

Dialysate Potassium, Dialysate Magnesium, and Hemodialysis Risk

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ABSTRACT

One of the fundamental goals of the hemodialysis prescription is to maintain serum potassium levels within a narrow normal range during both the intradialytic and interdialytic intervals. Considering the extraordinarily high rate of cardiovascular mortality in the hemodialysis population, clinicians are obligated to explore whether factors related to dialytic potassium removal can be modified to improve clinical outcomes. Observational studies and circumstantial evidence suggest that extreme concentrations of serum and dialysate potassium can trigger cardiac arrest. In this review, we provide an overview of factors affecting overall potassium balance and factors modulating potassium dialysate fluxes in dialysis, and we review data linking serum and dialysate potassium concentrations with arrhythmias, cardiovascular events, and mortality. We explore potential interactions between serum and dialysate magnesium levels and risks associated with dialysate potassium levels. Finally, we conclude with proposed dialytic and novel nondialytic approaches to optimize outcomes related to potassium homeostasis in patients on hemodialysis. Dialysis clinicians need to consider changes in the overall clinical scenario when choosing dialysate potassium concentrations, and an effective change in practice will require more frequent serum potassium monitoring and responsive dialysis care teams.

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Nearly all patients who receive treatment for ESRD require support with hemodialysis (HD) at some point in their lives. Currently, there are >466,000 patients on chronic HD in the United States, and this population continues to grow.¹ Receipt of regular HD treatments sustains life, but when faced with the extraordinarily high rate of mortality in the HD population, clinicians are obligated to explore whether dialysis treatments can be modified to improve clinical outcomes. To maintain homeostasis, conventional HD treatment involves rapid intradialytic removal of fluid and electrolytes three times per week followed by subacute postdialysis re-equilibration and then slow interdialytic accumulation of the same fluids and electrolytes. Technological advances

improved the efficiency and delivery of HD treatments, but these weekly patterns of rapidly undulating fluid and electrolyte profiles have not changed since it was first recognized as the “unphysiology” of HD in 1975.² More recent observations have linked the unphysiology of the HD procedure to the excess of morbidity and mortality that plagues the HD population; cardiovascular-related hospitalizations and sudden cardiac arrests occur most frequently on HD days, with the greatest frequency on the first HD treatment of the week after the long dialysis-free weekend.^{3,4}

One of the fundamental goals of the HD prescription is to maintain serum potassium levels within a narrow normal range during both the intradialytic and

interdialytic intervals. In this brief review, we review the physiology and factors related to potassium fluxes in patients on HD, the evidence supporting the link between dialysate potassium and outcomes, and the evidence regarding implementation of best practices to improve outcomes.

FACTORS AFFECTING POTASSIUM BALANCE IN PATIENTS ON HD

Maintenance of serum potassium homeostasis is critical to maintain a stable transmembrane potential of about -85 mV to permit normal cardiac and skeletal muscle function; acute changes in serum potassium levels result in deviations in membrane potential that can lead to muscle paralysis and fatal arrhythmias.^{5,6} In patients with ESRD, the ability to maintain potassium homeostasis *via* the kidney is lost or greatly reduced, and therefore, the normal condition must be approximated with dietary potassium restriction and dialytic maintenance. Ideal dialytic management is twofold: (1) to remove potassium that accumulates during the interdialytic interval and prevent serious predialysis hyperkalemia and (2) prevent serious intradialytic and postdialysis hypokalemia.⁷

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In a patients on HD, recommended potassium intake is about 60 mEq/d (420 mEq/wk).⁷ Although dialytic removal varies on the basis of factors that will be discussed below, a typical dialysis treatment removes 70–100 mEq (210–300 mEq/wk for patients on thrice weekly HD) through a combination of diffusive and convective clearance. Thus, assuming negligible urinary potassium clearance, for a patient on HD to maintain neutral potassium balance, some potassium elimination *via* the gastrointestinal tract is needed.

DIALYTIC FACTORS MODULATING POTASSIUM REMOVAL

HD removes potassium from the extracellular fluid compartment, which contains of only 2% of total body potassium; the remainder is found in the intracellular space. Diffusion accounts for 85% of dialytic potassium clearance,⁸ and the rate and amount of potassium removal are largely a function of the potassium serum-dialysate potassium gradient.

As serum potassium falls toward dialysate potassium levels (which are fixed) during the course of the treatment, the gradient is reduced, which in turn, decreases the rate of potassium removal. During the first hour of dialysis, rate of potassium decline is the most rapid when the serum-dialysate potassium gradient is largest; a 1-mEq/L fall is typical, but this fall can be greater with larger serum-dialysate gradients. The acute fall in the first hour is followed by a more gradual decline of an additional 1 mEq/L over next 2 hours as the serum-dialysate potassium gradient narrows (Figure 1). During the final hour, serum potassium levels remain steady, although diffusive clearance is still occurring, indicating equilibrium between the rates of potassium removal and the rate of re-equilibration from intracellular space.⁹ After HD, a subacute “rebound” of serum potassium levels occurs as continued mobilization of potassium from intracellular space to extracellular space occurs. The effect of the serum-dialysate gradient on the rate and amount of intradialytic fall in serum

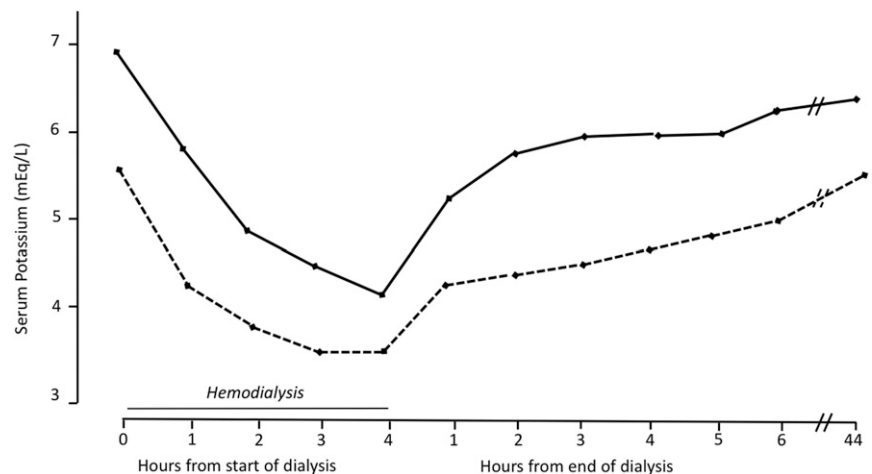


Figure 1. Comparison of intradialytic and postdialytic potassium levels between a serum-dialysate gradient of 5.8 mEq/L (solid line; predialysis serum potassium 6.8 mEq/L and dialysate potassium 1 mEq/L) and a gradient of 4.7 mEq/L (dashed line; predialysis serum potassium 5.7 mEq/L and dialysate potassium 1 mEq/L). The high serum-dialysate gradient condition results in a total excursion of serum potassium levels of approximately 5 mEq/L (3 mEq/L fall and 2 mEq/L rebound) in the 10 hours after the start of treatment compared with approximately 3 mEq/L with the lower gradient condition. Modified from Blumberg *et al.*,¹⁰ with permission.

potassium as well as the rate of postdialysis rebound in serum potassium levels was studied by Blumberg *et al.*¹⁰ A higher serum-dialysate gradient results in both more rapid fall in serum potassium levels during treatment and a rapid postdialysis rebound of potassium levels compared with smaller gradients (Figure 1).

Other aspects of the dialysis prescription other than dialysate potassium concentration influence the rate of potassium removal. Increases in serum bicarbonate levels during a dialysis treatment enhance the activity of Na/K/ATPase channels and result in larger shifts of potassium into the intracellular space, further lowering serum potassium levels during HD. This was shown experimentally in a randomized crossover study comparing the effect of three different dialysate bicarbonate concentrations on the rate of serum potassium decline, keeping dialysate potassium concentration stable.¹¹ High dialysate bicarbonate (39 mEq/L) was associated with the greatest decline in serum potassium levels compared with standard (35 mEq/L) and low (27 mEq/L) bicarbonate concentrations, but there was no significant difference in the total potassium removal, concordant with enhanced acute

intracellular potassium shifts rather than enhanced potassium removal. Convective clearance of potassium plays a small but not insignificant role in total dialytic potassium removal; recent mass-balance studies have shown that potassium mass removed by ultrafiltration accounts for approximately 6% of the total potassium mass removed.⁹ Finally, compared with glucose-free or low glucose-containing dialysates, high glucose-containing dialysate solutions can also lead to higher potassium removal *via* osmotic shifts of intracellular potassium to the extracellular space.^{12,13}

SERUM AND DIALYSATE POTASSIUM LEVELS AND CLINICAL OUTCOMES

Whereas the normal range for serum potassium levels is typically reported between 3.5 and 5.0 mEq/L in the general population, the optimal range of potassium concentration in patients on dialysis is higher. In a study of 2134 patients on HD, a predialysis serum potassium level of 5.1 mEq/L was associated with the lowest risk of peridialytic sudden cardiac arrest,

whereas potassium levels above and below 5.1 were associated with increasing risk.¹⁴ In another study examining predialysis serum potassium levels and survival within a cohort of 81,013 patients on HD, potassium concentrations between 4.6 and 5.3 mEq/L were associated with the lowest incidence of all-cause mortality.¹⁵ In the latter study, potassium levels ≥ 5.6 mEq/L were associated with significantly increased mortality after adjustment for confounders related to comorbidities and nutritional status, whereas risk relationships between potassium levels < 4.6 mEq/L and mortality were abrogated after accounting for confounding factors related to malnutrition. A more recent study of 55,183 patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) multinational cohort confirmed these findings, with the lowest risk of death among patients with predialysis serum potassium levels between 4 and 5.5 mEq/L, a significant increase in the risk of death and arrhythmia outcomes at levels ≥ 5.6 , and attenuation of risk associations with potassium levels < 4 mEq after accounting for potential confounding from malnutrition indicators.¹⁶ Even if risks associated with hypokalemia are not entirely mediated through malnutrition and inflammation-related factors, predialysis hypokalemia is encountered less frequently compared with hyperkalemia, making hyperkalemia management a more pressing public health concern. In two studies surveying predialysis serum potassium values obtained within a large dialysis organization, approximately 20% of all measurements were ≥ 5.5 mEq, and about 12.5% of measurements were ≥ 6.0 ,¹⁷ whereas predialysis potassium levels < 4.0 accounted for only 9% of all measurements.¹⁵

The prevalence and prognostic significance of immediate postdialysis potassium levels and in particular, postdialysis hypokalemia are unknown, because postdialysis levels are not routinely measured. Regardless, the potential effect of falling potassium levels during and after the HD procedure is compelling. In a study of patients with ESRD who had wearable defibrillators in place, 70.0% of the captured arrhythmia events occurred during the session, and

2.8% were captured immediately after the dialysis procedure.¹⁸

OPTIMAL DIALYSATE POTASSIUM LEVEL AND OUTCOMES

The challenge of selecting appropriate dialysate potassium levels is balancing the need to achieve sufficient potassium removal to avoid interdialytic hyperkalemia, while minimizing the potential hazards posed by lowering potassium too rapidly during treatment. The lack of consensus on the ideal dialysate potassium concentration to achieve these goals is reflected in the large variation in worldwide dialysate potassium prescription; recent data from the DOPPS report the range of prevalent use of potassium dialysate < 2 mEq/L from as low as 3% in the United States to as high as 62% in Spain.¹⁶ The challenge of selecting the appropriate dialysate potassium concentration is further compounded by a commonly applied standard of care to monitor predialysis serum potassium levels only once monthly, with no other data to guide dialysate potassium choice for the remainder of treatments throughout the month. The safety of low-potassium dialysate has been a focus of concern given the possibility that dialysis-induced potassium lowering may provoke cardiac arrhythmias and sudden cardiac death (SCD). An early study documented that higher efficiency dialysis could achieve dramatic removal of potassium with low-dialysate potassium concentration, but this study also noted that “only” one of the 11 patients studied with zero potassium bath experienced “high grade ventricular ectopy.”¹⁹ Since then, multiple large retrospective studies have investigated associations between dialysate potassium levels, predialysis serum potassium levels, and risk of sudden death, cardiac events, and all-cause mortality. These studies and their significant findings are summarized in Table 1. Although subject to indication bias and other sources of confounding, in general, large cohort studies have identified increased risks of SCD associated with use of low-potassium dialysate < 2 mEq/L,^{14,20} with one study identifying an increased risk of SCD

among patients exposed to dialysate potassium < 3 mEq/L compared with ≥ 3 mEq/L.²¹ The risks associated with low-potassium dialysate are principally seen among patients with low to normal predialysis serum potassium; importantly, no study has shown significant risk associated with low-potassium dialysate among patients with predialysis serum potassium levels ≥ 5 (Figure 2). A smaller retrospective study noted a significant reduction of SCD rates associated with a change in dialysis unit policy toward use of low-potassium (1 mEq/L) dialysate in all patients with predialysis serum potassium levels > 5.5 mEq/L, but this study was potentially confounded by other changes in dialysis care that occurred during the same time period.²² Although no long-term prospective controlled studies have been conducted to examine the effect of low-potassium dialysate on hard outcomes, several other short-term crossover studies using cardiac monitoring devices have been conducted to assess subclinical arrhythmic events, such as ventricular ectopy,^{19,23,24} premature ventricular complexes,²⁵ and changes in electrocardiographic conduction parameters, such as the QT interval and QT dispersion.^{26,27} Most but not all studies observed higher rates of ventricular ectopy and QTc prolongation associated with lower-potassium dialysates of 0 or 1 mEq/L compared with higher-potassium dialysates. However, the validity of these markers as predictors of SCD and mortality is questionable at best, with long-term studies finding no association between these ECG markers and mortality.²⁸

Overall, largely circumstantial evidence points to the hazards of lower-potassium dialysate < 2 mEq/L, and the evidence for risk is strongest for patients with predialysis serum potassium levels < 5 mEq/L. Whether lower-potassium dialysate is appropriate or potentially beneficial for patients with higher predialysis serum potassium levels is unclear. In patients who are hyperkalemic, randomized trials are needed to compare the effects of a strategy to reduce hyperkalemia-associated arrhythmias using low-potassium dialysate with a strategy that uses higher-potassium dialysate to

Table 1. Summary of cohort studies examining risks associated with different dialysate potassium levels

Authors	Study Description/Population	No. of Patients Studied	Outcome/No. of Events	Findings/Comments
Karnik <i>et al.</i> ²⁰	Retrospective patient-control study; large United States dialysis organization (FMCNA)	>77,000	400 In-center cardiac arrests	Patients with cardiac arrest were twice as likely to have been prescribed low-potassium dialysate (OR, 1.94 for Dk<2 mEq/L)
Kovesdy <i>et al.</i> ¹⁵	Retrospective cohort study; large United States dialysis organization (Davita)	81,013	8679 All-cause deaths	Highest risk of death among patients with serum potassium >5 exposed to dialysate potassium >3 (HR, 1.36; 95% CI 1.02, to 1.86); no increased risk of mortality associated with Dk<2 among patients with Sk>5
Al-Ghamdi <i>et al.</i> ³¹	Retrospective cohort study of regional Canadian dialysis program (Alberta)	1267	515 All-cause deaths	No significant risk associated with Dk<2 or >2 after adjustment for covariates; trend toward harm in higher Dk (HR, 1.29; 95% CI, 1.07 to 1.56 for Dk=3 mEq/L; HR, 1.74; 95% CI, 1.09 to 2.77 for Dk=4 mEq/L compared with Dk=2 in unadjusted analyses)
Pun <i>et al.</i> ¹⁴	Retrospective patient-control study; large United States dialysis organization (Gambro/Davita)	2134	502 In-center SCDs	Increased risk with last Dk <2 mEq/L before SCA (OR, 2.06; 95% CI, 1.48 to 2.86); increasing risk of Dk<2 with lower Sk; no benefit of Dk<2 among patients who are hyperkalemic
Jadoul <i>et al.</i> ⁶⁴	Retrospective cohort study; multinational DOPPS cohort	37,765	1734 Sudden deaths	HR, 1.39; 95% CI, 1.12 to 1.74 for Dk≤1.5; (HR, 1.17; 95% CI, 1.01 to 1.37) for Dk 2–2.5; lowest risk of SCD with Dk≥3 mEq/L
Buiten <i>et al.</i> ⁶⁵	Secondary analysis of randomized trial in The Netherlands	40	428 Episodes of atrial fibrillation (AF) among 14 patients	AF episodes associated with lower Dk (mean =1.6 mEq/L) compared with patients without AF (2 mEq/L)
Flythe <i>et al.</i> ⁶⁶	Retrospective patient-control study; large United States dialysis organization (FMCNA)	5538	924 Cardiopulmonary arrests in outpatient HD units	Increased risk associated with Dk 1 mEq/L (OR, 1.89; 95% CI, 1.23 to 2.90)
Huang <i>et al.</i> ²²	Retrospective cohort study; single Taiwanese dialysis center	312	31 SCD events	Change in HD unit policy to decrease Dk to 1 mEq for patients with Sk>5.5 associated with decrease in SCD risk (HR, 0.33; 95% CI, 0.13 to 0.85); no accounting for other changes to dialysis unit care during time period
Karaboyas <i>et al.</i> ¹⁶	Prospective cohort study; multinational DOPPS cohort	55,183	13,114 All-cause deaths; 3300 composite arrhythmia outcomes	No significant benefit of Dk 3 versus Dk 2; no interaction with Sk values

FMCNA, Fresenius Medical Care of North America; OR, odds ratio; Dk, dialysate potassium; HR, hazard ratio; Sk, serum potassium; SCA, sudden cardiac arrest. Modified from Tucker *et al.*,⁶⁷ with permission.

avoid the potential arrhythmic hazards of increased serum-dialysate gradients. These studies are made more feasible with the availability of miniaturized implantable loop monitors, which can be easily inserted

with minimal risk and provide full capture of all arrhythmias that occur over extended periods.^{29,30}

The potential hazards of using higher-potassium dialysate concentrations ≥ 3

should also be noted. A study of >81,000 United States patients examined mortality rates on the basis of various combinations of dialysate potassium concentrations and predialysis serum potassium levels, and the

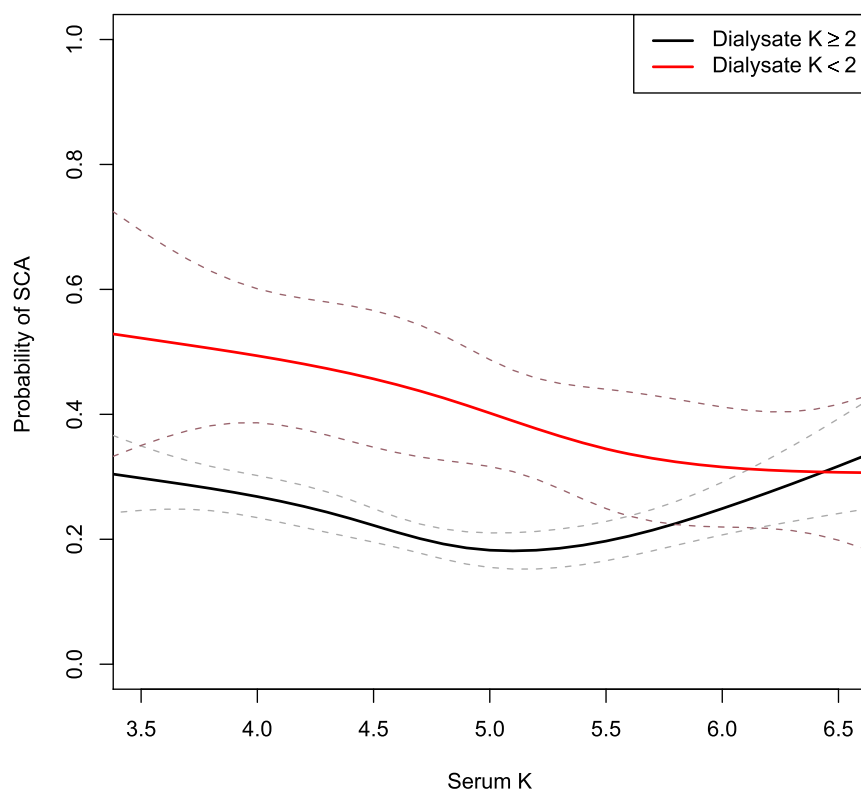


Figure 2. Sudden cardiac arrest (SCA) risk according to serum and dialysate potassium. The risk of SCA remains higher or equivalent (overlapping 95% confidence intervals) with lower-potassium dialysate <2 mEq/L compared with ≥ 2 , even among patients who are hyperkalemic. Reprinted from Pun et al.,¹⁴ with permission.

highest mortality rate was noted for patients exposed to high-potassium dialysate >3 mEq/L with predialysis serum potassium levels ≥ 5 .¹⁵ Studies done among Canadian patients on dialysis³¹ and the DOPPS international cohort¹⁶ have also observed an increased risk of death among users of dialysate potassium ≥ 3 mEq/L; however, in both studies, these risks were attenuated after adjustment for factors relating to malnutrition and inflammation.

In summary, although no randomized, controlled data exist to identify best dialysate potassium choices, current evidence most strongly supports the avoidance of low-potassium dialysate <2 mEq/L among patients with known predialysis serum potassium levels ≤ 5 . Little evidence exists to support the complete avoidance of dialysate potassium <2 mEq or >3 mEq/L at the extremes of predialysis serum potassium concentrations. However, given the reported risk associations, we suggest that

use of these dialysate concentrates be accompanied by frequent serum potassium monitoring and dialysate tailoring when serum levels come with the normal range.

SERUM AND DIALYSATE MAGNESIUM AND POTENTIAL INTERACTIONS WITH DIALYSATE POTASSIUM

The serum concentration of magnesium is recognized in the general population as a risk factor for arrhythmias, but in patients with ESRD, the risk of excursions in magnesium levels has been largely ignored. Magnesium is a divalent ion with a normal plasma concentration between 0.65 and 1.0 mmol/L (1.3–2.0 mEq/L; 1.6–2.4 mg/dl), and extracellular magnesium is estimated to represent only 1% of total body stores.³² In patients who have ESRD, magnesium concentrations tend to be slightly higher and

depend on native kidney function, dietary intake, concomitant medications, and dialytic clearance. A typical diet contains approximately 360 mg magnesium, and 70%–75% of this is excreted in the feces. Normal kidneys excrete about 100 mg magnesium per day. This allows balance between serum magnesium and magnesium contained in bone, muscle, and other tissues. During an HD session, the plasma magnesium is not fully “accessible” to shifts across the HD membrane, because magnesium has approximately 25% protein binding (predominantly albumin) and because 5%–16% of magnesium complexes with anions, such as bicarbonate, phosphate, and citrate.³² The amount of magnesium cleared with HD treatments depends on the magnesium concentration in dialysate. With dialysate magnesium 0.75 mmol/L, 565 mg magnesium will be cleared, and with dialysate magnesium 0.25 mmol/L, about 3100 mg will be cleared.^{33,34}

Extreme concentrations of serum magnesium can be common in clinical practice. In a recent survey of hospitalized patients, magnesium levels above 0.9 mmol/L (2.1 mg/dl) were present in 31.5% of patients, and levels below 0.7 mmol/L (1.7 mg/dl) were noted in 20.2% of patients.³⁵ Either extreme was associated with higher risk of adverse clinical outcomes, but the risk of hypermagnesemia was more pronounced. In the case of patients with CKD, why would extremes of magnesium be detrimental? High serum magnesium can cause over-suppression of PTH and other mineral metabolism adverse effects.³⁶ Low magnesium concentrations are speculated to cause endothelial dysfunction, enhance soft tissue calcification, and promote cardiac arrhythmias.^{37,38} Hypomagnesemia by itself is capable of prolonging QT interval and increasing risk for ventricular arrhythmias.³⁹ Therefore, it is imperative to avoid overlaying risk exposures, such as hypomagnesemia, with hypokalemia.

Risks associated with serum magnesium concentrations are not straightforward in patients with ESRD. Several studies evaluated risks associated with serum magnesium concentrations in patients who have ESRD, and the observations

differ. A retrospective cohort study of 142,555 Japanese patients on HD determined that there was a J-shaped relationship between serum magnesium concentrations and 1-year mortality, with a “sweet spot” around 1.2 mmol/L (2.8 mg/dl)⁴⁰ (Figure 3). Perhaps related to differences in dietary magnesium intake between countries, a study of United States patients on prevalent HD reported slightly different results.⁴¹ Among 27,544 patients followed in the latter study, a Cox proportional hazards model depicted a linear decline in death risk from the lowest to the highest serum magnesium category, with the best survival observed at serum magnesium levels ≥ 1.25 mmol/L (2.5 mEq/L; hazard ratio, 0.68; 95% confidence interval, 0.56 to 0.82) and no apparent risks associated with the highest magnesium category. Concordant results were reported in a retrospective study of 9359 United States patients on incident HD, but the study also suggested that the risk of low

serum magnesium was attenuated when statistical adjustments were made for markers of malnutrition and inflammation.⁴² More recently, a *post hoc* study of the Convective Transport Study (CONTRAST) evaluated associations of baseline serum magnesium values of patients assigned to either HD or hemodiafiltration.⁴³ In a subset of 365 randomized patients (who had stored blood samples), the CONTRAST analysis observed that, for every increase of serum magnesium concentration by 0.1 mmol/L, the hazard ratio for all-cause mortality was 0.85 (95% confidence interval, 0.77 to 0.94). Very few of the patients in the CONTRAST included in the study had magnesium concentrations above 1.4 mmol/L.

How should a clinician interpret these observations? It is evident that nutritional issues and medications, such as proton pump inhibitors, can lower serum magnesium levels along with nutritional issues, and part of the risks observed related to hypomagnesemia may be attributed to

these confounding factors.³² However, given the potential risks associated with hypomagnesemia and a growing awareness that proton pump inhibitors are often inappropriately prescribed,⁴⁴ a focused review of medication lists and a nutritional assessment should be a routine response to hypomagnesemia in patients on HD. However, if supplemental magnesium is to be considered, extremely high serum concentrations should be avoided.

Clearly, the dialysis prescription can affect serum concentrations of magnesium. Recent data suggest that hypomagnesemia occurs 33% of the time at dialysate concentrations of 0.25 mmol/L (0.5 mEq/L) and only 5% of the time among patients exposed to dialysate magnesium of 0.5 mmol/L (1.0 mEq/L).³² In fact, the trends in prescribed dialysate magnesium varied over the past three decades. Perhaps because of concerns about hypermagnesemia causing osteomalacia and an early report on the improvement of uremic pruritus after lowering dialysate magnesium concentration,⁴⁵ dialysate magnesium concentrations decreased from early values of approximately 0.75 mmol/L (1.5 mEq/L) to as low as 0.25 mmol/L (0.5 mEq/L).⁴⁶ However, with recognition that higher serum magnesium levels may limit arterial calcification, the pendulum has swung back in recent years.⁴⁷ Perhaps on the basis of these concepts, current manufacturers commonly provide dialysate products with final magnesium content of 0.5 mmol/L (1.0 mEq/L).⁴⁸

It is important to recognize, however, that important interactions exist among dialysate magnesium content and other dialysate constituents. For example, magnesium concentration in dialysate is likely influenced by citrate content. One study showed that citrate-containing dialysate created a mildly negative magnesium balance with routine HD.⁴⁹ In addition to biochemical interactions, low-magnesium dialysate could potentiate risks associated with low-potassium dialysate given the effects of hypomagnesemia on risk of hypokalemia *via* promotion of intracellular potassium shifts.⁴⁶ Given the high prevalence of hypomagnesemia, risk associations with mortality, and potentiating effect on potassium shifts, we

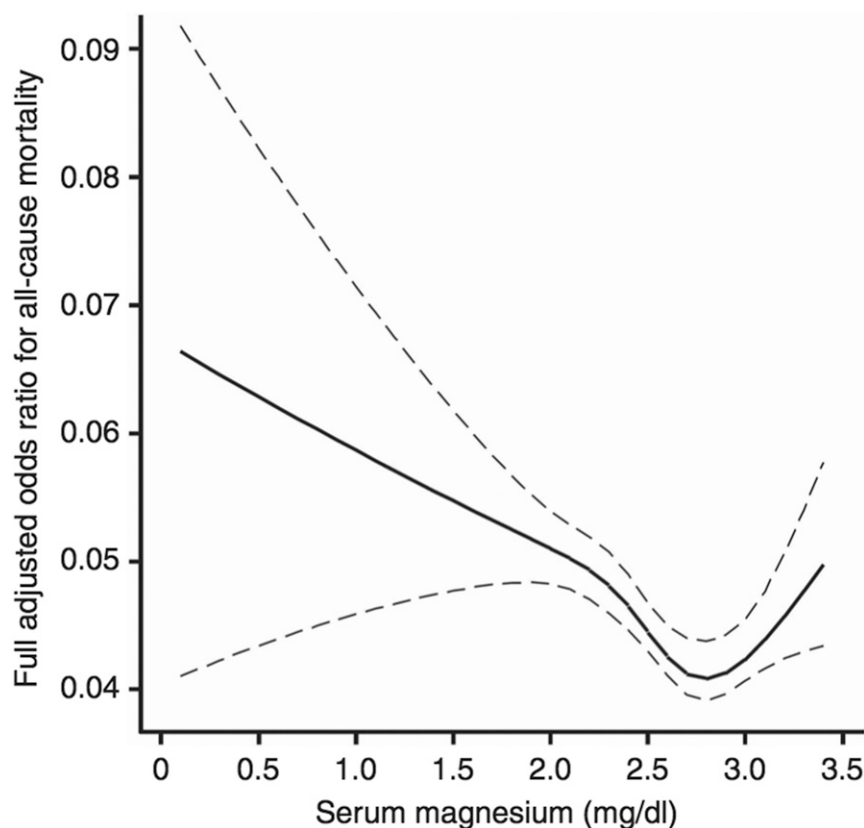


Figure 3. Adjusted associations between the serum magnesium level and all-cause mortality among 142,555 patients on HD. The dashed lines represent the 95% confidence intervals. Reprinted from Sakaguchi et al.,⁴⁰ with permission.

suggest standard prescription of higher-magnesium dialysate levels of 0.5 mmol/L (1.0 mEq/L), particularly among patients who are hypokalemic and patients subject to large serum-dialysate potassium gradients.

POTENTIAL NEW APPROACHES FOR MANAGING POTASSIUM HOMEOSTASIS IN PATIENTS ON HD

Optimizing the management of potassium in patients on HD involves reducing large intradialytic potassium shifts as well as providing adequate potassium removal to minimize hyperkalemia. Dialysate potassium profiling is an approach that can achieve both of these aims by maintaining a constant serum-dialysate potassium gradient by proportioning dialysate potassium separately from other components of the dialysate and gradually lowering dialysate potassium concentration as serum potassium levels fall.⁵⁰ Several investigators using this approach have shown a more gradual intradialytic fall in serum potassium levels,⁵¹ while maintaining the same total amount of potassium removal.⁵² Additionally, the investigators found that dialysate potassium profiling was associated with a reduction in the number of premature ventricular contractions, although only in a subset of patients prone to ventricular ectopy, and other investigators have observed improvement in QTc dispersion with dialysate profiling.²⁶ Other than the need to show the benefit of this approach with more clinically relevant outcomes, there are no current automated potassium profiling capabilities in modern three stream–proportioning HD machines; profiling must be done by physically changing out the dialysate concentrate throughout the course of a treatment, making this impractical for everyday use.⁵³

Some other ways to reduce large potassium shifts while maintaining total potassium removal are to extend dialysis treatment time or conduct more frequent treatments using higher dialysate potassium baths and/or lower blood and dialysate flow rates. A crossover study

comparing the potassium kinetics of patients assigned to either a 4- or 8-hour dialysis, which were pair matched for dialysate potassium concentration, total dialysate volume, and total ultrafiltration volume, showed a slower rate of serum potassium fall, a 15% overall increase in total potassium removal, and an identical end of treatment serum potassium in 8-hour treatments compared with 4-hour treatments.⁹ Potassium kinetics during short daily HD has not been directly observed, but one recent study used kinetic data from the HEMO Study to create a predictive model for expected potassium kinetics during quotidian dialysis modalities.⁵⁴ The authors reported that significantly higher dialysate potassium levels could be used in both short daily and long nocturnal dialysis prescriptions to achieve equivalent predialysis serum potassium levels and weekly total potassium removal rates compared with routine thrice weekly HD, which in turn, would reduce serum-dialysate gradients and rapid changes in serum potassium. However, the availability of long and/or daily HD treatments is generally limited and generally less desirable for patients and dialysis providers alike.⁷

Because there is evidence that the highest risk associated with dialysate potassium is among patients for whom there is an apparent serum-dialysate mismatch (*i.e.*, using dialysate potassium <2 mEq/L for patients with potassium ≤5 or using dialysate potassium >3 for patients with K ≥5), it is critical that the dialysate potassium prescription be reviewed and adjusted regularly in response to predialysis serum potassium levels, particularly during vulnerable periods where serum potassium levels may be acutely altered, such as after hospitalization. An example of failure to adjust dialysate potassium levels, despite several months of falling predialysis serum potassium levels in the months preceding an in-center sudden cardiac arrest, is shown in Figure 4. Several dialysate potassium adjustment algorithms have been proposed to avoid these serum-dialysate mismatches and target safe serum potassium concentrations. An informal algorithm that has been commonly advocated for decades is the

“rule of seven,” in which the predialysis serum potassium level is subtracted from seven to determine the dialysate potassium that should be assigned. Several other adjustment algorithms have been suggested, and some recent examples alongside our suggested approach are summarized in Table 2. A critically important aspect of any algorithm is the need to distinguish isolated changes in the predialysis serum potassium level due to acute or transient conditions (such as hypokalemia from diarrhea or hyperkalemia for a missed dialysis treatment) from chronic potassium trends. If changes are made to the dialysate potassium in response to acute changes without subsequent prompt monitoring of resulting predialysis serum potassium response, this can easily result in serum-dialysate mismatches as potassium levels return to normal when the acute condition resolves. This is particularly important if the treatment algorithm involves using dialysate potassium concentrations >3 and <2 mEq/L, because these dialysates have been associated with harm among patients with normal predialysis serum potassium levels as outlined previously. Given that the current standard of care is to monitor predialysis serum potassium levels only once monthly and that the workflow of many dialysis clinics may make reliability of more frequent monitoring difficult to guarantee, we advocate for the avoidance of dialysate potassium <2 and >3 to prevent inadvertent mismatches; in fact, many large dialysis organization and dialysis centers have abolished or severely restricted the use of low-potassium dialysate <2 mEq for this reason. However, it should be acknowledged that conscientious and careful use of a wider variety of dialysate potassium levels appropriately matched to serum potassium levels is an approach that may have merit. Ultimately, randomized, controlled trials are needed to determine if an approach coupling more frequent predialysis serum potassium assessment (perhaps using point of care handheld blood analyzers) with different algorithms for rigorous serum-dialysate matching could potentially

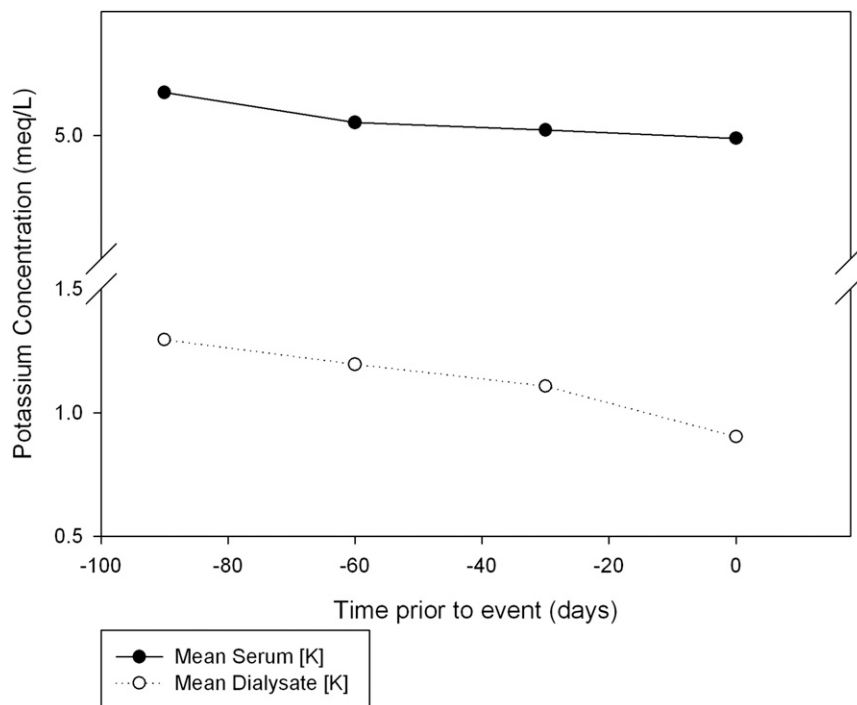


Figure 4. Mean serum and dialysate potassium levels in the months preceding peridialytic sudden cardiac arrest ($n=97$ patients with peridialytic sudden cardiac arrest exposed to low-potassium dialysate <2 mEq at the time of arrest). Despite falling average serum potassium levels, prescription of low dialysate potassium increased in the months preceding cardiac arrest. P.H. Pun et al., unpublished data.

reduce the incidence of dialysis-associated arrhythmias and sudden death compared with usual care.

NONDIALYTIC TREATMENTS TO IMPROVE POTASSIUM HOMEOSTASIS

It is important not to discount the potential utility of nondialytic management strategies to control serum potassium levels and decrease the need to expose patients to the potential hazards of low dialysate potassium. The involvement of renal dietitians to provide dietary counseling is indispensable, and as part of their dialysate potassium adjustment algorithm, Lee and Mendelssohn⁷ also engaged renal dietitians in reviewing all dialysate potassium levels, alerting providers to potential serum-dialysate potassium mismatches. Attention to other potential contributing factors to abnormal potassium levels, such as ongoing gastrointestinal losses or poor

nutrition among patients with acute or chronic hypokalemia, is also necessary. Studies have shown that angiotensin-converting enzyme inhibitors and spironolactone influence potassium levels even in patients on HD who are oligoanuric, presumably through their effects on colonic secretion; discontinuing these agents may have a small but appreciable effect on lowering predialysis serum potassium levels by 0.2–0.6 mEq/L.^{55,56} Large prospective clinical trials are underway to evaluate whether mineralocorticoid receptor blockers will improve clinical outcomes in patients on HD.⁵⁷ However, any positive result from use of these agents may be tempered by lowering of dialysate potassium concentrations in patients with resulting cases of predialysis hyperkalemia.

Potassium binding resins, including sodium polystyrene sulfonate and calcium polystyrene sulfonate, have been available for nearly 60 years; however, their efficacy in treating hyperkalemia has never been rigorously tested, and

potentially fatal risk of colonic necrosis is well known.⁵⁸ The use of these agents for chronic management of hyperkalemia in patients on HD is limited by poor gastrointestinal tolerability. A retrospective study of 70 chronically hyperkalemic patients on HD who were prescribed calcium polystyrene sulfonate found that only 40% of patients were adherent after 3 months, despite intensive adherence reinforcement; additionally, in the medication-adherent group, predialysis serum potassium levels did not decrease after 3 months of therapy and intensive dietary education.⁵⁹ Loop diuretics have been used to manage hyperkalemia, but their efficacy in patients on HD is limited to only patients with residual renal function and associated with high, potentially ototoxic doses required to produce kaliuresis.⁶⁰ Thus, these agents have poor utility for the management of chronic hyperkalemia.

However, two new oral potassium binding agents (sodium zirconium cyclosilicate and patiomer) have been shown to be effective in reducing serum potassium levels among patients with moderate CKD.^{61,62} These new medications have only been tested in small populations of patients on HD,⁶³ but in contrast to the well known gastrointestinal side effect profile of sodium polystyrene sulfonate and potential risks of fatal colonic necrosis that make chronic use impractical in patients on HD, these new agents appear to be well tolerated. If proven effective and safe in patients on HD, the potential for novel potassium binding agents to reduce predialysis hyperkalemia and allow for the use of higher dialysate potassium levels could be an important advance in reducing dialysis-induced arrhythmias.

CONCLUSION

Because of the overwhelming rate of cardiovascular complications associated with ESRD, clinicians are obliged to carefully explore how dialysis care can be modified to improve risk. Observational studies and circumstantial evidence suggest that extreme concentrations of serum potassium and exposure to conventional HD can act as triggers for cardiac

Table 2. Suggested algorithms for managing dialysate potassium levels according to predialysis serum potassium

Algorithm	Predialysis Potassium Level, mEq/L				Comments
	<4	4.1–5.5	5.6–6.4	>6.5	
Rule of 7	4 mEq/L	3 or 2 mEq/L	1 mEq/L	1 or 0 mEq/L	Potential for large serum-dialysate gradients; potential for large mismatches without frequent follow-up of serum potassium values
Lee and Mendelssohn ⁷	Increase current dialysate by 1 mEq/L to a maximum of 4 mEq/L	Increase dialysate by 1 mEq/L to a maximum of 3	2 mEq/L	2 mEq/L; Consider longer dialysis treatment time or frequent HD	Targets avoidance of low-K dialysate; found to result in only 4% of patients requiring dialysate potassium changes after using algorithm for 5 mo
Abuelo ⁶⁸	Increase current dialysate by 1 mEq/L to max of 4 mEq/L	Maintain current dialysate potassium level	Lower dialysate K by 1 mEq to minimum of 0; consider other potassium-lowering medications		Targets avoidance of hyperkalemia
P.H. Pun and J.P. Middleton	3 mEq/L 4 mEq/L if persistent Sk<3.5; Avoid dialysate magnesium <1 mEq/L and bicarbonate >35 mEq/L	2 mEq/L	2 mEq/L + add potassium binder + dietary counseling + lengthen treatment time; if these measures are inadequate, lower to 1 mEq/L or consider dialysate profiling		Frequent potassium monitoring at least every week if using Dk>3 and <2 mEq/L and when Sk is <3.5 and >6.5

Dk, dialysate potassium; Sk, serum potassium.

arrest. Until more information and new technologies become available, one of the most important tools that we currently have at our disposal is the ability to modify dialysate potassium concentration. Dialysis-based clinicians need to be attentive to changes in the overall clinical scenario when choosing dialysate potassium concentrations, because new-onset conditions, such as altered nutrition, hypomagnesemia, or systemic acidosis, can have bearing on the ideal dialysate potassium concentration. An effective change in practice will require more frequent serum potassium monitoring, nimble coordinated dialysis care teams, and attentive and responsive dialysis-based clinicians.

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