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Dialysate sodium, serum sodium and mortality in maintenance hemodialysis

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Abstract

Background. Individuals with end-stage kidney disease appear to have stable pre-dialysis serum sodium concentrations over time, with lower values associating with increased mortality. Dialysate sodium concentrations have increased over many years in response to shorter treatments, but the relationship between serum sodium, dialysate sodium and outcomes in chronic hemodialysis patients has not yet been systematically examined.

Methods. We studied a cohort of 2272 individuals receiving thrice-weekly hemodialysis treatment. Available data included demographics, laboratory and clinical measures, details of the dialysis prescription and 30-month follow-up. We examined the distribution of serum and dialysate sodium among subjects and compared mortality according to dialysate and serum sodium concentrations using Cox regression models.

Results. Dialysate sodium concentration varied within and among dialysis centers. The pre-dialysis serum sodium concentration (mean 136.1 mmol/L) did not differ across dialysate sodium concentrations. There was evidence for effect modification for mortality according to differing serum sodium and dialysate sodium concentrations ($P = 0.05$). For each 4 mmol/L increment in serum sodium, the hazard ratio for death was 0.72 [95% confidence interval (CI) 0.63–0.81] with lower dialysate sodium compared to 0.86 (95% CI 0.75–0.99) for higher dialysate sodium. Higher dialysate sodium concentration was associated with mortality at higher, but not lower, pre-dialysis serum sodium concentrations.

Conclusions. The pre-dialysis serum sodium concentration appears to be unaffected by the dialysate sodium concentration. The relationship between serum and dialysate sodium and mortality appears to be variable. Further research is warranted to

determine the biological mechanisms of these associations and to re-examine total body sodium handling in hemodialysis.

Keywords: dialysate; hemodialysis; hyponatremia; modeling; mortality

Introduction

Patients with oligo anuric end-stage kidney disease (ESKD) requiring dialysis are largely dependent on the dialysis procedure to control volume status, electrolyte concentrations and osmolality. The electrolyte composition of dialysate plays an important role in facilitating the diffusive clearance of potassium and gain of bicarbonate. However, the optimal dialysate sodium concentration is not known. Over the past several decades, higher dialysate sodium concentrations have been used by physicians in the USA, presumably to reduce the frequency of dialysis-associated symptoms and intra-dialytic hypotension, which became increasingly common as dialysis times were reduced [1]. In addition to fixed higher dialysate sodium concentrations, sodium modeling/profiling has gained popularity—this method involves programmed changes in dialysate sodium concentration, generally beginning with hyperosmolar concentrations and decreasing to isosmolar concentrations by the end of the dialysis treatment. As the net exposure over the course of dialysis is to a hypertonic bath, such treatments may be considered as utilizing higher dialysate sodium concentrations.

Individual hemodialysis patients may have stable pre-dialysis serum sodium concentrations over time [2], suggesting the possible existence of a patient-specific ‘sodium set point’ [3]. We have previously shown that hyponatremia (<135 mmol/L) associates with increased mortality in chronic hemodialysis patients [4]. Net sodium balance during dialysis depends on both diffusion (the concentration gradient between the serum and dialysate sodium) and convection (achieved through ultrafiltration) [5]. Alignment of the dialysate and serum sodium concentrations in small studies has been shown to reduce inter-dialytic weight gain (IDWG), thirst scores and improve blood pressure control [6], but data examining the interplay among plasma sodium, dialysate sodium and hard clinical outcomes, such as mortality, are lacking.

We undertook this study to explore the relationship between dialysate sodium, pre-dialysis serum sodium and outcomes in a cohort of prevalent hemodialysis patients.

Materials and methods

Study population

The Partners Institutional Review Board approved this protocol. We performed a non-concurrent cohort study of prevalent subjects receiving in-center maintenance hemodialysis in Satellite Healthcare dialysis facilities (Satellite Healthcare Inc.) in 2008. Patients became eligible for participation on the earliest date within this time period on which they were at least 18 years of age, had been receiving hemodialysis for >180 days and had available data for calculation of baseline serum sodium, estimated dry weight (EDW) and IDWG. Of the 2557 potential subjects thus eligible, we excluded the following: patients receiving dialysis on schedules other than thrice weekly ($n = 240$), patients with prescribed dialysis times <150 min per treatment ($n = 51$), patients who recovered renal function during follow-up ($n = 14$) and patients who died before at-risk time began ($n = 13$). The total number of subjects included in the final analysis was 2272.

Outcomes

The primary outcome was the time to death from any cause. At-risk time for all analyses began on Day 31 post-enrollment. Subjects remained at risk until death, kidney transplant, transfer to an outside facility or censoring at the end of follow-up (16 August 2010). Maximum potential follow-up time was 928 days. Additional outcomes included IDWG and blood pressure.

Study data

Covariate data were considered over the first 30 days in the study (which preceded the start of at-risk time). Variables of interest included demographic characteristics, dialysis vintage, comorbidities, dialysis treatment parameters, hemodynamic parameters, IDWG, laboratory data and dialysate sodium concentration. Details of the dialysis treatment were recorded at each dialysis session during the study period. All laboratory measurements (including sodium, potassium, hemoglobin, phosphorus and albumin) were measured on samples drawn immediately prior to dialysis on at least a monthly basis; all assays were performed in a central laboratory utilized by Satellite Healthcare (Satellite Laboratory Services, Redwood City, CA). Serum sodium measurements were made *via* an indirect method using ion-selective electrodes. Mean baseline laboratory (sodium, potassium, albumin, phosphorus, hemoglobin and Kt/V) and clinical (blood pressure and IDWG) variables were considered over the baseline 30 days. Dialysate sodium prescription was recorded at baseline and considered unchanged during the follow-up period.

Statistical analysis

Continuous variables were examined graphically and recorded as means ($\pm$ SD) for normally distributed data or medians (with inter-quartile ranges) for non-normally distributed data. Comparisons were made using *t*-tests, Wilcoxon rank sum tests, analysis of variance or Kruskal–Wallis tests as appropriate. Categorical variables were examined by frequency distribution, recorded as proportions and comparisons made using the chi-square or Fishers exact tests.

The joint association of serum and dialysate sodium with relative IDWG, absolute IDWG and pre-dialysis systolic blood pressure was examined using linear regression models with and without adjustment for case mix. Interaction between serum and dialysate sodium with each of these factors was explored (and excluded) by inclusion of two-way cross product terms and likelihood ratio testing.

Initially, associations with all-cause mortality were explored using unadjusted proportional hazards regression. Adjusted associations between serum sodium concentration ($[Na^+]$) and dialysate $[Na^+]$ and all-cause mortality were estimated using multivariable proportional hazards regression. Interaction between serum $[Na^+]$ and dialysate $[Na^+]$ was examined for through inclusion of a two-way cross product term and significance adjudicated *via* likelihood ratio testing. Stratum-specific hazard ratios were calculated *via* linear combination of regression coefficients for main effects and cross-product terms. Adjusted estimates were determined by analogous models, stratified on clinical center and included covariate terms for sex, race, age, dialysis vintage (<12 , 12–24, 24–48, >48 months), diabetes, congestive heart failure (CHF) status, albumin, hemoglobin, phosphorus and Kt/V ; these variables were selected based on clinical and biological plausibility. Linearity of continuous variables was examined graphically by plotting Martingale residuals against each continuous variable and by examination of model fit using Akaike’s Information Criterion. The proportionality assumption was tested by Schoenfeld residual testing. For those that violated the proportionality assumption, the corresponding time interaction term was included in the final model (albumin and hemoglobin).

Missing values for IDWG and Kt/V (each missing in $<4\%$ of the cohort) were imputed by carrying back the next available value after Day 30. Nominal two-sided *P*-values of <0.05 were considered statistically significant. Analyses were performed using SAS v9.2 (SAS Institute, Cary, NC) and STATA 10.0MP (College Station, TX).

Results

Dialysate sodium concentration

The primary cohort consisted of 2272 individuals who received hemodialysis at 24 different clinical centers. The mean age was 62.5 ± 15.2 years; 55.9% were male, 27.2% were black and 63.0% were diabetic. The most commonly used

dialysate $[\text{Na}^+]$ were fixed dialysate sodium of 140 mmol/L (47.9%) and sodium modeling/profiling (28.1%; of which 40.3% were linear and 59.7% stepped algorithms). The remaining individuals received either fixed dialysate sodium of >140 mmol/L (12.7% of total; of which 85% were 145 mmol/L) or fixed dialysate sodium of <140 mmol/L (11.3% of total; of which 84% were 137 mmol/L). We identified notable variations in the dialysate sodium prescription across centers, with apparent clustering of higher dialysate $[\text{Na}^+]$ and use of sodium modeling in certain centers (Figure 1).

Table 1 shows the baseline characteristics of the study sample according to the dialysate $[\text{Na}^+]$. Those on a fixed dialysate $[\text{Na}^+] <140$ mmol/L tended to be younger, with a lower prevalence of diabetes and CHF, longer treatment times and lower IDWG.

Pre-dialysis serum sodium concentration

The mean pre-dialysis serum $[\text{Na}^+]$ was 136.1 mmol/L (SD 3.2; range 120–146) and did not vary according to baseline dialysate $[\text{Na}^+]$ (Figure 2, $P = 0.36$). The intra-class correlation coefficient for the pre-dialysis serum $[\text{Na}^+]$ during the study period was 0.56 [95% confidence interval (CI): 0.55–0.58].

Dialysate sodium, IDWG and blood pressure

Higher dialysate $[\text{Na}^+]$, defined as >140 mmol/L or sodium modeling—compared to lower dialysate $[\text{Na}^+]$ (≤ 140 mmol/L)—was found to be a significant predictor of greater IDWG. On unadjusted analysis, use of higher compared to lower dialysate $[\text{Na}^+]$ was associated with greater relative and absolute IDWG: differences versus lower dialysate sodium were 0.19% of EDW ($P = 0.001$) and 0.16 kg ($P = 0.001$), respectively (Table 2). After adjustment for differences in sex, race, age, diabetes, CHF status, vintage, albumin, hemoglobin, phosphorus and Kt/V , higher dialysate $[\text{Na}^+]$ remained associated with greater relative and absolute IDWG: differences versus lower dialysate $[\text{Na}^+]$ of 0.14% EDW ($P = 0.02$) and 0.11 kg ($P = 0.01$), respectively. In both unadjusted and adjusted analyses, relative IDWG exhibited an inverse relationship with the pre-dialysis serum $[\text{Na}^+]$.

No association was observed between either dialysate or serum $[\text{Na}^+]$ and pre-dialysis systolic blood pressure.

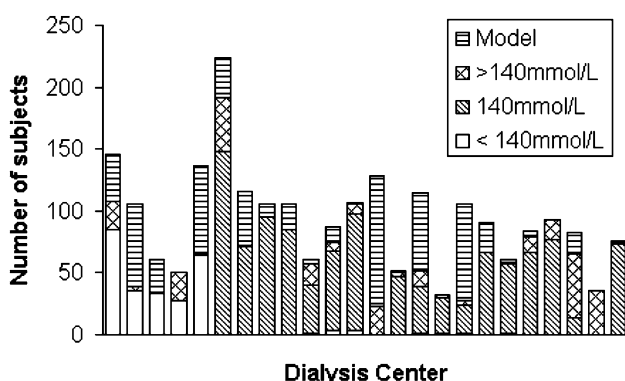


Fig. 1. Distribution of dialysate sodium concentrations according to dialysis center.

Dialysate sodium, serum sodium and mortality

Overall, participants contributed 4224 patient-years of at-risk time, during which 625 deaths were observed; median follow-up time was 2.4 years. We found evidence for interaction between dialysate $[\text{Na}^+]$ (higher versus lower) and pre-dialysis serum $[\text{Na}^+]$ and their association with mortality (P -interaction = 0.05; Figure 3). In the setting of lower dialysate $[\text{Na}^+]$, each 4 mmol/L increment in serum $[\text{Na}^+]$ was associated with a 28% reduction in mortality—adjusted hazard ratio (95% CI) 0.72 (0.63–0.81); $P < 0.001$. In the setting of higher dialysate $[\text{Na}^+]$, each 4 mmol/L increment in serum $[\text{Na}^+]$ was associated with a 14% reduction in mortality—adjusted hazard ratio (95% CI) 0.86 (0.75–0.99); $P = 0.05$. Considered alternatively, these data indicate that higher dialysate $[\text{Na}^+]$ was associated with greater mortality at higher serum $[\text{Na}^+]$, whereas no significant association was observed between higher dialysate $[\text{Na}^+]$ and mortality at lower serum $[\text{Na}^+]$ (Figure 4). Although pre-dialysis blood pressure and IDWG were not included in the primary models due to concerns of pathway intermediacy, results were nearly identical when these were added to the model (data not shown). The associations of dialysate $[\text{Na}^+]$ and serum $[\text{Na}^+]$ with mortality did not appear to be modified by the presence/absence of CHF or diabetes (P -interaction 0.19 and 0.29, respectively).

Repeated measures were available for laboratory and hemodynamic parameters in the 12-month period from entry into the study. Upon fitting of a time-updated Cox proportional hazards model, incorporating repeated measures of pre-dialysis serum sodium <1 year, our results were essentially changed (data not shown).

It is possible that the association between higher dialysate $[\text{Na}^+]$ and mortality related to preferential prescription of sodium modeling to patients with poorer prognosis (i.e. confounding by indication on the basis of cardiovascular disease). To explore this issue further, we compared mortality between subjects receiving fixed higher dialysate $[\text{Na}^+]$ (>140 mmol/L) versus those who were sodium modeled, within the overall higher dialysate $[\text{Na}^+]$ subgroup. There was no significant difference in mortality; in fact, mortality trended to be less among the modeled patients—adjusted hazard ratio (95% CI) 0.87 (0.60–1.27).

Discussion

This study represents the most comprehensive evaluation, to our knowledge, of the dialysate $[\text{Na}^+]$ and serum $[\text{Na}^+]$ in maintenance hemodialysis. The main findings of our study are as follows: (i) the dialysate $[\text{Na}^+]$ composition in a medium-sized US dialysis organization varies widely within and among centers; (ii) the pre-dialysis serum $[\text{Na}^+]$ is not associated with the dialysate sodium prescription; (iii) IDWG, but not pre-dialysis systolic blood pressure, is associated with higher dialysate $[\text{Na}^+]$ and (iv) the relationship between dialysate $[\text{Na}^+]$, serum $[\text{Na}^+]$ and mortality is variable.

There is no consensus on the optimal dialysate $[\text{Na}^+]$, as evidenced by the wide variety of prescriptions across and within centers. Over time in the USA, dialysate $[\text{Na}^+]$ has been increased gradually, in response to concerns over

Table 1. Characteristics of the total study cohort and comparisons across dialysate sodium categories^a

	Total Cohort	Dialysate sodium			Model	p ^b
		<140 mmol/L	140 mmol/L	>140 mmol/L		
N	2272	257	1088	289	638	
Male (%)	55.9	59.1	55.3	57.1	54.9	0.64
Black (%)	27.2	40.9	22.1	32.9	27.7	<0.001
Age (years)	62.5 ± 15.2	56.6 ± 15.1	64.2 ± 15.5	62.9 ± 14.6	62.0 ± 14.5	<0.001
Vintage (months)	30.6 (13.4, 55.4)	23.7 (10.1, 50.8)	29.1 (13.7, 54.2)	32.4 (9.0, 58.3)	35.4 (17.3, 60.6)	<0.001
Diabetes (%)	63.0	58.0	60.7	70.9	65.4	0.002
CHF (%)	29.0	24.9	28.6	32.2	30.1	0.26
Dialysis length (min)	194 ± 26.6	213.8 ± 30.2	188.5 ± 21.9	188.9 ± 28.5	197.8 ± 27.2	<0.001
Dialysis length ≥180 min (%)	89.0	92.6	89.2	79.9	91.4	<0.001
EDW (kg)	75.5 ± 20.8	79.0 ± 20.1	74.4 ± 20.6	75.1 ± 20.1	76.0 ± 21.5	0.01
Absolute IDWG (kg) ^c	2.78 ± 1.11	2.62 ± 1.10	2.73 ± 1.08	2.90 ± 1.02	2.88 ± 1.19	0.002
Relative IDWG (%) ^d	3.79 ± 1.44	3.41 ± 1.51	3.77 ± 1.34	3.97 ± 1.39	3.89 ± 1.54	<0.001
Pre-dialysis SBP (mmHg)	152.2 ± 20.3	154.1 ± 20.2	151.7 ± 20.4	154.3 ± 20.3	151.2 ± 19.9	0.05
Dialysate K (%)						
1 mmol/L	22.8	9.0	25.4	22.5	24.1	<0.001
2 mmol/L	50.6	76.6	42.8	49.5	53.9	<0.001
3 mmol/L	26.6	14.4	31.8	28.0	21.9	<0.001
Serum K (mmol/L)	5.0 ± 0.6	4.8 ± 0.6	5.0 ± 0.6	5.0 ± 0.6	5.0 ± 0.6	0.004
Serum Na (mmol/L)	136.1 ± 3.2	136.3 ± 3.1	136.1 ± 3.1	136.1 ± 3.0	135.9 ± 3.5	0.36
Albumin (g/L)	37.7 ± 3.5	37.0 ± 4.0	38.0 ± 3.0	38.0 ± 4.0	38.0 ± 4.0	0.43
Hemoglobin (g/dL)	12.0 ± 1.2	11.9 ± 1.2	12.0 ± 1.2	12.0 ± 1.1	12.0 ± 1.2	0.24
Phosphorus (mmol/L)	1.7 ± 0.5	1.9 ± 0.5	1.7 ± 0.4	1.8 ± 0.5	1.7 ± 0.5	<0.001
Kt/V	1.69 ± 0.40	1.66 ± 0.4	1.70 ± 0.4	1.68 ± 0.4	1.69 ± 0.4	0.65

^aContinuous variables are expressed as means ± SD or medians (inter-quartile range). SBP, systolic blood pressure; K, potassium; Na, sodium. Conversion factor for units: serum albumin in g/L to g/dL—divide by 10; serum phosphorus in mmol/L to mg/dL—divide by 0.323.

^bP-value refers to global testing the null of no difference across dialysate sodium groups, calculated by analyses of variance or Kruskal–Wallis tests for continuous variables and chi-square test for categorical variables.

^cAbsolute IDWG = pre-dialysis weight – post-dialysis weight of previous dialysis session.

^dRelative IDWG = (absolute IDWG/EDW) × 100.

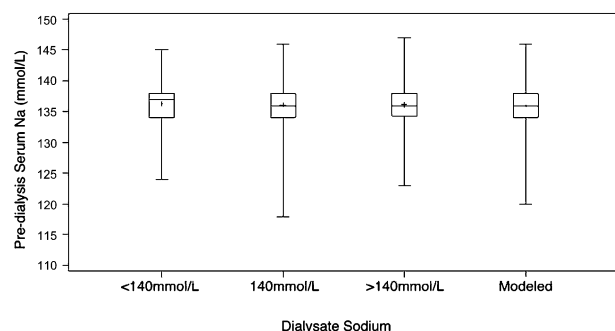


Fig. 2. Distribution of the pre-dialysis serum sodium according to subgroup of dialysate sodium concentration. The plus corresponds to the mean; upper edge corresponds to the upper quartile; middle line corresponds to the median; lower edge corresponds to the lower quartile; upper whisker is the maximum value; lower whisker is the minimum value.

intra-dialytic hypotension, as dialysis times have progressively shortened [1, 7]. Dialysate sodium prescriptions in the present study ranged from 132 mmol/L to sodium modeling, in which the dialysate [Na⁺] starts high and is reduced during the course of the hemodialysis treatment. Proponents of sodium modeling have argued that hemodynamic stability is preserved during dialysis [8, 9], whereas its detractors have suggested that higher dialysate [Na⁺] leads to diffusive transfer of sodium during dialysis, with potentially adverse consequences related to increased thirst [10], IDWG [11]

and higher blood pressure [12]. Few data exist on contemporary treatment patterns with respect to dialysate sodium composition. In a study of dialysis centers in the greater London area during 2004, Davenport reported 57% use of 140 mmol/L dialysate sodium, with very infrequent use of dialysate [Na⁺] exceeding 140 mmol/L or the use of sodium profiling [13]. In a report from a single Austrian dialysis center during 2009, 70% of the patients were treated with 138 mmol/L dialysate sodium, while the majority of the remainder were treated with 140 or 142 mmol/L dialysate sodium [14]. Another report from Satellite Healthcare during September 2009 confirmed our findings of the variability in dialysate [Na⁺] prescriptions [15].

We found that IDWG, but not blood pressure, increased with higher dialysate [Na⁺]. We chose not to focus on the sodium gradient (i.e. the difference between the dialysate [Na⁺] and serum [Na⁺]), due to the fact that lower serum [Na⁺] is in itself associated with higher IDWG. Therefore, the finding of an association between the sodium gradient and IDWG, as shown by Mendoza [15], may reflect the association between IDWG and pre-dialysis serum [Na⁺], given the relatively constrained values for dialysate [Na⁺]. Moreover, dialysate [Na⁺] is the only readily modifiable component of the sodium gradient. As shown in Table 2, for higher versus lower dialysate [Na⁺], the pre-dialysis serum [Na⁺] decreases as the IDWG increases, suggesting that the net inter-dialytic fluid gain is generally hypotonic in relation to plasma. The consistent increase observed in IDWG

Table 2. The unadjusted and adjusted joint association of serum and dialysate sodium with relative IDWG^a, absolute IDWG^b and pre-dialysis systolic blood pressure (SBP)^c

	Difference per 4 mmol/L increment in serum sodium		Difference for higher (versus lower) dialysate sodium	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Relative IDWG (% EDW)	−0.44 (−0.52, −0.37); P < 0.001	−0.48 (−0.55, −0.41); P < 0.001	0.19 (0.08, 0.31); P = 0.001	0.14 (0.03, 0.25); P = 0.02
Absolute IDWG (kg)	−0.25 (−0.31, −0.20); P < 0.001	−0.26 (−0.31, −0.21); P < 0.001	0.16 (0.07, 0.25); P = 0.001	0.11 (0.03, 0.19); P = 0.009
Pre-dialysis SBP (mmHg)	−0.2 (−1.3, 0.8); P = 0.67	0.1 (−1.6, 1.7); P > 0.9	0.0 (−1.0, 1.0); P > 0.9	−0.8 (−2.4, 0.9); P = 0.36

^aRelative IDWG = (absolute IDWG/EDW) × 100.

^bAbsolute IDWG = pre-dialysis weight − post-dialysis weight of previous dialysis session.

^cAdjusted effect estimates were estimated by adding sex, race (black versus non-black), age, diabetes, CHF status, vintage (<12, 12–24, 24–48, >48 months), albumin, hemoglobin, phosphorus and *Kt/V*.

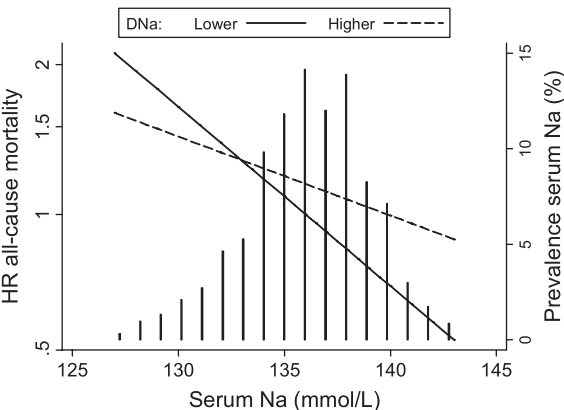


Fig. 3. Adjusted hazard ratios (log scale) for all-cause mortality associated with pre-dialysis serum sodium [Na⁺] concentration, according to the use of higher (>140 mmol/L or modeling; dashed line) versus lower (≤140 mmol/L; solid line) dialysate sodium concentration. The histogram of the pre-dialysis serum sodium concentration is shown in the background. Adjusted effect estimates were stratified on clinical center and adjusted for sex, race (black versus non-black), age, diabetes, CHF status, vintage (<12, 12–24, 24–48, >48 months), albumin, hemoglobin, phosphorus and *Kt/V*; two-way time interaction terms were included for albumin and hemoglobin due to non-proportional hazards.

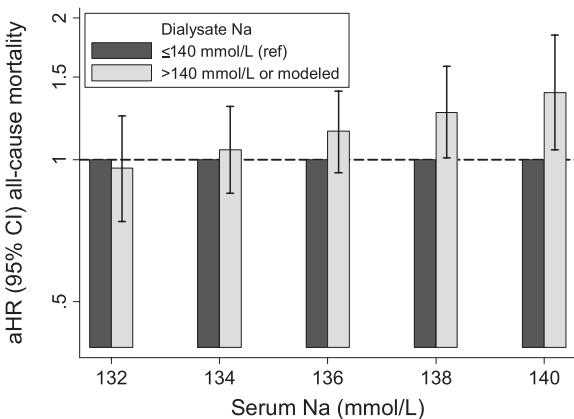


Fig. 4. Adjusted hazard ratios (log scale) for all-cause mortality associated with higher (>140 mmol/L or modeling; gray bars) versus lower (≤140 mmol/L; reference; black bars) dialysate sodium concentration evaluated at varying pre-dialysis serum sodium concentrations. Adjusted effect estimates were stratified on clinical center and adjusted for sex, race (black versus non-black), age, diabetes, CHF status, vintage (<12, 12–24, 24–48, >48 months), albumin, hemoglobin, phosphorus and *Kt/V*; two-way time interaction terms were included for albumin and hemoglobin due to non-proportional hazards.

with higher dialysate [Na⁺]⁺—even after multivariable adjustment for a number of clinical factors, including pre-dialysis serum [Na⁺] and measures of nutrition—suggests that sodium loading through diffusive gain with higher dialysate [Na⁺] may stimulate thirst and be an iatrogenic cause of excessive IDWG in the hemodialysis population.

Consistent with this concept is our finding of constancy of the pre-dialysis serum [Na⁺] across individuals treated with a wide range of dialysate sodium compositions. Peixoto *et al.* [2] reported relative constancy of serum [Na⁺] over time but did not have comparisons across different dialysate sodium compositions. Previous studies have shown that differing dialysate sodium composition does not affect the pre-dialysis serum [Na⁺] but have been limited by small sample size [6, 9, 13]. When treated with a higher dialysate [Na⁺], hemodialysis patients may experience an increase in tonicity that drives thirst and leads to ingestion of water to return the serum [Na⁺] closer to a preferred set point.

We previously showed, in a *post hoc* analysis of the HEMO Study, that lower pre-dialysis serum [Na⁺] was independently associated with an increased risk of death, but we lacked information on the dialysate [Na⁺] [4]. In the present study, we found evidence of statistical interaction between dialysate [Na⁺] and serum [Na⁺]; in other words, the association between serum [Na⁺] and mortality differed according to the dialysate [Na⁺]; likewise, the association between dialysate [Na⁺] and mortality differed according to the serum [Na⁺]. We have confirmed our earlier finding of an association between lower serum [Na⁺] and increased mortality and added the nuance that the association appears to be more marked in those treated with lower dialysate [Na⁺]. We had hypothesized that individuals with lower serum [Na⁺] who were treated with higher dialysate [Na⁺] would have the highest mortality, as a result of sudden osmolar or tonicity shifts induced by the dialysis procedure. We did not find evidence to support this hypothesis. It should

be noted, however, that we lacked statistical power due to the relatively small number of individuals with lower serum $[\text{Na}^+]$. At higher serum $[\text{Na}^+]$, we found evidence that treatment with lower dialysate $[\text{Na}^+]$ was associated with lower mortality. Our findings suggest that the potential benefit of lowering dialysate $[\text{Na}^+]$ may be most pronounced in individuals with higher serum $[\text{Na}^+]$. It may be the case that diffusive sodium gain occurs during dialysis in individuals with lower serum $[\text{Na}^+]$ irrespective of the dialysate $[\text{Na}^+]$, thereby accounting for the lack of difference in mortality; whereas diffusive gain may occur in those with higher serum $[\text{Na}^+]$ only if treated with higher dialysate $[\text{Na}^+]$. Alternatively, serum $[\text{Na}^+]$ may be a marker of a pathophysiologic state that responds differently to higher or lower dialysate $[\text{Na}^+]$. Whether certain subgroups may in fact benefit from higher dialysate $[\text{Na}^+]$ or sodium modeling remains unclear but is an important area for future investigation. It is important to note that the apparent trends towards better survival with higher dialysate $[\text{Na}^+]$ at lower serum $[\text{Na}^+]$ occur only at the lower extreme of the serum $[\text{Na}^+]$ distribution; accordingly, our estimates in this regard are underpowered and did not exclude the null hypothesis of no association. Future randomized studies of dialysate $[\text{Na}^+]$ should consider stratified block randomization on the basis of serum sodium concentration, based on our findings.

There are several limitations of our study that deserve mention. We did not have accurate dietary information nor information relating to measured residual renal function. Serum glucose measurements were unavailable, preventing us from correcting serum sodium concentration for hyperglycemia. In previous analyses of the relationship between hyponatremia and mortality in hemodialysis patients, we found that adjusting for serum glucose did not materially alter the results and that few patients demonstrated pre-dialysis hyperglycemia of sufficient magnitude to bear a meaningful impact on serum sodium concentration [4]. The demographic structure of our cohort differs from that of the national hemodialysis population, potentially limiting the generalizability of our findings. The possibility of residual confounding based on variables not considered, or due to incomplete adjustment of those which were considered, remains a possibility. Confounding by indication may also bias our results on dialysate $[\text{Na}^+]$. In particular, sodium modeling (two-third of the higher dialysate $[\text{Na}^+]$ category) may be selectively prescribed to sicker, less hemodynamically stable patients, which may spuriously induce or exaggerate an association between higher dialysate $[\text{Na}^+]$ and mortality. In this regard, it is re-assuring that patients who were sodium modeled at baseline had a similar survival to those who had fixed higher dialysate $[\text{Na}^+]$ at baseline, suggesting that statistical adjustments reasonably controlled for patient differences. Data limitations precluded more granular examination of the dialysate $[\text{Na}^+]$, which would be of both biological and clinical importance. Finally, given the finite number of dialysis centers for which data were available, we were unable to perform a facility-level analysis (in which each facility was characterized by the prevailing dialysate $[\text{Na}^+]$ used), which may have otherwise lessened the opportunity for confounding.

The optimal dialysate $[\text{Na}^+]$ for individual patients remains unknown and may vary according to clinical circumstances. Lower dialysate $[\text{Na}^+]$ may be beneficial, but

additional research is required to investigate the factors that influence net sodium flux during dialysis and the resultant impact on clinical outcomes.

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