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Mortality Associated with Low Serum Sodium Concentration in Maintenance Hemodialysis

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Abstract

BACKGROUND—Low serum sodium concentrations are associated with an increased risk of death in the general population, but causality is uncertain due to confounding from clinical conditions such as congestive heart failure and cirrhosis, in which hyponatremia results from elevated levels of arginine vasopressin.

METHODS—To examine the association between predialysis serum sodium concentration and mortality in patients undergoing hemodialysis for end-stage renal disease, a condition in which arginine vasopressin does not affect water excretion and osmoregulation, we studied 1549 oligoanuric participants in the HEMO study, a randomized controlled trial of hemodialysis patients examining the effect of hemodialysis dose and flux. We used proportional hazards models to compare the risk of death according to predialysis serum sodium concentration.

RESULTS—Considered as a continuous variable, each 4-mEq/L increment in baseline predialysis serum sodium concentration was associated with a hazard ratio for all-cause mortality of 0.84 (95% confidence interval (CI), 0.78–0.90). Multivariable adjustment for demographic, clinical, laboratory, and dialysis-specific covariates, including ultrafiltration volume, did not appreciably change the results (hazard ratio for all-cause mortality of 0.89; 95% CI, 0.82–0.96). The results also were consistent in time-updated analyses using repeated measures of serum sodium and other relevant covariates.

CONCLUSION—Lower predialysis serum sodium concentration is associated with an increased risk of death. Considering the unique physiology in the dialysis population, these findings raise the possibility that hyponatremia itself may be a causal determinant of mortality in the broader population.

Keywords

End-stage renal disease; Hemodialysis; Hyponatremia; Mortality

Serum sodium concentration in humans is tightly regulated, with normal levels between 135 and 144 mEq/L. Hyponatremia (serum sodium concentration <135 mEq/L) is a common electrolyte abnormality seen in a variety of medical conditions, including congestive heart

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failure, cirrhosis, and the syndrome of inappropriate antidiuretic hormone.¹ Hyponatremia is strongly associated with an increased risk of death; even mild hyponatremia (serum sodium concentration 130–134 mEq/L) is associated with a 47% increased risk of in-hospital mortality.² The reasons underlying this association are unclear, and causality remains in doubt due to potential confounding on the basis of the underlying disease process. For example, in congestive heart failure and cirrhosis, hyponatremia derives (at least in part) from high levels of circulating arginine vasopressin (AVP), which in turn reflect the severity of heart failure and liver disease, respectively.

The hemodialysis population provides a unique opportunity to examine the nature of the association between hyponatremia and risk of death. In advanced chronic kidney disease, the kidneys lose the ability to concentrate urine in response to circulating AVP;³ in end-stage renal disease, particularly when accompanied by oligoanuria, water and salt removal are almost exclusively determined by the dialysis procedure. Therefore, the presence or absence of an association between hyponatremia and death in the hemodialysis population may be less subject to confounding, and shed light on whether serum sodium concentration may be causally related to health outcomes.

The objective of this study was to examine the association between serum sodium concentration and outcomes in individuals on maintenance hemodialysis.

METHODS

Study Population

This protocol was deemed exempt by the Partners Health Care Institutional Review Board. We performed a nonconcurrent cohort study of participants in the HEMO Study, the details of which have been previously published.^{4–6} Briefly, HEMO was a 2 × 2 factorial randomized control trial in which participants were assigned 1:1 to 1 of 2 levels of each dialysis dose and membrane flux (n = 1846). All participants were between 18 and 80 years old at study entry and had been receiving thrice weekly hemodialysis for at least 3 months. We excluded subjects missing baseline serum sodium data (n = 36). For the purposes of the primary analysis, we excluded nonoligoanuric patients (baseline residual urine output >200 mL/day; n = 261) in order to minimize the possibility of confounding on the basis of comorbid diseases that predispose to hyponatremia and to death. Sensitivity analyses were conducted to investigate whether results differed according to presence or absence of congestive heart failure and after inclusion of nonoliguric patients.

Outcomes

The primary outcome was time to death from any cause. Secondary analyses considered time to death from cardiovascular disease. Cause of death was adjudicated by a blinded outcomes committee.⁷

Enrollment began in March 1995 and concluded in October 2000. At-risk time for all analyses began concurrent with randomization. Subjects remained at risk until death, receipt of a kidney transplant (n = 151), or administrative censoring at the end of study (December 31, 2001).

Study Data

Demographic data including age, race, sex, height, clinical center, and dialysis vintage were recorded by study investigators at the time of randomization. Details of dialysis treatments including access type, estimated dry weight, and ultrafiltration volume were assessed at baseline and at monthly intervals during follow-up. Information on interdialytic weight gain

was not available; the high degree of association between estimated dry weight and postdialysis weight ($r > .99$; $P < .001$) indicated that ultrafiltration volume was a good marker of interdialytic weight gain. Predialysis laboratory values including serum sodium, albumin, creatinine and phosphate, and hematocrit were recorded at baseline and then semi-annually; all measurements were made at a centralized laboratory (Spectra East, Rockleigh, NJ). Co-morbidities including diabetes and congestive heart failure were recorded at baseline and at annual intervals based on subject interviews and review of medical records from the dialysis center, as well as those related to inter-current hospitalization. Sodium, protein, and caloric intake were estimated by 24-hour dietary recall.⁸

Statistical Analysis

All analyses were performed using Stata 10.0MP (College Station, Tex). Continuous variables were examined graphically and in terms of their mean, standard deviation, median, and interquartile range. Categorical variables were examined by frequency distribution. Effect modification of the serum sodium-mortality association on the basis of randomization assignment (separately for dose and flux) was tested for and excluded by likelihood ratio testing.⁹

Unadjusted measures of association between serum sodium concentration and individual covariates were estimated by a series of linear regression models. In baseline survival analyses, the unadjusted association between serum sodium (by quartile) and outcome was assessed via Kaplan-Meier plots, with significance determined by the log-rank test.¹⁰ Grouping of subjects according to quartiles of serum sodium concentration was unequal due to the frequency of ties. Unadjusted hazards ratios were assessed by fitting unadjusted proportional hazards models (stratified on clinical center). Adjusted hazard ratios were estimated by addition of covariate terms for age, sex, race, dialysis vintage, height, estimated dry weight, ultrafiltration volume, access type, congestive heart failure, diabetes, serum albumin, creatinine, phosphate, hematocrit, and dietary sodium, protein, and caloric intake;¹¹ these were chosen on the basis of biological and clinical plausibility.¹² For all models, the proportionality assumption was tested by examination of log-log survival plots and by Schoenfeld residual testing.¹³ Two-way time interaction terms were included for variables violating the proportionality assumption. A priori stipulated tests for interaction between serum sodium concentration and ultrafiltration and serum sodium concentration and congestive heart failure were conducted by comparing nested models via the likelihood ratio test.⁹

Time-updated proportional hazards models were fit as per baseline models except that serum sodium concentration and time-varying covariates (age, dialysis vintage, access type, estimated dry weight, ultrafiltration, comorbidity status, and other laboratory measures) were time-updated.¹¹ In the time-updated analyses, one implausible value of serum sodium concentration (70 mEq/L) was observed in one individual; the associated observations were omitted from the analyses, but results were unaltered when this observation was retained (data not shown). Sensitivity analyses were performed by including non-oligoanuric patients in analyses and then by excluding patients with ultrafiltration volume >4 L.

Role of the Funding Source

The study was funded by a Norman S. Coplon Extramural Grant from Satellite Healthcare. The funding source had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

RESULTS

The primary cohort consisted of 1549 individuals. Overall, the mean (SD) age was 57.7 (14.2) years; 57% of participants were women; 64.2% were black. At baseline, mean (SD), median (interquartile range), minimum, and maximum predialysis serum sodium concentrations were 138.2 (4.0), 138 (136–141), 115, and 154 mEq/L, respectively (Figure 1). Over the course of the study, the median number of serum sodium measurements per subject was 5 (inter-quartile range 3–8). Considered over time, the overall standard deviation for serum sodium concentrations was 3.8 mEq/L ($n = 8771$ measurements). Demographic, clinical, and laboratory data according to quartile of predialysis serum sodium concentration are provided in Table 1. The most statistically significant bivariable predictors of higher baseline serum sodium concentration were black race, longer vintage, higher estimated dry weight, serum albumin, and creatinine; the most significant predictors of lower serum sodium concentration were diabetes, higher ultrafiltration volume, and serum glucose (Table 2).

Baseline Survival Analyses: All-cause Mortality

Subjects contributed 4491 years of at-risk time, during which 767 died, including 291 from cardiovascular causes (causes of death are presented in Table 3). Median survival time was 2.6 years. Unadjusted Kaplan-Meier analysis demonstrated that lower serum sodium concentration was associated with greater all-cause mortality ($P < .001$; Figure 2A). Considered as a continuous variable, each 4-mEq/L (the observed SD in the sample) increment in serum sodium concentration was associated with a hazard ratio (HR) for all-cause mortality of 0.84 (95% confidence interval [CI], 0.78–0.90). Upon multivariable adjustment, the association between serum sodium concentration and mortality was modestly attenuated, but remained statistically significant: HR 0.89; 95% CI, 0.82–0.96 (Figure 3). (In this model, the HR for ultrafiltration [per 1 L] was 1.05; 95% CI, 0.98–1.12.)

The association between serum sodium concentration and all-cause mortality was not materially altered upon additional covariate adjustment for serum glucose or upon correction of the serum sodium concentration for the glucose concentration¹⁴ (adjusted HR 0.87; 95% CI, 0.80–0.94 in both instances). Moreover, the serum sodium–mortality association was essentially unchanged in sensitivity analyses that: 1) included non-oligoanuric patients (adjusted HR 0.90; 95% CI, 0.84–0.97); 2) excluded patients with ultra-filtration volumes >4 L (adjusted HR 0.86; 95% CI, 0.79–0.94); and 3) considered a 90-day lag period between exposure and the start of at-risk time (to guard against the possibility of observing a reverse-causal association).

There was no evidence of effect modification on the basis of ultrafiltration volume (P -interaction = .28) or by the presence or absence of congestive heart failure (P -interaction = .25), suggesting that these factors did not fundamentally alter the association between serum sodium concentration and all-cause mortality.

Baseline Survival Analyses: Cardiovascular Mortality

Lower serum sodium concentration was associated with higher risk for cardiovascular mortality ($P < .001$; Figure 2B). Considered as a continuous variable, each 4-mEq/L increment in serum sodium concentration was associated with a HR for cardiovascular mortality of 0.84 (95% CI, 0.75–0.95). Unlike the case for all-cause mortality, the association between serum sodium and cardiovascular mortality was attenuated upon multivariable adjustment, and was no longer statistically significant: HR 0.93; 95% CI, 0.82–1.05 (Figure 3). The adjusted HR for noncardiovascular mortality was 0.86 (95% CI, 0.78–0.95).

Time-updated Analyses

Because serum sodium concentration varies over time, we fit time-updated proportional hazards models to estimate the association between serum sodium and all-cause mortality. Unadjusted Kaplan-Meier analysis demonstrated that lower serum sodium concentration was associated with greater mortality ($P < .001$; Figure 2C). Considered as a continuous variable, each 4-mEq/L increase in serum sodium concentration was associated with a HR of 0.81 (95% CI, 0.75–0.87). As with the baseline models, the serum sodium–all-cause mortality association was somewhat attenuated but remained statistically significant upon multivariable adjustment: HR 0.91; 95% CI, 0.83–0.98 (Figure 3). Again, no effect modification on the basis of ultrafiltration volume was detected (P -interaction = .70).

Lower serum sodium concentration was associated with greater cardiovascular mortality on Kaplan-Meier ($P = .03$; Figure 2D) and unadjusted proportional hazards analyses (HR 0.81; 95% CI, 0.72–0.91). As in baseline analyses, the serum sodium–cardiovascular mortality association was attenuated and no longer statistically significant upon multivariable adjustment: HR 0.94; 95% CI, 0.82–1.07 (Figure 3). The adjusted HR for noncardiovascular mortality was 0.89 (95% CI, 0.80–0.98).

DISCUSSION

The primary finding of this study is that among oligoanuric individuals on maintenance hemodialysis, lower serum sodium concentrations were associated with a greater risk of mortality. This association remained statistically significant upon adjustment for a number of demographic factors, comorbid disease, and laboratory measures that might plausibly confound the observed association. The association did not differ according to ultrafiltration volume or in those with or without congestive heart failure. Furthermore, the independent prognostic significance of serum sodium concentration was confirmed in analyses that accounted for repeated measures of sodium and other time-updated covariates.

Previous studies have described an association between low serum sodium concentrations and mortality,^{2,15} especially in clinical disorders associated with decreased effective circulating volume such as congestive heart failure and cirrhosis.^{16–18} In these conditions, hyponatremia is mediated by nonosmotic release of AVP and reduced free water clearance by the kidney, which in turn may reflect the severity of the underlying disease process through mechanisms such as reduced glomerular filtration rate and activation of the sympathetic nervous system. A causal association between hyponatremia and poor clinical outcomes from congestive heart failure and cirrhosis is therefore difficult to infer, given the high likelihood for confounding by disease underlying severity. Among oligoanuric hemodialysis patients, removal of water and solute is achieved almost exclusively via the dialysis procedure, and thereby less subject to the influence of comorbid disease. Consequently, this population provides a unique opportunity to explore the nature of the serum sodium–mortality association. That low serum sodium concentrations were associated with mortality in this population lends favor to the interpretation that hyponatremia might be directly toxic. The mechanism(s) by which low serum sodium concentration may affect survival are not entirely clear. Maintenance of serum osmolality and sodium concentrations within tight boundaries is a hallmark of all terrestrial mammals. Sodium concentrations affect the 3-dimensional conformations of proteins and enzymes and play a critical role in nerve-impulse transmission, muscle excitation, and maintenance of transmembrane electrical gradients that are critical to cellular function. The effects of abnormal serum sodium concentration on cerebral function have been well described,^{19,20} but further study is needed to examine the effects of hyponatremia on other organ systems.

Alternative explanations must be considered to account for the observation that lower serum sodium concentration is associated with an increased risk of death. Serum sodium concentration in oligoanuric dialysis patients is determined by the relative intake of solute and free water during the interdialytic interval; excessive free water intake or reduced solute intake leads to lower predialysis serum sodium concentrations. Angiotensin II is a potent dipsogenic hormone that can be elevated in hemodialysis patients and drive polydipsia.^{21–23} Therefore, disease processes that lead to elevated AVP and angiotensin II levels could still confound the association between lower serum sodium levels and mortality in the hemodialysis population, even absent effects on water and salt handling by the kidney. However, our findings remained significant after adjusting for congestive heart failure and ultrafiltration volume (a marker of interdialytic fluid intake), reducing the likelihood that we observed an association confounded on this basis. Moreover, adjustment for measures of dietary intake lessens the likelihood of confounding on the basis of conditions that predispose to hyponatremia via cachexia and malnutrition.

Interdialytic weight gain was higher in those with lower serum sodium concentration, and could itself be toxic to hemodialysis patients because of maladaptive changes in cardiac structure (eg, left ventricular hypertrophy and fibrosis) brought on by chronic volume overload, or by hemodynamic instability resulting from greater need for fluid removal during dialysis. Previous studies have shown that increased interdialytic weight gain was associated with mortality.^{24,25} However, those studies did not adjust for serum sodium concentration. In the present study, we found that the serum sodium-mortality association remained potent and significant, whereas the ultrafiltration-mortality association was not statistically significant when both variables were included in the multivariable model, suggesting that serum sodium and not interdialytic weight gain was the more proximate mediator of death. In addition, we found that the association between serum sodium and mortality was unchanged when subjects with ultrafiltration volumes >4 L were excluded.

A third consideration is that cyclical alterations in serum osmolality may be directly toxic. Because the dialysate sodium concentration is typically 140 mEq/L, patients with lower predialysis serum sodium concentration will experience an increase in serum sodium during each dialysis treatment, possibly followed by a thirst-driven reduction in osmolality back to the set point.²⁶ The use of supranormal sodium levels in the dialysate also is common (termed “sodium modeling”) and may further drive thirst and cyclical changes in osmolality.²⁷ The possibility that osmolar fluctuations might be the toxic determinant could be studied by examination of the association between dialysate–serum sodium concentration gradient and outcome; we were unable to do so here because of missing information on dialysate sodium concentration in the majority of subjects. Further study is warranted because of the implied treatment implications. If low serum sodium is the causal determinant of mortality, increasing dialysate sodium in hyponatremic patients, limiting free water intake, or liberalizing sodium intake (so as to normalize serum levels) may be expected to be beneficial. Conversely, if cyclical changes in serum osmolality or excessive interdialytic weight gain are the causal factor, then dialysate sodium reduction might be the appropriate clinical response. Adjustment of the dialysate concentration has been suggested by others in order to accommodate individual preferred serum osmolality setpoints.²⁶

Several limitations of the present study should be noted. First, we did not have information on dialysate sodium concentration or direct measurement of interdialytic weight gain. However, the dialysate sodium concentration is not typically adjusted according to the predialysis sodium concentration; and ultrafiltration volume is a reasonable surrogate for interdialytic weight gain. Second, we cannot exclude the possibility of residual confounding due to incomplete adjustment or on the basis of other variables not considered. Third, given the highly selected nature of participants in randomized trials, generalizability to the broader

hemodialysis population remains uncertain. Strengths of this study include the quality of available data collected rigorously and prospectively, rather than from an administrative database; uniform laboratory measurements from a central core laboratory; and close follow-up of participants.

In conclusion, our results suggest that low serum sodium concentrations are associated with increased mortality among oligoanuric hemodialysis patients. Considering the unique physiology in this population, this finding may provide evidence in support of the hypothesis that hyponatremia itself may be a causal determinant of mortality in the broader population.

CLINICAL SIGNIFICANCE

- Patients receiving maintenance hemodialysis display a range of predialysis serum sodium concentrations.
- Lower serum sodium concentrations in dialysis patients are associated with an increased risk of death, even after adjustment for demographic, clinical, laboratory, and dialysis-specific covariates, including ultrafiltration volume.
- The findings raise the possibility that lower serum sodium concentration or its determinants are toxic.

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Figure 1.
Distribution of observed predialysis serum sodium at baseline (n = 1549).

Figure 2.

Kaplan-Meier cumulative failure curves. Panel **A** demonstrates all-cause mortality by quartile of baseline serum sodium concentration. Panel **B** demonstrates cardiovascular mortality by quartile of baseline serum sodium. Panels **C** and **D** demonstrate all-cause and cardiovascular mortality, respectively, based on quartile of serum on time-updated analysis. Quartiles of serum sodium concentration were ≤ 136 , 137–138, 139–141, >141 mEq/L in baseline analyses, and ≤ 136 , 137–139, 140–141, >141 mEq/L in time-updated analyses.

Figure 3.

Adjusted hazard ratios (95% confidence intervals) for all-cause and cardiovascular mortality per 4-mEq/L increment in serum sodium concentration. All models were stratified on clinical center and adjusted for age, sex, race, dialysis vintage, height, estimated dry weight, ultrafiltration, access type (graft, fistula, catheter), congestive heart failure, diabetes, serum albumin, creatinine, phosphate, hematocrit, and dietary intake of sodium, protein, and calories. The baseline models included 2-way cross-product terms with time for serum albumin due to nonproportional hazards. CI = confidence interval.

Table 1

Baseline Description of Primary Cohort According to Quartile of Predialysis Baseline Serum Sodium Concentration

	Serum Sodium Concentration (mEq/L)			
	Quartile 1 (115–136)	Quartile 2 (137–138)	Quartile 3 (139–141)	Quartile 4 (142–154)
Number	454	354	449	292
Mean serum sodium (mEq/L)	133.6	137.5	139.9	143.4
Age (years)	57.4	57.9	57.1	58.8
% Female	60	58	54	55
% Black	57	65	67	69
Median vintage (years)	2.0	2.4	2.8	2.7
Height (cm)	165	165	166	165
EDW (kg)	66.7	68.2	68.8	69.6
Ultrafiltration volume (L)	3.2	3.1	3.0	2.7
Access (%)				
Graft	62	60	58	62
Fistula	29	34	36	31
Catheter	9	6	6	7
SBP predialysis (mm Hg)	150	151	150	149
% CHF	44	38	37	40
% Diabetes	55	42	39	38
Serum albumin (g/dL)	3.6	3.6	3.7	3.6
Serum creatinine (mg/dL)	9.8	10.4	10.8	10.7
Serum phosphate (mg/dL)	5.6	5.9	5.8	5.8
Serum glucose (mg/dL)	173	137	122	121
Hematocrit (%)	33.1	33.8	33.5	33.6
Dietary sodium (mg/day)	2208	2232	2282	2370
Dietary protein (g/day)	61.6	64.5	65.3	62.5
Dietary calories (kcal/day)	1502	1520	1570	1551

CHF = congestive heart failure; EDW = estimated dry weight; SBP = systolic blood pressure.

Continuous variables are presented as means unless otherwise noted.

Table 2**Bivariate Predictors of Baseline Predialysis Serum Sodium Concentration**

Variable	Difference in Serum Sodium Concentration, mEq/L (95% Confidence Interval)	P Value
Age (per 10 years)	0.05 (−0.15–0.25)	.6
Female (ref male)	−0.44 (−0.85–−0.02)	.04
Black (ref nonblack)	0.78 (0.35–1.20)	.002
Vintage (per 1 year)	0.06 (0.02–0.10)	.004
Height (per 10 cm)	0.11 (−0.06–0.29)	.2
EDW (per kg)	0.03 (0.01–0.05)	.005
Ultrafiltration volume (per L)	−0.33 (−0.51–−0.16)	.001
Access		.006
Graft	0 (ref)	
Fistula	0.25 (−0.12–0.68)	
Catheter	−0.98 (−1.81–−0.15)	
SBP pre-dialysis (per 10 mm Hg)	−0.06 (−0.16–0.05)	.28
CHF (ref no CHF)	−0.30 (−0.83–0.23)	.25
Diabetes (ref no DM)	−1.23 (−1.58–−0.89)	<.001
Serum albumin (per 1 g/dL)	1.16 (0.72–1.60)	<.001
Serum creatinine (per 1 mg/dL)	0.18 (0.14–0.23)	<.001
Serum phosphate (per 1 mg/dL)	0.08 (−0.02–0.19)	.11
Serum glucose (per 10 mg/dL)	−0.17 (−0.19–−0.14)	<.001
Hematocrit (per 1%)	0.03 (−0.01–0.08)	.12
Dietary sodium (per 1000 mg/day)	0.17 (−0.08–0.41)	.17
Dietary protein (per 10 g/day)	0.02 (−0.08–0.12)	.6
Dietary calories (per 100 kcal/day)	0.02 (−0.03–0.07)	.4

CHF = congestive heart failure; DM = diabetes; EDW = estimated dry weight; SBP = systolic blood pressure.

Positive results correspond to a higher predialysis sodium concentration.

Table 3**Causes of Death**

Cause of Death	n (%)
Cardiovascular	291 (37.9)
Cerebrovascular	58 (7.6)
Peripheral vascular	58 (7.6)
Infectious (not access-related)	54 (7.0)
Malignancy	48 (6.3)
Respiratory	44 (5.7)
Dialysis vascular access complication	42 (5.5)
Gastrointestinal	32 (4.2)
Unknown	31 (4.0)
Nervous system, nonvascular	25 (3.3)
Other surgical complications	16 (2.1)
Hepatobiliary	12 (1.6)
Musculoskeletal and connective tissue	12 (1.6)
Diabetes and endocrine	7 (0.9)
Urosepsis	3 (0.4)
HIV/AIDS	1 (0.1)
Non-malignant hematological	1 (0.1)
Other	32 (4.2)

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.