RRT	- Higher serum sodium concentration is associated with the progression of CKD, independently of other established risk factors - 1 mmol/L increase in baseline serum sodium was associated with a 1.5 mL/min/1.73 m^2 decline in eGFR during the study period (95% CI 0.9, 2.0)	2019

[a]Chronic hypocalcemia (serum calcium concentration <8.8 mg/dL, serum ionized calcium concentration <4.7 mg/dL) is often due to inadequate levels of parathyroid hormone or vitamin D, or resistance to these hormones.
PD: peritoneal dialysis; RRT: renal replacement therapy; RAAS: renin-angiotensin-aldosterone system:, CVD: cardiovascular disease; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; RR: relative risk; ALP: alkaline phosphatase; BIC: bicarbonate; Na: sodium.

Table 2: Studies looking at serum and dialysate concentrations and reported outcomes.

	Authors	Study description	Number of patients	Outcomes	Publication year
Potassium	Pun *et al.* [24]	Case–control	2134 MHD patients	- 502 in-center SCAs - Increased risk with last dialysate potassium <2 mEq/L before SCA (OR 2.06; 0.95 CI 1.48–2.86) - Increasing risk of dialysate potassium <2 mEq/L with lower serum potassium; no benefit of dialysate potassium <2 mEq/L among patients who are hyperkalemic	2011
	Jadoul *et al.* [25]	Retrospective cohort study	37 765 MHD patients	- Compared with a dialysate potassium level of ≥3 mEq/L the sudden death rate was higher for dialysate potassium levels ≤1.5 and dialysate potassium levels of 2–2.5 mEq/L	2012
	Buiten *et al.* [26]	Secondary analysis of randomized trial in the Netherlands	40 MHD patients	- 428 episodes of atrial fibrillation among 14 patients - AF episodes associated with lower dialysate potassium (mean 1.6 mEq/L) compared with patients without atrial fibrillation (2 mEq/L)	2014
	Karaboyas *et al.* [27]	Prospective cohort study	45 511 MHD patients	- 3300 had an arrhythmia composite event during follow-up - Significant association between dialysate potassium, serum potassium levels - Increased risk of mortality and arrhythmia events in HD patients	2017
	Ferrey *et al.* [28]	Prospective cohort study	624 MHD patients	- 161 death events observed - Lower dialysate potassium of 1 mEq/L was linked to higher overall mortality, particularly in patients with serum potassium ≥5 mEq/L	2018
Magnesium	Del Giorno *et al.* [29]	Randomized cross over study	39 MHD patients	Magnesium dialysate concentrations of 0.50 vs 0.75 mmol/L, 6-month follow-up - A significant reduction in systolic blood pressure of 12.96 mmHg (–24.71 to –1.22, P = .03) was observed on the higher dialysate magnesium concentrations compared with the standard one	2020
	Bressendorff *et al.* [30]	*Post hoc* analysis	57 MHD patients	Magnesium dialysate of 0.50 vs 1.00 mmol/L, 28-day treatment period - High dialysate magnesium treatment may have beneficial effects on calcification, inflammation and bone turnover in HD patients	2021
Bicarbonate	Gabutti *et al.* [31]	Randomized controlled trial	26 MHD patients	Two different bicarbonate concentrations, 32 mmol/L and 26 mmol/L, in 26 patients - Mild metabolic alkalosis resulting from standard bicarbonate HD (32 mmol/L) may induce symptomatic hypotension	2003
	Tentori *et al.* [32]	Prospective cohort study	17 031 MHD patients	- Positive association of dialysate bicarbonate concentration with mortality (adjusted HR 1.08 per 4 mEq/L higher, 95% CI 1.01–1.15) - HR for dialysate bicarbonate 38 vs 33–37 mEq/L, 1.07 (95% CI 0.97–1.19)	2013

Table 2: Continued

	Authors	Study description	Number of patients	Outcomes	Publication year
	Cuadrado *et al.* [33]	Prospective cohort study	123 MHD patients	Individualization of dialysate bicarbonate prescription with an adjustment formula: pre- and post-dialysis tCO_2 levels significantly decreased from 23.25 ± 2.24 mEq/L and 27.38 ± 1.77 mEq/L at baseline to: 21.33 ± 1.46 and 25.35 ± 1.11 at 2 months, 21.56 ± 1.49 and 25.54 ± 1.11 at 4 months, 22.85 ± 1.48 mEq/L and 26.81 ± 1.27 at 6 months	2022
Calcium	Gabutti *et al.* [34]	Randomized controlled trial	21 MHD patients	The dialysate bicarbonate and calcium concentrations changed (between 26 and 35 mmol/L for bicarbonate and either 1.25 or 1.50 mmol/L for calcium). Using either a high calcium or bicarbonate concentration resulted in the following effects: - Increased systolic blood pressure (+5.6 and –4.7 mmHg; $P < .05$) - Increased stroke volume (+12.3 and +5.2 mL; $P < .05$ and ns) - Decreased peripheral resistances (–190 and –171 dyne s cm^{-5}; $P < .05$) - Variable central augmentation index (+1.1% and –2.9%; ns and $P < .05$) - Decreased BNP levels (–5 and –170 ng/L; ns and $P < .05$)	2009
	Pun *et al.* [35]	Case—control study	43 200 MHD patients	- Low dialysate calcium (2.50 mEq/L), higher corrected serum calcium, and increasing serum-dialysate calcium gradient were associated with an increased risk of sudden cardiac arrest	2013
	Brunelli *et al.* [36]	Retrospective cohort study	39 MHD patients	Transitioning from predominant use of 2.5 mEq/L dialysate calcium to lower concentrations or maintaining the current practice. Facility conversion increased hospitalization for: - Heart failure exacerbation (late RRR 1.27, 95% CI 1.06–1.51) - Hypocalcemia (early RRR 1.19, 95% CI, 1.05–1.35; late RRR 1.39, 95% CI 1.20–1.60) - Intradialytic hypotension (early RRR 1.07, 95% CI 1.02–1.11; late RRR 1.05, 95% CI 1.01–1.10) - No impact on all-cause mortality or hospitalization rates	2015
	Ok *et al.* [37]	Randomized controlled trial	284 MHD patients	Patients with intact PTH ≤300 pg/mL were randomly assigned to two groups: 1.25 mEq/L calcium and 1.75 mEq/L calcium dialysate arms for 24 months - Lowering dialysate calcium levels slowed the progression of coronary artery calcification and improved bone turnover in patients on MHD with baseline intact PTH ≤300 pg/mL	2016
	Sakoh *et al.* [38]	Nonrandomized intervention study	12 MHD patients	Use of 2.75-mEq/L dialysate calcium concentration: - Conversion of dialysate calcium concentration from 2.5 to 2.75 mEq/L increased intradialytic calcium loading and serum total and ionized calcium levels - Conversion of dialysate calcium from 3.0 to 2.75 mEq/L decreased intradialytic calcium loading and serum total and ionized calcium concentrations	2019

Table 2: Continued

	Authors	Study description	Number of patients	Outcomes	Publication year
Sodium	Mendoza *et al.* [39]	Cross sectional study	1084 MHD patients	- Significant positive correlation ($r = 0.21$, $P < .0001$) between IDWG and the sodium gradient - After adjusting for confounders and clustering by facilities, the sodium gradient remained independently associated with IDWG (70 g/mEq/L, $P < .0001$)	2011
	Mendoza *et al.* [40]	Quasi—interventional study	15 MHD patients	High DNa (140 mmol/L) and low DNa (136 mmol/L) were compared for 12 weeks - IDWG, IDWG% and pre-dialysis systolic blood pressure decreased significantly by 0.6 ± 0.6 kg, $0.6\% \pm 0.8\%$ and 8.3 ± 14.9 mmHg ($P < .05$)	2011
	Aybal Kutlugun *et al.* [41]	Quasi—interventional study	30 MHD patients	Two consecutive 6-week HD periods. DNa was 143 mEq/L in the first period (standard) and 137 mEq/L in the second period (low) - IDWG was significantly lower during low DNa HD (2.35 ± 0.86 kg vs 2.71 ± 0.89 kg; $P < .001$) - Dialysis-related symptoms were more frequent during low DNa HD ($P < .05$)	2011
	Hecking *et al.* [42]	Prospective Cohort Study	23 593 MHD patients	Patients divided by DNa >140 mmol/L, DNa 140 mmol/L and DNa <140 mmol/L - Higher DNa was not associated with higher mortality in a fully adjusted model (HR 0.98 per 2 mEq/L higher DNa, 95% CI 0.95–1.02) - Higher DNa was associated with lower hospitalization risk (HR 0.97 per 2 mEq/L higher DNa, 95% CI 0.95–1.00, $P = .04$)	2012
	Mc Causland *et al.* [43]	Prospective Cohort Study	2272 MHD patients	- No difference in pre-dialysis serum sodium was observed - Mortality rates varied based on serum and dialysate sodium levels - With higher DNa linked to increased mortality at higher pre-dialysis serum sodium concentrations [for each 4 mmol/L increment in serum sodium, the HR for death was 0.72 (95% CI 0.63–0.81) with lower DNa compared with 0.86 (95% CI 0.75–0.99) for higher DNa]	2012
	Beduschi *et al.* [44]	Randomized controlled trial	38 MHD patients	High DNa (138 mmol/L) vs low DNa (135 mmol/L): - Systolic and diastolic blood pressure and IDWG showed no significant changes during the follow-up	2013
	Kim *et al.* [45]	Before—after trial	24 MHD patients	High DNa (140 mmol/L) vs low DNa (135 mmol/L): - Effectively reduced IDWG, pre-dialysis blood pressure and pre-dialysis extracellular water without causing any significant increase in adverse events	2014
	Mc Causland *et al.* [46]	Randomized controlled trial	139 MHD patients	Hospitalized maintenance HD patients were randomized to receive higher (142 mmol/L) or lower (138 mmol/L) DNa for up to six sessions - No significant differences were found in the average systolic blood pressure decline between the higher and lower DNa groups (23 ± 16 versus 26 ± 16 mmHg; $P = .57$)	2022

OR: odds ratio; CI: confidence interval; HR: hazard ratio; ns: not significant; BNP: brain natriuretic peptide; RRR: relative risk ratio; IDWG: intradialytic weight gain, DNa: dialysate sodium.

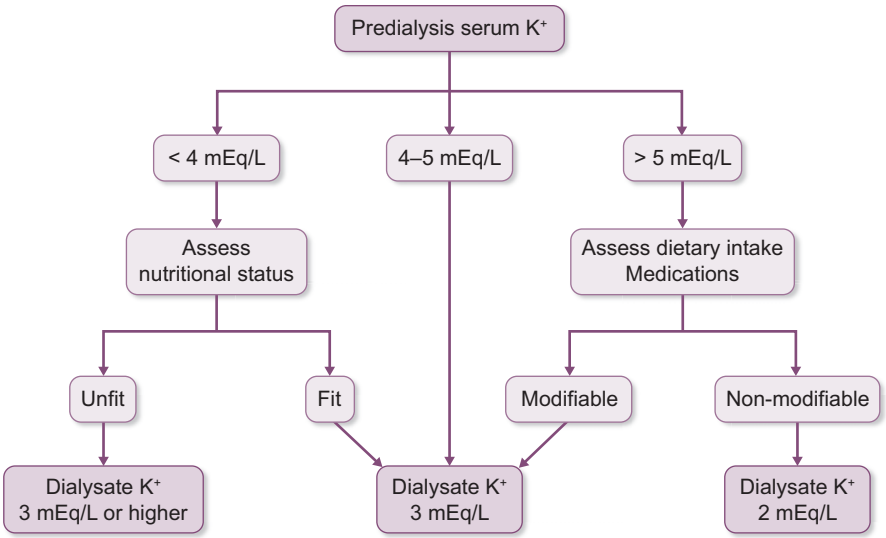

Figure 1: Stepwise management of dialysate composition of potassium.

dietary nutrient intake, is essential. If the dietary nutrient intake is not adequate, the dialysate potassium concentration should be maintained at 3 mEq/L or higher until patients improve their total body potassium stores. Of note, using high dialysate potassium concentrations to replete body stores is not advisable. In patients with pre-dialysis serum potassium between 4 and 5 mEq/L, the dialysate potassium can be set at 3 mEq/L, which is the current standard of care in most countries. In patients with pre-dialysis serum potassium concentrations consistently above 5 mEq/L, dietary discretion and impact of medications should be considered first. If these aspects are not modifiable satisfactorily, the use of dialysate potassium of 2 mEq/L is indicated. Very low dialysate potassium concentrations should be spared and used only in unique cases, to avoid large serum-to-dialysate potassium gradients and associated risk of mortality [28]. An important consideration about personalizing dialysate potassium as well other electrolytes is the need for more ample data points to guide prescription. The current practice of once-a-month blood draws may not necessarily reflect fluctuations in serum potassium concentrations at each dialysis. Implementation of point of care serum electrolytes measurement could be a potential solution to this problem.

Magnesium

Magnesium is involved in several enzymatic reactions in the body and any abnormality in its serum concentration is a risk factor for arrhythmias in the general population [49]. In MHD patients, its serum concentrations are largely dependent on dietary intake and dialysate magnesium and the incidence of hypo- or hypermagnesemia is therefore higher than in the healthy population [50]. Hypomagnesemia is associated with endothelial dysfunction, soft tissue calcification and arrhythmias, especially prolonged QT interval which is associated with an increased risk of the life-threatening arrhythmia, Torsades de Pointes (TdP). The risk for clinically significant arrythmias increases with co-existing hypokalemia [51–53]. Hypermagnesemia may result in neuromuscular toxicity (including somnolence, decreased deep tendon reflexes and muscle paralysis etc.), cardiovascular effects (including hypotension, conduction abnormalities, bradycardia, complete heart block etc.) and hypocalcemia. Hypocalcemia is thought to be related to moderate hypermagnesemia due to its inhibitory effect on parathyroid hormone (PTH) secretion [54, 55].

Despite their potential impact, serum and dialysate magnesium levels are studied less than those of other electrolytes. van Zuijdewijn *et al*. reported that the mean pre-dialysis serum magnesium was 1.96 ± 0.26 mEq/L (0.98 ± 0.13 mmol/L or 2.38 ± 0.3 mg/dL) in ESKD patients, and they found a powerful inverse association between baseline serum magnesium and all-cause mortality [13]. In another study, Sakaguchi *et al*. examined the adjusted risk ratio for mortality with serum magnesium concentrations in 142 555 Japanese MHD patients and showed that low magnesium concentrations were inversely associated with CVD mortality. They also reported a J-shaped curve showing that both high and low serum magnesium concentrations are associated with increased morbidity and mortality, suggesting that the optimal range for serum magnesium concentrations is 2–3 mg/dL [12, 53].

Several studies have suggested that serum magnesium concentrations in MHD patients are largely dependent on the magnesium content of the dialysate. Del Giorno *et al*. showed that increasing magnesium in dialysate represented an easy, effective therapeutic option to increase serum magnesium [29]. A study by Bressendorf *et al*. reported a decrease in systemic inflammatory markers and an increase in markers of bone formation in a 28-day study with 2.0 mEq/L dialysate Mg compared with 1.0 mEq/L, suggesting additional pleiotropic benefits of raising dialysate magnesium levels [30]. Figure 2 depicts a stepwise management algorithm for dialysate magnesium composition. Although not examined in detail, a threshold of pre-dialysis serum magnesium concentration of 1.5 mg/dL is a reasonable target for decision making. In patients above this limit, the dialysate magnesium level can be set at 1 mEq/L. In patients with pre-dialysis serum magnesium concentration consistently lower than 1 mg/dL, a more thorough approach that takes pre-dialysis potassium concentration into account should be applied. If serum potassium levels are also on the lower side, the dialysate magnesium level should be increased slightly, in addition to changing dialysate potassium concentrations, if applicable.

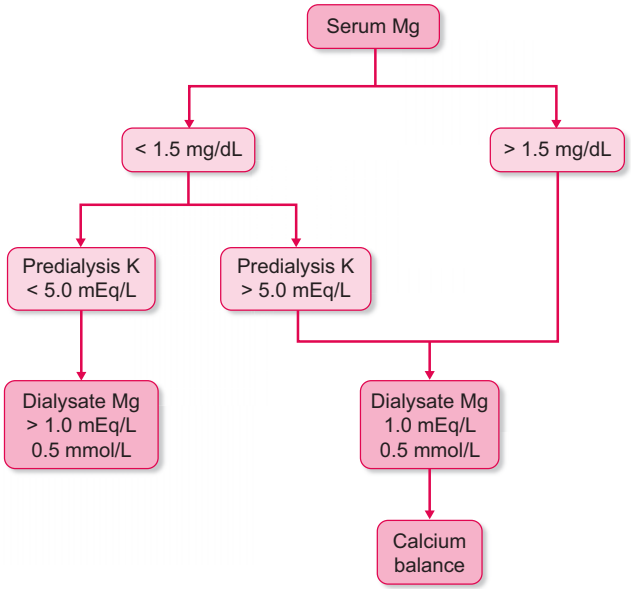

Figure 2: Stepwise management of dialysate composition of magnesium.

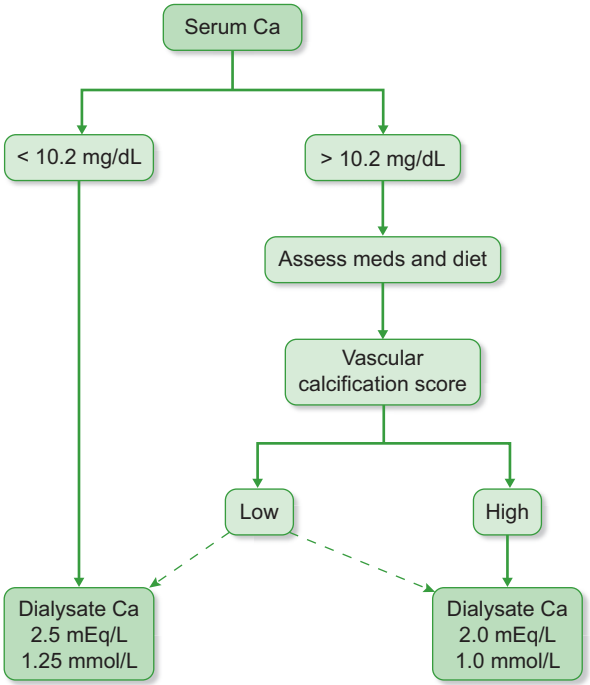

Figure 3: Stepwise management of dialysate calcium concentration.

Calcium

Calcium is involved in many metabolic functions such as nerve impulse transmission, muscle contraction, blood coagulation, hormone secretion and intracellular adhesion [56, 57]. Epidemiological studies suggest that higher serum calcium concentrations than normal are associated with higher mortality risk regardless of residual renal function, emphasizing the need to control its concentration at a reasonable range [15]. MHD patients have a tightly controlled serum calcium concentration based on a substantial number of epidemiological studies and regulatory requirements. It is, however, notable that over the last several decades, vitamin D derivatives, calcium-containing phosphate binders and calcimimetics had varying effects on serum calcium concentrations as they became available or less utilized.

When long-term HD therapies were initially introduced in the USA in the 1960s, the dialysate calcium concentration was set at 2.5 mEq/L (or 1.25 mmol/L) based on the proximity to the physiologic ionized calcium concentrations. As the number of MHD patients increased over time, it was quickly recognized that hypocalcemia and related metabolic problems were emerging, mostly due to the amount of calcium lost in the ultrafiltrate, the limited absorption from the gastrointestinal tract and profound active vitamin D deficiency in these patients. These observations instigated a trend to raise dialysate calcium concentrations to 3.5 mEq/L in the following years, but combined with the increasing use of active vitamin D derivatives and calcium-containing phosphorus binders led to heightened concerns for vascular calcification and its association with cardiovascular disease and adynamic bone disease, especially if the patient has hyperphosphatemia [58].

Based on the available data, the Kidney Disease Outcome Quality Initiative 2003 guidelines recommended an optimal dialysate calcium concentration of 2.5 mEq/L, with the use of calcium-based phosphorus binders initially to prevent complications related to hypocalcemia and non-calcium-based phosphorus binders subsequently, if applicable. Based on subsequent studies showing that higher dialysate calcium concentrations may be associated with improved intradialytic hypotension risk, a common complication observed in MHD patients, Kidney Disease: Improving Global Outcomes 2009 guidelines updated the recommended range for dialysate calcium concentration to 2.5–3 mEq/L [59, 60]. The additional potential advantages of a higher dialysate calcium concentration are less risk of arrhythmia and lower intact PTH concentrations [61]. Overall, the risk to benefit ratio of using higher calcium concentration in the dialysate remains unclear, and the ideal dialysis calcium concentration is still not clearly defined. Given the opportunity to manage serum calcium and phosphorus levels more effectively using calcimimetics, the positive calcium balance due to slightly higher dialysate calcium is unlikely a major risk for MHD patients [60, 62]. Figure 3 depicts a simplified approach to stepwise management of dialysate calcium concentration. In the USA, regulatory agencies have set the target for maximum allowable serum calcium at 10.2 mg/dL. Accordingly, if pre-dialysis serum calcium concentrations are consistently below 10.2 mg/dL, a dialysate calcium concentration of 2.5 mEq/L is reasonable. If the pre-dialysis serum calcium is above 10.2 mg/dL, it is important to evaluate and adjust a patient's diet and medications, in addition to obtaining their vascular calcification score to provide aid in clinical decision making. If the vascular calcification score is high, the dialysate calcium can be adjusted to 2.0 mEq/L.

Bicarbonate

Metabolic acidosis is a common condition in patients with advanced kidney disease, especially those on MHD, leading to various abnormalities such as increased bone demineralization, muscle wasting and insulin resistance [63]. Correction of metabolic acidosis is associated with improvements of these abnormalities in most cases, although not completely. MHD patients tend to have low pre-dialysis serum bicarbonate

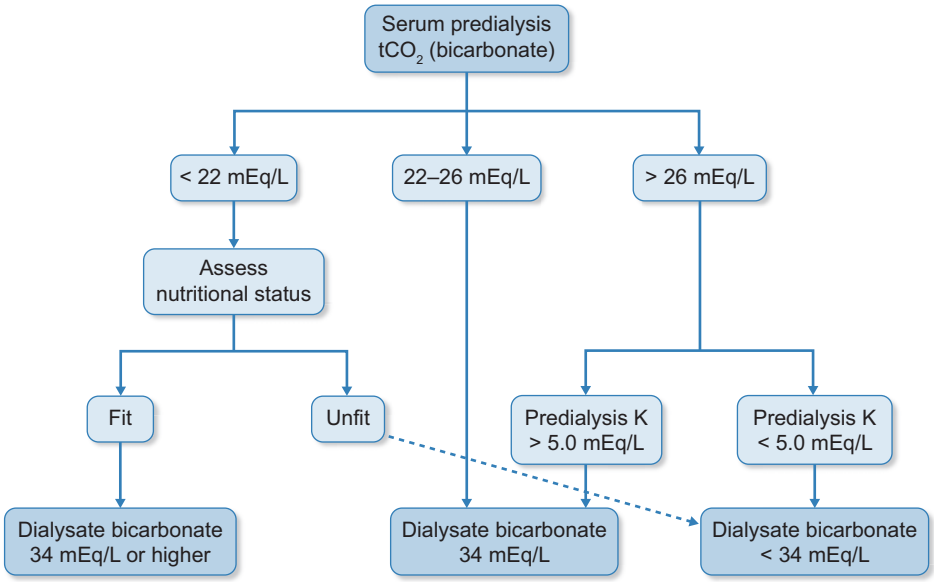

Figure 4: Stepwise management of dialysate bicarbonate concentration.

concentrations. Since low pre-dialysis serum bicarbonate concentration was strongly associated with higher mortality rates in several epidemiological studies, a high dialysate bicarbonate is generally considered. That said, multiple other studies have also shown a more U-shaped association between pre-dialysis plasma bicarbonate concentrations and adverse effects including mortality and hemodynamic instability [17, 31]. These observations have led to some controversy regarding the optimal dialysate bicarbonate concentrations, especially with the advent of three-loop systems to avoid precipitation.

The study by Tentori *et al.* using DOPPS data provided additional descriptive information about the international practice patterns for dialysate bicarbonate prescriptions suggesting that there was a tendency to maintain dialysate bicarbonate concentrations between 33 and 37 mEq/L (or 33–37 mmol/L) in most countries [32]. In the same study, they also showed that patients treated with higher concentrations showed higher all-cause mortality rates, particularly due to infection-related causes. While this observation was contrary to the belief that higher dialysate bicarbonate concentrations would precipitate intra- and inter-dialytic cardiac arrhythmias, it could also be attributed to metabolic alkalosis impairing immune system mechanisms [64]. Given the lack of any randomized clinical trials, the current approach to management of metabolic acidosis requires optimization of dialysate bicarbonate concentration to prevent extreme pre-dialysis metabolic acidosis and post-dialysis alkalosis.

In contrast to potassium or calcium, the current dialysis systems allow a wider range of options for dialysate bicarbonate concentrations. This allows a more personalized approach to prescriptions as shown in a prospective single-center study from Spain in 123 patients on MHD. The investigators modified the dialysate bicarbonate concentrations using a specific formula that is based on pre- and post-dialysis serum bicarbonate concentrations individualizing the dialysate prescription according to these measurements with a goal to maintain total carbon dioxide levels 19–25 mEq/L and <29 mEq/L, pre- and post-dialysis, respectively. Using this approach, they improved the percentage of patients within those ranges from 67.9% at baseline to over 95% at the end of the study. Of note, while 100% of patients were prescribed a standard dialysate bicarbonate of 32 mEq/L at baseline, there was a wide range of prescription at the end of the study, with only 75% of patients being prescribed within range of 32–34 mEq/L [33]. This study provides an excellent example of how dialysis prescription can be personalized based on abundance of data. Clearly, current practice of monthly serum bicarbonate measurements, which are prone to significant misrepresentation due to timing and handling of specimens, would not allow such a personalized approach.

Figure 4 depicts a simplified algorithm for dialysate bicarbonate prescription. Available data suggest that most MHD patients are expected to tolerate the dialysate bicarbonate concentration of 34 mEq/L without adverse effects. In patients with persistently low pre-dialysis serum total carbon dioxide concentrations such as <22 mg/dL, one should initially assess the patient's nutritional status. If they are nutritionally fit, this would indicate high protein intake and require consideration of increasing the dialysate bicarbonate concentration to 34 mEq/L or higher for improved management of acid–base balance. Other factors that may contribute to acidosis in MHD patients with low total carbon dioxide levels include underlying medical conditions such as diabetes or respiratory disease, certain medications and electrolyte imbalances. In this case, dialysate bicarbonate can be kept below 34 mEq/L because the amount of hydrogen released from protein breakdown will not be high. If the serum pre-dialysis total carbon dioxide (tCO_2) concentration is between 22 and 26 mEq/L it would be appropriate to maintain dialysate bicarbonate at 34 mEq/L to maintain acid–base balance. If the serum pre-dialysis tCO_2 concentration is >26 mEq/L, the serum potassium concentration should also be monitored prior to HD. If the potassium concentration is <5 mEq/L with high tCO_2, the dialysate potassium can easily be lowered below 34 mEq/L because the effect of extracellular potassium shift will not reach significant levels as the metabolic alkalosis resolves. If the serum potassium is >5 mEq/L, the dialysate bicarbonate should be kept at 34 mEq/L. Otherwise, the rapid resolution of the metabolic alkalosis will increase the extracellular potassium shift, which may either worsen hyperkalemia or prevent its correction.

Sodium

Among the entire dialysate electrolytes, sodium concentration has seen the greatest number of adjustments since MHD has been available to patients. As the dialysis technology advanced over time, the need to use very low dialysate sodium concentrations to avoid major fluid shifts dissipated. The risk of overt hyponatremia and associated symptoms such as headache, vomiting, blurred vision, tremors, seizures and disorientation at very low dialysate concentrations have led to a trend for higher dialysis sodium concentrations, closer to serum concentrations. Studies showing that dialysate sodium concentrations even slightly lower than serum concentrations are associated with increased intradialytic symptoms such as muscle cramps, hypotension, nausea, vomiting and fatigue combined with data showing better-tolerated fluid removal with dialysate sodium concentrations higher than serum concentrations led to a trend towards higher targets (>138 mEq/L, or >138 mmol/L). On the other hand, while higher dialysate sodium concentrations help to maintain blood volume and stabilize blood pressure, they may also result in sodium loading, thirst, weight gain and hypertension [65–67]. Mendoza *et al*. showed that a higher sodium gradient during HD was associated with sodium loading such that as the sodium gradient increased by 1 mEq/L, there was a significant increase in the intradialytic weight gain in the amount of 70 g/mEq/L [39].

The optimal dialysate sodium concentration for MHD patients is still not clear. A randomized controlled trial by Mc Causland *et al*. in 139 MHD patients compared low (138 mEq/L) and high (142 mEq/L) dialysate sodium concentrations in terms of intradialytic hypotension [46]. The study showed that the higher dialysate sodium concentration was safe compared with the lower dialysate sodium concentration but did not result in a significant difference in the severity of intradialytic hypotension. A recent study by Marshall and Karaboyas showed that dialysate sodium prescriptions have been lowered within that decade with most dialysis units prescribing a standard dialysate sodium that is between 138 and 140 mEq/L [68, 69]. When completed, the ongoing RESOLVE (Randomized Evaluation of Sodium Dialysate Levels on Vascular Events) study could provide useful information regarding the optimal dialysate sodium concentration and provide guidance for clinical practice before applying individualized treatment approaches (Clinical Trial Identifier: NCT02823821). The study will evaluate major cardiac events by comparing two different dialysate sodium concentrations (137 mEq/L and 140 mEq/L). Finally, online sodium profiling, a method that customizes dialysate sodium concentration for each patient, can improve patient outcomes and comfort when properly implemented [70]. Data to date suggest that a one size fits all approach for sodium profiling leads increased thirst, weight gain between treatments and high blood pressure [71].

SUMMARY

Adjustments in dialysate electrolyte concentrations represent an opportunity to improve patient care and outcomes in MHD patients. To move the field forward, there must be concentrated efforts to collect more granular data, improve dialysis technology, provide adequate human resources and set policy as applicable. Clinically meaningful information can be obtained from patient data such as their symptoms, hemodynamic parameters, activity trackers, dietary patterns and medications that can be incorporated when prescribing dialysis treatment. Most importantly, involvement of patients and their caregivers in the decision-making process by incorporating their symptom severity, care preferences and treatment choices is critical to achieve the fundamental objectives of precision medicine.

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No new data were generated or analysed in support of this research.

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