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Hyponatremia in the Dialysis Population

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Sodium derangements are among the most frequently encountered electrolyte disorders in patients with end-stage renal disease. As dialysis patients are predisposed to hyponatremia via multiple pathways, assessment of extracellular volume status is an essential first step in disentangling potential etiologic factors. In addition, multiple large population-based studies indicate that proxies of malnutrition (e.g., low body mass index, serum albumin, and serum creatinine levels) and loss of residual kidney function are important determinants of hyponatremia in dialysis patients. Among hemodialysis and peritoneal dialysis patients, evidence suggests that incrementally lower sodium levels are associated with increasingly higher death risk, highlighting the long-term risk of hyponatremia. Whereas in conventional survival models incrementally lower serum sodium concentrations are associated with worse mortality in hemodialysis patients, studies that have examined repeated measures of predialysis sodium have demonstrated mixed associations of time-varying sodium with higher mortality risk (i.e., U-shaped vs. inverse linear relationships). Although the causality of the hyponatremia-mortality association in dialysis patients remains uncertain, there are several plausible pathways by which lower sodium levels may lead to higher death risk, including central nervous system toxicity, falls and fractures, infection-related complications, and impaired cardiac function. Areas of uncertainty ripe for future studies include the following: (i) mechanistic pathways by which lower serum sodium levels are linked with higher mortality in dialysis patients, (ii) whether correction of sodium derangements improves outcomes, (iii) the optimal sodium target, and (iv) the impact of age and other sociodemographic factors on hyponatremia-outcome associations.

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Hyponatremia is among the most common electrolyte disorders in dialysis patients.[1–3] Although prevalence estimates vary depending on the criteria used for the definition of hyponatremia and underlying study population characteristics (e.g., incident vs. prevalent dialysis patients, dialysis modality), epidemiologic data suggest that approximately 6% to 29% of hemodialysis[3–8] and 11% to 26% of peritoneal dialysis patients[2,9–14] have serum sodium levels ≤135 mEq/l (Table 1), which is substantially higher than that of the general population. However, despite the frequent occurrence of sodium derangements in dialysis patients, there remain substantial knowledge gaps regarding its prognostic implications and management in this population. Indeed, a growing body of evidence suggests that hyponatremia is a risk factor for mortality as well as substantial morbidity, including central nervous system toxicity,[15–17] hip fracture,[18] immune dysfunction and infection,[14,19–21] and cardiovascular complications.[22,23] In this review, we examine the pathophysiology of serum sodium derangements in dialysis patients; review epidemiologic data of correlates of hyponatremia; summarize existing studies of hyponatremia and mortality, including underlying mechanisms and optimal sodium targets; and outline potential management strategies for dysnatremia in hemodialysis and peritoneal dialysis patients.

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Pathophysiology of Hyponatremia in Dialysis Patients

Patients with end-stage renal disease are uniquely predisposed to hyponatremia, and a number of shared and distinct risk factors may be contributory among those receiving hemodialysis versus peritoneal dialysis. One framework for disentangling potential causes of hyponatremia is to consider accompanying changes in extracellular volume (ECV) status (Figure 1).[24,25] First, if

Table 1. Prevalence and incidence of low serum sodium levels in selected hemodialysis (HD) and peritoneal dialysis (PD) cohorts

HD patients			
Author (year)	**Study population**	**Definition**	**Incidence/prevalence**
Waikar *et al.* (2011)[8]	1549 prevalent HD patients from HEMO trial (US)	Lowest quartile (Sodium ≤136 mEq/l)	Prevalence: 29%
Hecking *et al.* (2012)[5]	11,555 prevalent HD patients (DOPPS I & III)	Mean sodium <135 mEq/l	Prevalence: 10%
Sahin *et al.* (2012)[7]	697 prevalent HD patients (Turkey)	Sodium <135 mEq/l	Prevalence: 6%
Nigwekar *et al.* (2012)[6]	6127 incident HD patients (US – ArMORR)	Sodium <135 mEq/l	Prevalence: 13%
Dekker *et al.* (2016)[4]	8883 HD patients (Europe – MONDO)	Sodium <135 mEq/l	Prevalence: 13%
Rhee *et al.* (2016)[3]	27,180 incident HD patients (US)	Sodium <134 mEq/l	Prevalence: 8%
PD patients			
Author (year)	**Study population**	**Definition**	**Incidence/prevalence**
Dimitriadis *et al.* (2014)[11]	198 PD patients (Canada)	Sodium <130 mmol/l	Incidence: 15%
Kang *et al.* (2013)[12]	387 PD patients (Korea)	Sodium <135 mmol/l	Incidence: 75%
Chen *et al.* (2014)[10]	318 incident/prevalent PD patients (Taiwan)	Sodium ≤135 mEq/l	Prevalence: 26%
Chang *et al.* (2014)[9]	441 incident PD patients (Korea)	Sodium <135 mEq/l	Prevalence: 13%
Tseng *et al.* (2014)[13]	99 PD patients admitted for peritonitis (China)	Sodium ≤130 mEq/l (2 occasions)	Prevalence: 27%
Xu *et al.* (2015)[48]	476 incident/prevalent PD patients (China)	Sodium ≤135 mmol/l	Prevalence: 11%
Ravel *et al.* (2016)[2]	4687 incident PD patients (US)	Sodium <136 mEq/l	Prevalence: 9%

ArMORR, Accelerated Mortality on Renal Replacement; DOPPS, Dialysis Outcomes and Practice Patterns; HD, hemodialysis; HEMO, Hemodialysis; MONDO, MONitoring Dialysis Outcomes; PD, peritoneal dialysis.

hyponatremia is accompanied by (i) an *increase in ECV* or weight, this suggests that a gain in electrolyte-free water is the basis for the sodium derangement, and may be a consequence of increased free water intake, and potentially excess sodium intake relative to the capacity for excretion although not to the same degree as free water. In the presence of excess free water intake, hyponatremia may be further exacerbated by dysregulation of thirst, loss of residual kidney function, or inadequate ultrafiltration. Although there are fluctuations in hemodialysis patients' ECV status over the course of the inter-dialytic interval, it is likely that a large proportion of observed hyponatremia cases are those of increased ECV status, given their tendency toward free water accumulation and routine laboratory testing before hemodialysis (i.e., predialysis serum sodium measurement).

In contrast, if there is (ii) *no change in ECV status*, the differential diagnosis of hyponatremia includes a gain of osmotically active solutes restricted to the extracellular fluid compartment (e.g., glucose, paraproteins). In terms of the former, in patients with severe hyperglycemia, elevated glucose levels increase serum tonicity, leading to a shift of electrolyte-free water from the intracellular to extracellular fluid compartments and subsequent hyponatremia.[24] In addition, in the context of kidney dysfunction, infusion of exogenous solutes (e.g., mannitol; immune globulin suspended in mannitol, maltose, or sucrose; glycine, sorbitol, or mannitol-based surgical irrigation solutions) will also result in extracellular fluid compartment solute retention, electrolyte-free water shifts, and isotonic or hypertonic hyponatremia.[24,26–28] With respect to the latter, with certain analytic methods presence of hyperlipidemia and hyperproteinemia may lead to pseudohyponatremia, a laboratory artifact, in which the sodium concentration in the water portion of plasma is not *per se* altered but the sodium concentration per unit of plasma is reduced.[29] Alternatively, loss of intracellular solutes (e.g., potassium, inorganic phosphate) due to protein-energy wasting may lead to a compensatory shift of sodium from the extracellular to intracellular fluid compartments; in the absence of residual kidney function or in the presence of vasopressin, electrolyte-free water will remain in the body, and a large proportion will distribute to the extracellular fluid compartment, leading to hyponatremia.[24] Indeed, rigorous examination of several well-described hemodialysis and peritoneal dialysis cohorts have observed that indices of malnutrition (e.g., low lean tissue mass, decreased body weight, lower serum creatinine as a proxy of muscle mass) were potent predictors of hyponatremia,[4,8,11] and it has been hypothesized that this may be related to inadequate sodium consumption relative to free water intake,[4] low potassium intake,[11] and catabolism of intracellular inorganic phosphates.[4,24]

Notably in peritoneal dialysis patients, the osmotically active molecules of icodextrin solution metabolites (e.g., maltose, maltotriose, other glucose multimers) may also lead to decrements in serum sodium levels via a dilutional effect.[30] Although only a fraction of icodextrin is absorbed, the portion that is absorbed is converted to oligosaccharides and maltose, and further metabolism is prevented by absence of circulating maltase.[31] Previous studies have observed that, over the course of an icodextrin exchange, sodium levels acutely decline with initiation, stabilize over time, then return to baseline levels following completion of the exchange; small increases in tonicity with icodextrin also may be observed.[30,32] Although icodextrin-related sodium

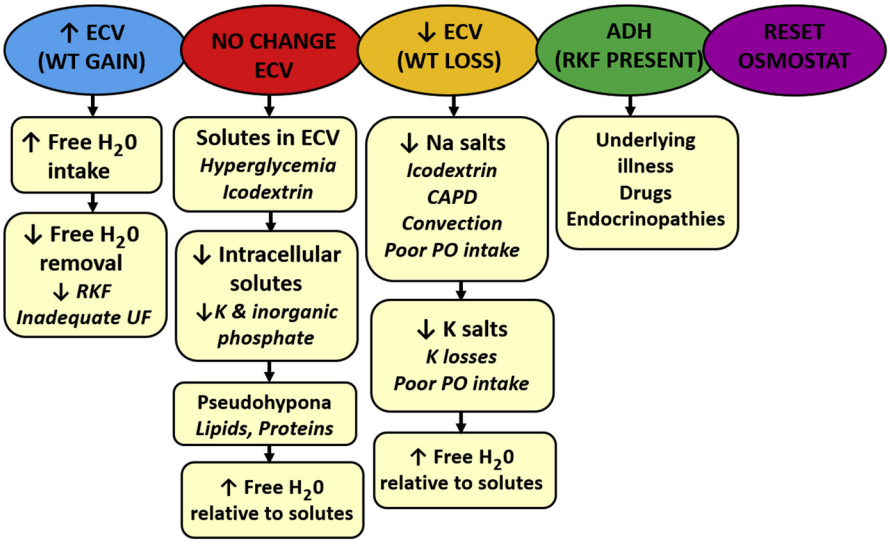

Figure 1. Risk factors for hyponatremia in dialysis patients. Upward-pointing arrow = increased; downward-pointing arrow = decreased. ADH, antidiuretic hormone; CAPD, continuous ambulatory peritoneal dialysis; ECV, extracellular volume; H_2O, water; K, potassium; PO, oral; RKF, residual kidney function; UF, ultrafiltration; WT, weight.

changes are typically mild, there have been case reports of adverse neurologic events (e.g., seizures) in the context of severe hyponatremia ensuing from icodextrin treatment in the presence of other hyponatremia-related risk factors (i.e., hyperglycemia from underlying diabetes).[33]

Although infrequently observed in the dialysis population, if hyponatremia is accompanied by (iii) an *ECV deficit*, this may be due to a loss of sodium and potassium salts resulting from poor nutritional intake or excess losses (e.g., gastrointestinal, peritoneal dialysate). Although hyponatremia in peritoneal dialysis patients is predominantly related to sodium and free water retention (i.e., resulting in increased ECV status) and accumulation of osmotically active icodextrin metabolites (i.e., resulting in unchanged ECV status), length of the dwell time may have some impact on the relative removal of sodium versus water and subsequent serum sodium levels.[2,11,34] Although "small pores" remove both sodium and water, "aquaporins" remove water only. Given that ultrafiltration largely occurs via aquaporins versus small pores during early versus later phases of the dwell, respectively, long dwell times observed with continuous ambulatory peritoneal dialysis (in contrast to more rapid-cycling automated peritoneal dialysis) may result in greater sodium removal. Furthermore, long day dwells using icodextrin will result in greater sodium removal due to increased ultrafiltration occurring via small pores.[35] Finally, although partial nephrogenic diabetes insipidus and impaired urinary concentration are typically characteristic of advanced chronic kidney disease,[36] in dialysis patients with substantial residual kidney function, inadequate vasopressin suppression leading to free water excess, as well as change in the set point for serum sodium may be contributory.[24,25]

Correlates of Hyponatremia in Dialysis Patients

Hemodialysis Patients

A number of epidemiologic studies have sought to identify clinical characteristics associated with hyponatremia in the hemodialysis population. In a secondary analysis of 1549 prevalent hemodialysis patients from the Hemodialysis (HEMO) trial with oligoanuria (residual urine output <200 ml/d), key predictors of higher baseline serum sodium concentrations included having higher estimated dry weight, serum albumin, and serum creatinine levels (proxy of muscle mass), suggesting that nutritional status may be an important determinant of having normonatremia versus dysnatremia.[8] In contrast, the strongest predictors of having lower serum sodium concentrations were receipt of higher ultrafiltration volumes, having underlying diabetes, and higher serum glucose levels. In an analysis of 11,555 prevalent hemodialysis patients across 12 countries from the Dialysis Outcomes and Practice Patterns Study (DOPPS) I and III cohorts, Hecking *et al.*[5] similarly observed that proxies of favorable nutritional status such as higher body mass index, serum albumin, and serum creatinine levels were associated with higher serum sodium levels, whereas greater intradialytic weight loss was associated with lower sodium levels. Notably, there was also a positive association between residual kidney function (present in 42% of the cohort) and serum sodium levels. To further elucidate the interrelationships between hyponatremia, protein-energy wasting (as one of the most potent predictors of death in chronic kidney disease

and dialysis patients[37,38]), and mortality, Dekker *et al.*[4] examined 8883 hemodialysis patients from the MONitoring Dialysis Outcomes (MONDO) initiative who underwent nutritional and fluid status assessment by bioimpedance spectroscopy and ascertainment of inflammation using C-reactive protein levels. Logistic regression analyses showed that malnutrition (defined as lean tissue index <10th percentile of age- and sex-matched controls) and inflammation (defined as C-reactive protein >6.0 mg/l) were associated with higher likelihood of hyponatremia (sodium <135 mEq/l), whereas fluid overload (defined as overhydration >+1.1 liters) was associated with lower likelihood of hyponatremia. Data on residual kidney function and urine output were not reported in this study.

There has been mixed data with respect to dialysis treatment characteristics as predictors of serum sodium levels. Although ultrafiltration volume has been linked with hyponatremia,[5,8] not all studies have not shown a consistent association between dialysate sodium concentration and serum sodium levels. In a cohort of DOPPS participants among whom 55%, 20%, and 25% of patients were prescribed dialysate sodium concentrations of 140 mEq/l, >140 mEq/l, and <140 mEq/l, respectively, the dialysate sodium concentration was not associated with serum sodium level.[5] Similarly, in a cohort of prevalent hemodialysis patients from a large US dialysis organization among whom 48%, 13%, and 11% of patients received fixed dialysate sodium prescriptions of 140 mmol/l, >140 mmol/l, and <140 mmol/l, respectively, and 28% were prescribed sodium modeling/profiling regimens, mean predialysis serum sodium levels did not vary according to dialysate sodium concentrations.[39] However, further studies are needed to determine the optimal dialysis prescription approach that best aligns dialysate-serum sodium concentrations and favorably impacts serum sodium levels while avoiding interdialytic weight gain, thirst, and hypertension.

Peritoneal Dialysis

There have been comparatively fewer reports of clinical characteristics associated with hyponatremia in peritoneal dialysis patients. To address this knowledge gap, one recent study by Dimitriadis *et al.*[11] examined risk factors associated with incident hyponatremia among patients receiving care in a Toronto Home Peritoneal Dialysis Unit. Among 166 patients who underwent at least 2 consecutive serum sodium measurements separated by at least 1 month, and who had follow-up of at least 60 days, 15% of patients developed hyponatremia (defined as sodium <130 mmol/l on 2 consecutive measures) over the course of 1 year. In multivariable adjusted analyses, higher levels of residual kidney function were independently correlated with higher serum sodium levels, whereas greater use of icodextrin was associated with lower sodium levels. Among a subcohort of 24 patients who developed hyponatremia, the investigators found that weight loss and a decline in serum potassium levels correlated with a decline in serum sodium, corroborating that poor nutritional status is a risk factor for incident hyponatremia in peritoneal dialysis patients. In a cross-sectional analysis of peritoneal dialysis patients from a large national dialysis organization in the United States, higher levels of residual kidney function (defined by renal urea clearance) and serum albumin levels (as an index of nutritional and inflammation status) had an inverse association with lower sodium levels (defined as <136 mEq/l).[2]

Hyponatremia and Mortality in Dialysis Patients

Hemodialysis

A large body of data has shown that there is an inverse association between lower serum sodium levels and higher mortality risk in hemodialysis patients (Table 2).[3,5–8,39–41] Among 11,555 prevalent hemodialysis patients across 12 countries from the DOPPS I and III cohorts, higher serum sodium levels (ascertained from the mean of patients' first 3 sodium measurements) examined in 4-mEq/l increments was associated with lower mortality risk.[5] When examined as tertiles (categorized as <137, 137 to <140, and ≥140 mEq/l), sodium levels <137 mEq/l were independently associated with a 45% higher mortality risk in analyses that comprehensively accounted for confounders such as sociodemographics, comorbidities, laboratory tests, intradialytic weight loss, dialysate sodium concentrations, and residual kidney function. In a subsequent study of 8883 patients from 17 European countries in the international MONDO initiative (median dialysis vintage 3.6 years), baseline serum sodium levels <135 mEq/l were associated with a 65% to 70% higher death risk (reference: sodium ≥ 135 mEq/l) independent of protein-energy wasting indices and markers of fluid overload.[4] With respect to incident hemodialysis patients who manifest distinct characteristics (i.e., greater residual kidney function yet higher mortality rates and less survivor bias) compared with prevalent patients, Nigwekar *et al.*[6] examined 6127 patients who newly initiated hemodialysis from the Accelerated Mortality on Renal Replacement (ArMORR) cohort, and found that each 3-mEq/l decrement in baseline sodium level was associated with increasingly higher death risk. When examined as a categorical variable, serum sodium levels <135 mEq/l (reference: sodium ≥135 mEq/l) were associated with a 42% higher 1-year all-cause death risk and a 29% higher cardiovascular death risk. Although the

Table 2. Selected studies of association of serum sodium levels and mortality risk in hemodialysis (HD) and peritoneal dialysis (PD) patients

HD

Author (year)	Cohort	Sodium definition	Outcome[a]	Analytic notes on multivariable adjustment
Waikar *et al.* (2011)[8]	1549 prevalent HD patients (US – HEMO)	• Baseline and time-varying sodium. • Examined as continuous variable with 4-mEq/l increments.	• Baseline analyses ➢ Each 4-mEq/l increment associated with 11% ↓ mortality risk. • Time-varying analyses ➢ Each 4-mEq/l increment associated with 9% ↓ mortality risk.	• Adjusted for nutritional status and diabetes. • Not adjusted for RKF.
Hecking *et al.* (2012)[5]	11,555 prevalent HD patients (12 countries - DOPPS I & III)	• Mean of first 3 sodium measurements. • Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <137, 137 to <140, ≥140 mEq/l).	• Continuous analyses ➢ Each 1-mEq/l increment associated with 5% ↓ mortality risk. • Categorical analyses ➢ Lowest tertile associated with 45% ↑ mortality risk.	• Adjusted for nutritional status, diabetes, and RKF.
McCausland *et al.* (2012)[39]	2272 prevalent HD patients (US - Satellite)	• Baseline sodium level. • Examined as continuous variable with 4-mmol/l increments. • Stratified by low versus high dialysate sodium concentration (<140 vs. ≥140 mmol/l).	• Low dialysate strata ➢ Each 4-mmol/l increment associated with 28% ↓ mortality risk. • High dialysate strata ➢ Each 4-mmol/l increment associated with 14% ↓ mortality risk.	• Adjusted for nutritional status and diabetes. • Not adjusted for RKF.
Sahin *et al.* (2012)[7]	697 prevalent HD patients (Turkey)	• Baseline sodium level. • Examined as continuous (1-mmol/l increments) and categorical variable (quartiles).	• Continuous analyses ➢ Each 1-mmol/l increment associated with 13% ↓ mortality risk. • Categorical analyses ➢ Lowest sodium quartile associated with 2.13-fold ↑ mortality risk.	• Adjusted for nutritional status and diabetes. • Not adjusted for RKF.
Mandai *et al.* (2013)[41]	332 prevalent HD patients (Japan)	• Baseline sodium level. • Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <138, 138–140, >140 mEq/l).	• Continuous analyses ➢ Each 1-mEq/l increment associated with 9% ↓ mortality risk. • Categorical analyses ➢ No association with mortality.	• Adjusted for nutritional status and diabetes. • Not adjusted for RKF.
Nigwekar *et al.* (2013)[6]	6127 incident HD patients (US – ArMORR)	• Baseline sodium <135 mEq/l.	• Sodium <135 mEq/l associated with 42% ↑ 1-year mortality.	• Adjusted for nutritional status and diabetes. • Not adjusted for RKF.
Dekker *et al.* (2016)[4]	8883 HD patients (Europe – MONDO)	• Baseline sodium <135 mEq/l.	• Sodium <135 mEq/l associated with 65%–70% ↑ mortality.	• Adjusted for nutritional status and diabetes. • Not adjusted for RKF.
Rhee *et al.* (2016)[3]	27,180 incident HD patients (US - DaVita)	• Baseline and time-varying sodium categories: <130, 130 to <132, 132 to <134, 134 to <136, 136 to <138, 138 to <140, 140 to <142, 140 to <144, ≥144 mEq/l.	• Baseline analyses ➢ Sodium <138 mEq/l associated with ↑ mortality. ➢ Sodium ≥144 mEq/l associated with ↓ mortality. • Time-dependent analyses: ➢ Sodium <138 mEq/l associated with ↑ mortality. ➢ Sodium ≥144 mEq/l associated with ↑ mortality.	• Adjusted for nutritional status and diabetes. • Not adjusted for RKF.

PD

Author (year)	Cohort	Sodium definition	Outcome	Analytic notes on multivariable adjustment
Kang *et al.* (2013)[12]	387 PD patients (Korea)	• Baseline sodium <135 mmol/l.	No association with mortality.	• Adjusted for nutritional status and RKF. • Not adjusted for diabetes nor icodextrin use.
Chen *et al.* (2014)[10]	318 incident/prevalent PD patients (Taiwan)	• Baseline sodium quartiles: 124–135, 136–139, 140–141, 142–148 mEq/l.	No association with mortality.	• Adjusted for nutritional status. • Not adjusted for diabetes, RKF, nor icodextrin use.
Kim *et al.* (2015)[22]	441 incident PD patients (Korea)	• Time-averaged sodium level. • Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <137, 137 to <139, ≥139 mEq/l).	• Continuous analyses ➢ Each 1-mEq/l increment associated with 10% ↓ incident CV events. • Categorical analyses ➢ Lowest tertile associated with 94% ↑ incident CV events.	• Adjusted for nutritional status, RKF, and icodextrin use. • Not adjusted for diabetes.
Chang *et al.* (2014)[9]	441 incident PD patients (Korea)	• Time-averaged sodium level. • Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <137, 137 to <139, ≥139 mEq/l).	• Continuous analyses ➢ Each 1-mEq/l increment associated with 21% ↓ all-cause mortality and 23% ↓ infection-related mortality. • Categorical analyses ➢ Lowest tertile associated with 3.35-fold ↑ all-cause mortality and 3.18-fold ↑ infection-related mortality.	• Adjusted for nutritional status, RKF, and icodextrin use. • Not adjusted for diabetes.

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Table 2. (Continued)

PD

Author (year)	Cohort	Sodium definition	Outcome	Analytic notes on multivariable adjustment
Tseng *et al.* (2014)[13]	99 PD patients admitted for peritonitis (China)	• Sodium ≤130 mEq/l (2 occasions).	• Sodium ≤130 mEq/l 77-fold ↑ in-hospital mortality.	• Not adjusted for nutritional status, diabetes, RKF, nor icodextrin use.
Al-Chidadi *et al.* (2016)[43]	3108 incident PD patients (UK)	• Baseline sodium level. • Examined as continuous (1-mEq/l increments) and categorical variable (tertiles: <138, 138 to <140, >140 mmol/l).	• Continuous analyses ➢ Each 1-mmol/l increment associated with 5% ↓ mortality. • Categorical analyses ➢ Lowest tertile associated with 49% ↑ mortality.	• Adjusted for nutritional status and diabetes. • Not adjusted for RKF nor icodextrin use.
Ravel *et al.* (2016)[2]	4687 incident PD patients (US)	• Baseline and time-varying sodium categories: <134, 134 to <136, 136 to <138, 138 to <140, 140 to <142, 140 to <144, ≥144 mEq/l.	• Baseline analyses ➢ Sodium <140 mEq/l associated with ↑ mortality. • Time-dependent analyses: ➢ Sodium <136 mEq/l associated with ↑ mortality.	• Adjusted for nutritional status, diabetes, and RKF. • Not adjusted for icodextrin use.

ArMORR, Accelerating Mortality on Renal Replacement; CV, cardiovascular; DOPPS, Dialysis Outcomes and Practice Patterns; HD, hemodialysis; HEMO, Hemodialysis; MONDO, MONitoring Dialysis Outcomes; PD, peritoneal dialysis; RKF, residual kidney function.
[a]All estimates presented from multivariable adjusted models.
Upward-pointing arrow = increased; downward-pointing arrow = decreased.

aforementioned studies might suggest that lower serum sodium levels are harmful, while higher levels are protective, the lack of repeated measures data did not allow for assessment of longitudinal changes in serum sodium over time. Furthermore, the relatively narrow spectrum of serum sodium levels (i.e., exclusion of patients with serum sodium >145 mEq/l in the latter study[6]) may have precluded granular assessment of serum sodium levels at higher ranges. In a study of 1549 prevalent hemodialysis patients from the HEMO trial with longitudinal laboratory data, predialysis serum sodium levels were examined as a continuous variable.[8] Analyses of baseline and time-varying sodium showed that each 4-mEq/l sodium increment was associated with a 9% to 11% lower death risk. However, it should be noted that examination of sodium as a continuous variable in 4-mEq/l increments (i.e., as opposed to a categorical variable or spline) precluded detection of nonlinear associations of sodium and death risk. To address these limitations, Rhee *et al.*[3] evaluated both baseline and time-varying sodium levels granularly categorized into 9 groups among 27,180 incident US hemodialysis patients in the largest study of dysnatremia and mortality in dialysis patients to date. Using conventional Cox regression models that comprehensively adjusted for confounders such as interdialytic weight gain, comorbidities, and nutritional status, analyses of baseline sodium (as a proxy of long-term sodium-mortality associations[40]) demonstrated an inverse linear association between serum sodium and mortality, such that sodium levels <138 mEq/l were incrementally associated with higher mortality, whereas levels ≥144 mEq/l were associated with lower mortality risk (Figure 2a). In contrast, analyses of time-dependent sodium (as a proxy of short-term sodium-mortality associations[40]) demonstrated a U-shaped relationship, such that sodium levels <138 mEq/l and ≥144 mEq/l were associated with higher death risk (Figure 2b). Recent data from the MONDO initiative have also shown that higher levels of sodium variability across all predialysis serum sodium levels were associated with higher mortality risk, highlighting the need for future studies examining variability as a clinical predictor of adverse outcomes.[42]

Peritoneal Dialysis

Although existing studies of dysnatremia and mortality in peritoneal dialysis patients have been conducted in comparatively smaller-sized cohorts, many but not all have shown a potent association between lower serum sodium and higher death risk in this population (Table 2).[2,9,10,12,13,22,43] Among the positive studies, Chang *et al.*[9] first examined the association between time-averaged sodium levels categorized as tertiles (<138, 137 to <139, ≥139 mEq/l) with mortality in a prospective study of 441 incident peritoneal dialysis patients from Korea. The investigators found that sodium levels <137 mEq/l were associated with higher all-cause and infection-related mortality risk. In a subsequent rigorous study, Al-Chidadi *et al.*[43] examined 3108 incident peritoneal dialysis patients from the UK Renal Registry who underwent sodium measurement at a single-point-in-time 90 days after treatment initiation. Upon examining sodium levels categorized into tertiles (<138, 138 to <140, ≥140 mmol/l), the investigators also found that lower sodium levels <138 mmol/l were associated with higher death risk. When sodium-mortality associations were examined across age strata, associations between the lowest sodium tertile with death persisted in the youngest age group (ages 18–54 years) only. In the largest study of sodium and outcomes conducted among peritoneal dialysis patients to date, Ravel *et al.*[2]

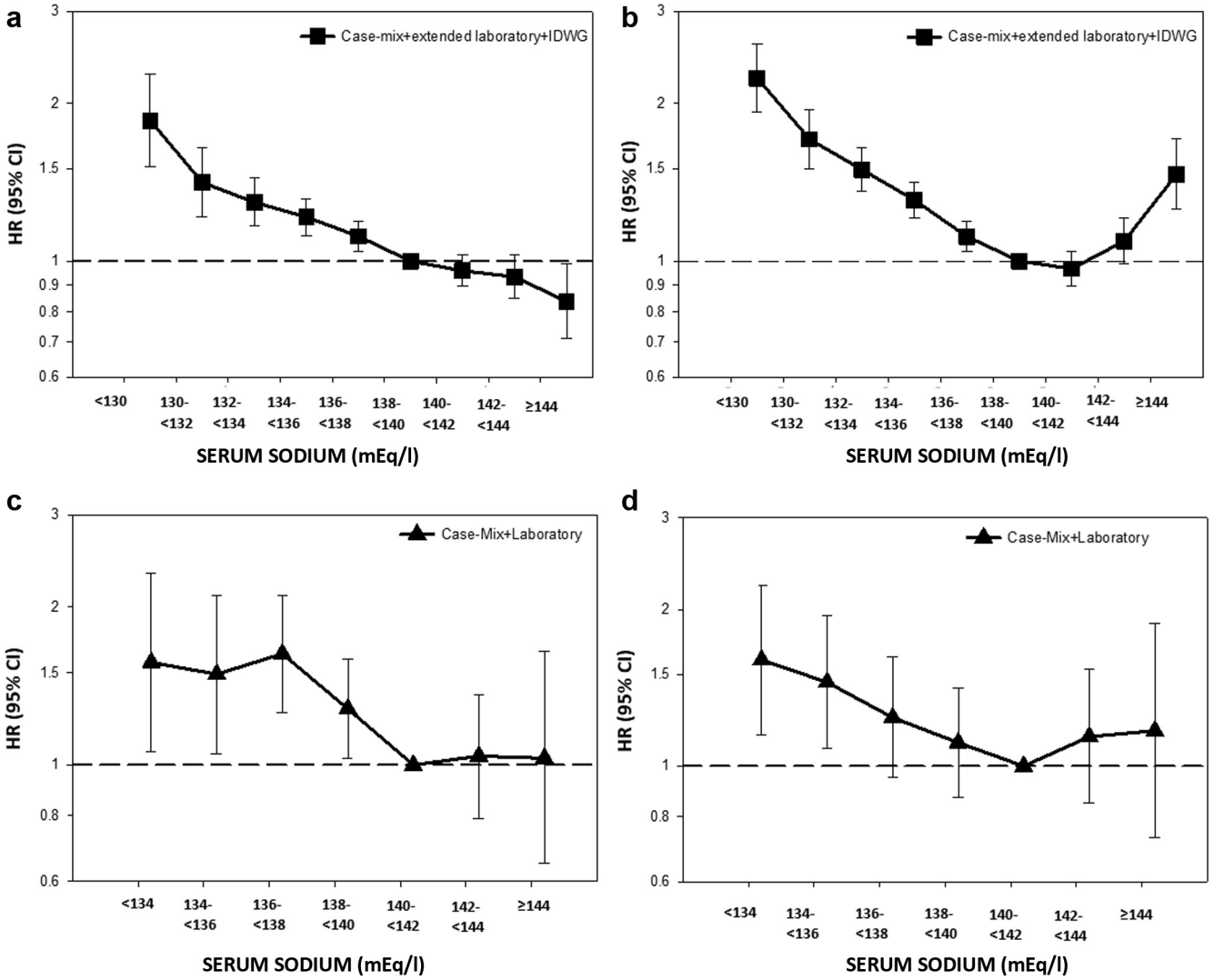

Figure 2. Association of baseline (a) and time-varying (b) serum sodium levels and mortality in hemodialysis patients. Association of baseline (c) and time-varying (d) serum sodium levels and mortality in peritoneal dialysis patients. CI, confidence interval; HR, hazard ratio; IDWG, interdialytic weight gain. Adapted from Ravel *et al.*[2] and Rhee *et al.*[3]

examined 4687 incident peritoneal dialysis patients from a large dialysis organization who had availability of both baseline and longitudinal sodium measurements. Assessment of fine gradations of baseline sodium showed that levels <140 mEq/l were associated with higher death risk independent of case-mix and laboratory covariates (Figure 2c), whereas time-varying analyses showed that sodium levels <136 mEq/l were associated with incrementally higher mortality risk (Figure 2d). These findings may suggest that the impact of lower sodium levels on long-term and short-term mortality in peritoneal dialysis patients may exist at different thresholds.[4]

Potential Mechanisms Underlying Hyponatremia and Mortality

It remains uncertain as to whether the hyponatremia-mortality associations in dialysis patients are causal, or due to confounding by conditions that predispose to low serum sodium levels (e.g., interdialytic weight gain and volume overload; low solute intake and protein-energy wasting; underlying comorbidities; Figure 3a). However, there are several potential pathways by which lower serum sodium levels may directly lead to higher mortality risk (Figure 4).

Central Nervous System Toxicity

Hyponatremia may promote injury to the central nervous system by engendering cerebral edema, herniation, encephalopathy, seizures, and coma.[15–17] Even mild reductions in sodium may lead to disequilibrium, gait instability, and falls and subsequent fractures.[1,44–47] For example, in a study of 476 incident and prevalent peritoneal dialysis patients recruited from 5 treatment centers in China by Xu *et al.*,[48] cross-sectional analyses of serum sodium with 3 cognitive tests were examined, including the (i) Modified Mini-Mental State Examination to ascertain global cognition, (ii) Trail making

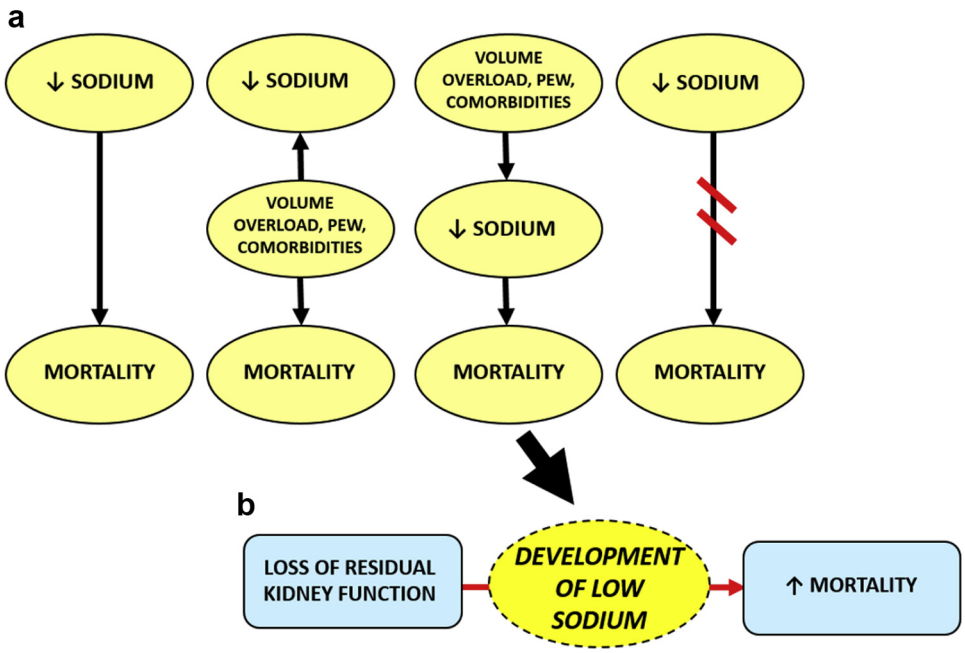

Figure 3. Varying scenarios of the interrelationship between serum sodium and mortality in dialysis patients (a). Low serum sodium as a mechanistic link between loss of residual kidney function and higher mortality risk (b). Upward-pointing arrow = increased; downward-pointing arrow = decreased. PEW, protein-energy wasting.

tests A and B to assess executive function, and (iii) Repeatable Battery for the Assessment of Neuropsychological Status to measure immediate and delayed memory and language ability. It was found that serum sodium levels ≤135 mmol/l were associated with worse global cognition and executive function.

Fracture Risk

In addition to causing disequilibrium and gait abnormalities, hyponatremia may further augment risk of fracture via reduction of bone mineral density and volume.[49,50] Experimental models have demonstrated that hyponatremia activates osteoclasts, manifesting higher calcium and suppressed parathyroid hormone levels.[6,50,51] It has also been suggested that lower sodium levels directly stimulate osteoblasts, leading to increased alkaline phosphate levels. Indeed, in a cross-sectional analysis of incident hemodialysis patients from the ArMORR cohort, hyponatremia was associated with hypercalcemia, hypoparathyroidism, and

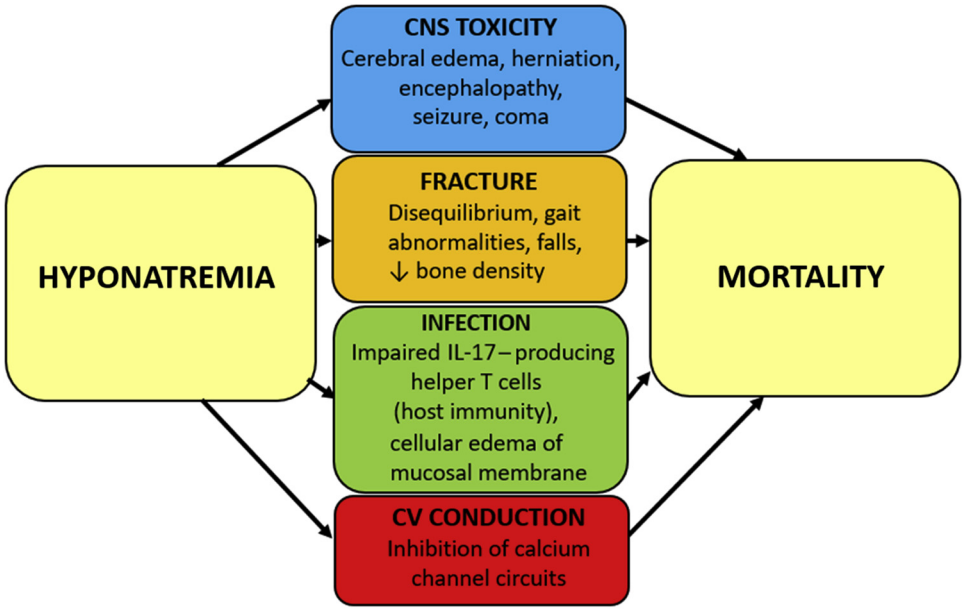

Figure 4. Potential mechanisms underlying the relationship between hyponatremia and mortality. Downward-pointing arrow = decreased. CNS, central nervous system; CV, cardiovascular; IL, interleukin.

elevated alkaline phosphatase levels.[6] These findings were corroborated by a study of US incident/prevalent peritoneal dialysis patients which showed that higher parathyroid hormone levels were associated with a lower likelihood of having a low sodium defined as <136 mEq/l (i.e., positive association between parathyroid hormone and sodium levels).[2] Finally, in a study of elderly patients >60 years of age from a health maintenance organization with 2 or more sodium measurements, those with prolonged chronic hyponatremia, defined as having a sodium of <135 mmol/l for more than 90 days, had a 4.5-fold higher risk of hip fracture compared with normonatremic patients.[18] Risk was even higher (i.e., 7.6-fold higher risk) among patients with moderate hyponatremia, defined as sodium levels <130 mmol/l.

Immune Dysfunction and Infection

Emerging data also indicate that hyponatremia may be a risk factor for infection due to impaired function of interleukin-17 producing helper T-cells that play a key role in host immunity and breakdown of microbial barrier function due to cellular edema or mucosal membranes.[14,19–21,41] In a study of 332 prevalent hemodialysis patients from Japan, incrementally lower serum sodium tertiles (derived from 3 monthly sodium measurements) were associated with increasingly higher infection-related hospitalization risk.[41] In another retrospective analysis of 99 peritoneal dialysis patients in China admitted for peritonitis, 27% of patients were found to have sodium levels of <130 mEq/l based on 2 consecutive measurements from the first 2 days of their hospitalization, among whom there was a higher frequency of gram-negative bacilli infection.[13]

Cardiovascular Complications

Finally, hyponatremia may also contribute to adverse cardiovascular outcomes vis-à-vis inhibition of calcium channel circuits in the heart leading to impaired cardiac function.[23] These findings bear particular importance to dialysis patients in whom cardiovascular disease and infection are the 2 most common causes of death.[52] Indeed, in a study of 441 incident peritoneal dialysis patients whose baseline serum sodium levels were categorized as tertiles (<137, 137 to <139, ≥139 mEq/l), those in the lowest tertile had a higher risk of a new-onset fatal or nonfatal cardiovascular events, defined as coronary artery disease (ascertained by receipt of angioplasty or coronary artery bypass graft surgery, or sustaining a myocardial infarction/angina), congestive heart failure, cerebrovascular disease, or peripheral artery disease (defined as receipt of revascularization or amputation).[22] Further rigorous studies including clinical trials are needed to determine whether correction of dysnatremia is associated with improved outcomes in dialysis patients, as well as the optimal sodium target in this population.

Hyponatremia as a Link Between Loss of Residual Kidney Function and Mortality

A large body of evidence has demonstrated that preservation of residual kidney function and urine output is associated with greater survival in both peritoneal dialysis and hemodialysis patients, whereas a decline in these parameters over time is associated with incrementally higher death risk.[53–57] Furthermore, in peritoneal dialysis patients, the attenuation in their early survival advantage over time has been attributed to loss of residual kidney function. Indeed, given its continuous nature, residual kidney function offers considerable benefits with respect to volume control, solute clearance, and uremic toxin removal even among patients receiving dialysis.[58,59] As several epidemiologic studies have shown that the loss of residual kidney function is characterized by transition from normal to low sodium levels,[11] it has been posited that hyponatremia may be a mechanistic link between decline in residual kidney function and mortality risk (Figure 3b). Further studies of the interplay between residual kidney function and sodium balance, as well as the causal implications upon survival in dialysis patients are needed.

Prevention and Management of Hyponatremia in Dialysis Patients

Given limited data addressing management of dysnatremia in dialysis patients, based on case report data, expert opinion, and extrapolation of observations from the nondialysis population, in the rare occasion in which a hemodialysis or peritoneal dialysis patient is hyponatremic and symptomatic (i.e., hyponatremic encephalopathy), we would support treatment similar to that of patients with normal kidney function, namely administration of 3% hypertonic saline.[19,60] Although further rigorous study of optimal dysnatremic management approaches in patients with end-stage renal disease are needed, there has been a published report of a hemodialysis patient with severe symptomatic hyponatremia (serum sodium 98 mEq/l) treated with i.v. hypertonic saline and immediate hemodialysis with a standard bath afterward, with subsequent improvement in mental status.[61] However, appropriate precautions should be taken when using this intervention. For example, it is extremely important to use hypertonic saline cautiously to avoid potential complications, including assessment of fluid overload, particularly among patients who are anuric, and ensuring there is adequate access to dialysis if required. In this regard, we recommend providing a 100-ml bolus of 3% hypertonic saline, which will mitigate risk of overaggressive correction and can conveniently be administered via peripheral i.v. route.[19,60,62] It

is also important to highlight that other pharmacotherapies that are used in hyponatremia such as vasopressin receptor antagonists (e.g., vaptans) do not have a role in dialysis patients. Among patients with chronic and/or recurrent asymptomatic hyponatremia, prevention and correction of free water excess is a cornerstone of management. Patients should first be counseled to avoid excess free water intake relative to the amount removed with dialysis. Among hemodialysis patients, if free water overload cannot be controlled with conventional thrice-weekly treatment, we recommend short daily hemodialysis, which has been shown to be effective in controlling fluid status and electrolyte abnormalities (i.e., phosphorus), while maintaining predialysis serum sodium levels within normal range.[63,64]

In peritoneal dialysis patients, hyponatremia is more commonly observed and may also be confounded by the high prevalence of diabetes and uncontrolled hyperglycemia in this population. Although management of hyponatremia in peritoneal dialysis may be more challenging for these reasons, modification of the dialysis prescription to augment fluid removal is also recommended. Dextrose-based solutions may also be used in lieu of icodextrin given their preferential aquaporin-mediated removal of water versus sodium[25]; however, this approach should be accompanied by careful attention to and adequate control of glycemic status, given the potential risks of (i) hyperglycemia-induced dilutional hyponatremia,[24] as well as (ii) elevated glucose levels driving increased thirst and free water consumption. In both peritoneal dialysis and hemodialysis patients with residual kidney function, loop diuretics can also be prescribed to augment free water excretion.

Given the high prevalence of malnutrition in dialysis patients and its associations with dysnatremia[4,8,11] and mortality,[37] nutritional status should also be prioritized. Although there are compelling data in support of fluid restriction in dialysis patients,[65–68] there is a paucity of evidence demonstrating the benefits of dietary sodium restriction in this population,[69] and further study of the latter's effects on clinical outcomes (e.g., including fluid status, survival, hospitalization, and patient's perceptions of thirst) is needed. Although we do not recommend complete relaxation of dietary recommendations, the restriction of fluid and dietary sodium intake should be reserved for patients with adequate nutritional status, and excess dietary limitations that could potentially compromise energy and protein intake in this population should be avoided.[69–71] Finally, among both hemodialysis and peritoneal dialysis patients, preservation of residual kidney function should be optimized in preventing the development of hyponatremia.[11,24,25]

Future Directions and Conclusion

There has been considerable progress in our understanding of serum sodium derangements in the dialysis population. Multiple population-based studies have demonstrated a substantially higher prevalence of dysnatremia in both hemodialysis and peritoneal dialysis patients,[2,3,5–13,40,48] and have also identified several shared risk factors for hyponatremia across these 2 modalities, including poor nutritional status[5,8,40] and loss of residual kidney function.[2,4] Across multiple studies of dialysis patients, lower serum sodium levels even in the normal range have been associated with adverse outcomes, including higher risk of all-cause mortality,[2–9,13,39,41,43] cardiovascular events,[22] infection-related complications,[13,41] and cognitive deficits.[48] However, many areas of uncertainty remain, including (i) mechanistic pathways by which lower serum sodium levels are linked with higher mortality in dialysis patients, (ii) whether hyponatremia contributes to the heightened mortality associated with loss of residual kidney function, (iii) the impact of correction or prevention of sodium derangements through proper dietary intake (e.g., fluid <1 liter/d and sodium intake <3 g/d[70]) and dialytic interventions (i.e., altered ultrafiltration, dialysate sodium concentrations) on outcomes, (iv) the optimal sodium target and degree of variability in this population, and (v) the impact of sociodemographic factors (e.g., race/ethnicity[72]) on hyponatremia-outcome associations and implications in pediatric[73,74] versus adult dialysis patients. Given the disproportionate prevalence and high mortality risk of dialysis patients, there is compelling need for further studies of the optimal management of sodium derangements in this population.

DISCLOSURE

All the authors declared no competing interests.

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REFERENCES

1. Hoorn EJ, Zietse R. Hyponatremia and mortality: moving beyond associations. *Am J Kidney Dis*. 2013;62:139–149.
2. Ravel VA, Streja E, Mehrotra R, et al. Serum sodium and mortality in a national peritoneal dialysis cohort. *Nephrol Dial Transplant*. 2017;32:1224–1233.

3. Rhee CM, Ravel VA, Ayus JC, et al. Pre-dialysis serum sodium and mortality in a national incident hemodialysis cohort. *Nephrol Dial Transplant*. 2016;31:992–1001.
4. Dekker MJ, Marcelli D, Canaud B, et al. Unraveling the relationship between mortality, hyponatremia, inflammation and malnutrition in hemodialysis patients: results from the international MONDO initiative. *Eur J Clin Nutr*. 2016;70:779–784.
5. Hecking M, Karaboyas A, Saran R, et al. Predialysis serum sodium level, dialysate sodium, and mortality in maintenance hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2012;59:238–248.
6. Nigwekar SU, Wenger J, Thadhani R, Bhan I. Hyponatremia, mineral metabolism, and mortality in incident maintenance hemodialysis patients: a cohort study. *Am J Kidney Dis*. 2013;62:755–762.
7. Sahin OZ, Asci G, Kircelli F, et al. The impact of low serum sodium level on mortality depends on glycemic control. *Eur J Clin Invest*. 2012;42:534–540.
8. Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium concentration in maintenance hemodialysis. *Am J Med*. 2011;124:77–84.
9. Chang TI, Kim YL, Kim H, et al. Hyponatremia as a predictor of mortality in peritoneal dialysis patients. *PLoS One*. 2014;9:e111373.
10. Chen KH, Chen CY, Lee CC, et al. Baseline hyponatremia does not predict two-year mortality in patients with chronic peritoneal dialysis. *Ren Fail*. 2014;36:1371–1375.
11. Dimitriadis C, Sekercioglu N, Pipili C, et al. Hyponatremia in peritoneal dialysis: epidemiology in a single center and correlation with clinical and biochemical parameters. *Perit Dial Int*. 2014;34:260–270.
12. Kang SH, Cho KH, Park JW, et al. Characteristics and clinical outcomes of hyponatraemia in peritoneal dialysis patients. *Nephrology (Carlton)*. 2013;18:132–137.
13. Tseng MH, Cheng CJ, Sung CC, et al. Hyponatremia is a surrogate marker of poor outcome in peritoneal dialysis-related peritonitis. *BMC Nephrol*. 2014;15:113.
14. Wu C, Yosef N, Thalhamer T, et al. Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1. *Nature*. 2013;496:513–517.
15. Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med*. 1986;314:1529–1535.
16. Ayus JC, Achinger SG, Arieff A. Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia. *Am J Physiol Renal Physiol*. 2008;295:F619–F624.
17. Riggs JE. Neurologic manifestations of fluid and electrolyte disturbances. *Neurol Clin*. 1989;7:509–523.
18. Ayus JC, Fuentes NA, Negri AL, et al. Mild prolonged chronic hyponatremia and risk of hip fracture in the elderly. *Nephrol Dial Transplant*. 2016;31:1662–1669.
19. Ayus JC, Caputo D, Bazerque F, et al. Treatment of hyponatremic encephalopathy with a 3% sodium chloride protocol: a case series. *Am J Kidney Dis*. 2015;65:435–442.
20. Kleinewietfeld M, Manzel A, Titze J, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature*. 2013;496:518–522.
21. van der Meer JW, Netea MG. A salty taste to autoimmunity. *N Engl J Med*. 2013;368:2520–2521.
22. Kim HW, Ryu GW, Park CH, et al. Hyponatremia predicts new-onset cardiovascular events in peritoneal dialysis patients. *PLoS One*. 2015;10:e0129480.
23. Movafagh S, Cleemann L, Morad M. Regulation of cardiac Ca(2+) channel by extracellular Na(+). *Cell Calcium*. 2011;49:162–173.
24. Cherney DZ, Zevallos G, Oreopoulos D, Halperin ML. A physiological analysis of hyponatremia: implications for patients on peritoneal dialysis. *Perit Dial Int*. 2001;21:7–13.
25. Musso CG, Bargman JM. Asymptomatic hyponatremia in peritoneal dialysis patients: an algorithmic approach. *Int Urol Nephrol*. 2014;46:2239–2241.
26. Daphnis E, Stylianou K, Alexandrakis M, et al. Acute renal failure, translocational hyponatremia and hyperkalemia following intravenous immunoglobulin therapy. *Nephron Clin Pract*. 2007;106:c143–c148.
27. Palevsky PM, Rendulic D, Diven WF. Maltose-induced hyponatremia. *Ann Intern Med*. 1993;118:526–528.
28. Zhang R, Szerlip HM. Reemergence of sucrose nephropathy: acute renal failure caused by high-dose intravenous immune globulin therapy. *South Med J*. 2000;93:901–904.
29. Turchin A, Seifter JL, Seely EW. Clinical problem-solving. Mind the gap. *N Engl J Med*. 2003;349:1465–1469.
30. Gokal R, Moberly J, Lindholm B, Mujais S. Metabolic and laboratory effects of icodextrin. *Kidney Int Suppl*. 2002;(81):S62–S71.
31. Silver SA, Harel Z, Perl J. Practical considerations when prescribing icodextrin: a narrative review. *Am J Nephrol*. 2014;39:515–527.
32. Plum J, Gentile S, Verger C, et al. Efficacy and safety of a 7.5% icodextrin peritoneal dialysis solution in patients treated with automated peritoneal dialysis. *Am J Kidney Dis*. 2002;39:862–871.
33. Gradden CW, Ahmad R, Bell GM. Peritoneal dialysis: new developments and new problems. *Diabet Med*. 2001;18:360–363.
34. Diaz-Buxo JA. Prescription writing: CAPD and PD plus. *Clin Nephrol*. 2007;68:349–353.
35. Rodriguez-Carmona A, Fontan MP. Sodium removal in patients undergoing CAPD and automated peritoneal dialysis. *Perit Dial Int*. 2002;22:705–713.
36. Moeller HB, Rittig S, Fenton RA. Nephrogenic diabetes insipidus: essential insights into the molecular background and potential therapies for treatment. *Endocr Rev*. 2013;34:278–301.
37. Kalantar-Zadeh K, Rhee C, Sim JJ, et al. Why cachexia kills: examining the causality of poor outcomes in wasting conditions. *J Cachexia Sarcopenia Muscle*. 2013;4:89–94.
38. Nourbakhsh N, Rhee CM, Kalantar-Zadeh K. Protein-energy wasting and uremic failure to thrive in children with chronic kidney disease: they are not small adults. *Pediatr Nephrol*. 2014;29:2249–2252.
39. Mc Causland FR, Brunelli SM, Waikar SS. Dialysate sodium, serum sodium and mortality in maintenance hemodialysis. *Nephrol Dial Transplant*. 2012;27:1613–1618.

40. Dekker FW, de Mutsert R, van Dijk PC, et al. Survival analysis: time-dependent effects and time-varying risk factors. *Kidney international*. 2008;74(8):994–997.
41. Mandai S, Kuwahara M, Kasagi Y, et al. Lower serum sodium level predicts higher risk of infection-related hospitalization in maintenance hemodialysis patients: an observational cohort study. *BMC Nephrol*. 2013;14:276.
42. Ye X, Kooman JP, van der Sande FM, et al. Increased mortality associated with higher pre-dialysis serum sodium variability: results of the International MONitoring Dialysis Outcome Initiative. *Am J Nephrol*. 2018;49:1–10.
43. Al-Chidadi A, Nitsch D, Davenport A. The effect of serum sodium on survival in patients treated by peritoneal dialysis in the United Kingdom. *Perit Dial Int*. 2017;37:70–77.
44. Ayus JC, Moritz ML. Bone disease as a new complication of hyponatremia: moving beyond brain injury. *Clin J Am Soc Nephrol*. 2010;5:167–168.
45. Ayus JC, Negri AL, Kalantar-Zadeh K, Moritz ML. Is chronic hyponatremia a novel risk factor for hip fracture in the elderly? *Nephrol Dial Transplant*. 2012;27:3725–3731.
46. Kinsella S, Moran S, Sullivan MO, et al. Hyponatremia independent of osteoporosis is associated with fracture occurrence. *Clin J Am Soc Nephrol*. 2010;5:275–280.
47. Renneboog B, Musch W, Vandemergel X, et al. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med*. 2006;119, 71.e1–e8.
48. Xu R, Pi HC, Xiong ZY, et al. Hyponatremia and cognitive impairment in patients treated with peritoneal dialysis. *Clin J Am Soc Nephrol*. 2015;10:1806–1813.
49. Barsony J, Manigrasso MB, Xu Q, et al. Chronic hyponatremia exacerbates multiple manifestations of senescence in male rats. *Age (Dordr)*. 2013;35:271–288.
50. Verbalis JG, Barsony J, Sugimura Y, et al. Hyponatremia-induced osteoporosis. *J Bone Miner Res*. 2010;25:554–563.
51. Barsony J, Sugimura Y, Verbalis JG. Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. *J Biol Chem*. 2011;286:10864–10875.
52. *USRDS 2014 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. Bethesda, MD: US Renal Data System; 2014.
53. Bargman JM, Golper TA. The importance of residual renal function for patients on dialysis. *Nephrol Dial Transplant*. 2005;20:671–673.
54. Bargman JM, Thorpe KE, Churchill DN, Group CPDS. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol*. 2001;12:2158–2162.
55. Obi Y, Rhee CM, Mathew AT, et al. Residual kidney function decline and mortality in incident hemodialysis patients. *J Am Soc Nephrol*. 2016;27:3758–3768.
56. Paniagua R, Amato D, Vonesh E, et al. Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol*. 2002;13:1307–1320.
57. Shafi T, Jaar BG, Plantinga LC, et al. Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. *Am J Kidney Dis*. 2010;56:348–358.
58. Rhee CM, Ghahremani-Ghajar M, Obi Y, Kalantar-Zadeh K. Incremental and infrequent hemodialysis: a new paradigm for both dialysis initiation and conservative management. *Panminerva Med*. 2017;59:188–196.
59. Rhee CM, Unruh M, Chen J, et al. Infrequent dialysis: a new paradigm for hemodialysis initiation. *Semin Dial*. 2013;26:720–727.
60. Achinger SG, Ayus JC. Treatment of hyponatremic encephalopathy in the critically ill. *Crit Care Med*. 2017;45:1762–1771.
61. Ayus JC, Olivero JJ, Frommer JP. Rapid correction of severe hyponatremia with intravenous hypertonic saline solution. *Am J Med*. 1982;72:43–48.
62. Moritz ML, Ayus JC. 100 cc 3% sodium chloride bolus: a novel treatment for hyponatremic encephalopathy. *Metab Brain Dis*. 2010;25:91–96.
63. Ayus JC, Mizani MR, Achinger SG, et al. Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. *J Am Soc Nephrol*. 2005;16:2778–2788.
64. Zimmerman DL, Ruzicka M, Hebert P, et al. Short daily versus conventional hemodialysis for hypertensive patients: a randomized cross-over study. *PLoS One*. 2014;9:e97135.
65. Kalantar-Zadeh K, Regidor DL, Kovesdy CP, et al. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. *Circulation*. 2009;119:671–679.
66. Weiner DE, Brunelli SM, Hunt A, et al. Improving clinical outcomes among hemodialysis patients: a proposal for a "volume first" approach from the chief medical officers of US dialysis providers. *Am J Kidney Dis*. 2014;64:685–695.
67. Zoccali C. Lung ultrasound in the management of fluid volume in dialysis patients: potential usefulness. *Semin Dial*. 2017;30:6–9.
68. Zoccali C, Moissl U, Chazot C, et al. Chronic fluid overload and mortality in ESRD. *J Am Soc Nephrol*. 2017;28:2491–2497.
69. Kalantar-Zadeh K, Tortorici AR, Chen JL, et al. Dietary restrictions in dialysis patients: is there anything left to eat? *Semin Dial*. 2015;28:159–168.
70. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. *N Engl J Med*. 2017;377:1765–1776.
71. Ko GJ, Kalantar-Zadeh K, Goldstein-Fuchs J, Rhee CM. Dietary approaches in the management of diabetic patients with kidney disease. *Nutrients*. 2017;9:E824.
72. Laster M, Soohoo M, Hall C, et al. Racial-ethnic disparities in mortality and kidney transplant outcomes among pediatric dialysis patients. *Pediatr Nephrol*. 2017;32:685–695.
73. Ingelfinger JR, Kalantar-Zadeh K, Schaefer F. World Kidney Day Steering Committee. World Kidney Day 2016: averting the legacy of kidney disease-focus on childhood. *Pediatr Nephrol*. 2016;31:343–348.
74. Ingelfinger JR, Kalantar-Zadeh K, Schaefer F, World Kidney Day Steering Committee. Reply to comment on World Kidney Day 2016: averting the legacy of kidney disease-focus on childhood. *Pediatr Nephrol*. 2016;31:1711.