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Hyponatremia, Mineral Metabolism, and Mortality in Incident Maintenance Hemodialysis Patients: A Cohort Study

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Abstract

Background—Hyponatremia is associated with increased mortality in chronic diseases. Recent animal studies also implicate hyponatremia in bone abnormalities. However, associations between hyponatremia, mineral bone abnormalities, and mortality in incident hemodialysis patients are unknown.

Study Design—Nonconcurrent prospective cohort study.

Setting & Participants—Incident hemodialysis patients from the Accelerated Mortality on Renal Replacement (ArMORR) cohort with available serum sodium measurements from the time of dialysis therapy initiation (n = 6,127) were classified as hyponatremic (sodium, <135 mEq/L) or normonatremic (sodium, 135–145 mEq/L) based on glucose-corrected sodium level at the time of dialysis therapy initiation. Patients with sodium levels >145 mEq/L were excluded (n = 74).

Predictor—Hyponatremia (sodium, <135 mEq/L).

Outcomes—Mineral bone abnormalities; rates of falls, fractures, and mortality.

Measurements—Hyponatremia and mineral bone abnormalities were assessed at the time of hemodialysis therapy initiation. Data for other outcomes were collected during a 1-year follow-up. Univariate and multivariable logistic and Cox proportion hazard analyses were conducted to compute ORs and HRs, respectively, with 95% CIs.

Results—775 patients were hyponatremic and 5,278 were normonatremic at baseline. In univariate analyses, hyponatremia was associated with hypercalcemia (OR, 1.92; 95% CI, 1.11–3.30), elevated alkaline phosphatase level (OR, 1.36; 95% CI, 1.12–1.66), and hypoparathyroidism (OR, 1.40; 95% CI, 1.18–1.65). Similar relationships were observed in multivariable models. No statistically significant relationships were observed with phosphorus abnormalities, hypovitaminosis D, falls, or fractures. 965 (15.8%) patients had died at the 1-year follow up. Compared with normonatremic patients, hyponatremic patients had higher 1-year mortality in univariate (HR, 1.59; 95% CI, 1.34–1.87) and multivariable analyses (HR, 1.42; 95% CI, 1.19–1.69).

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Limitations—Low rate of falls and fractures, lack of data for bone density and fibroblast growth factor 23.

Conclusions—In incident hemodialysis patients, hyponatremia is associated with hypercalcemia, elevated alkaline phosphatase levels, hypoparathyroidism, and increased 1-year mortality. Future studies are needed to examine whether treatments to alter hyponatremia have effects on mineral bone abnormalities and mortality.

INDEX WORDS

Sodium; hyponatremia; mortality; mineral bone disease; vitamin D

Hyponatremia (serum sodium <135 mEq/L) is among the most common electrolyte abnormalities encountered in clinical practice.¹ A number of studies have described an association between hyponatremia and higher mortality in hospitalized patients^{2,3} and in chronic conditions such as congestive heart failure,^{4–6} coronary artery disease,⁷ and cirrhosis.⁸ However, only a few recent studies have focused on patients with end-stage renal disease.^{9–11} These studies have been conducted largely in prevalent maintenance hemodialysis (HD) patients and thus may reflect the effects of dialysis treatment rather than underlying biological differences. The association between baseline hyponatremia (at the time of HD therapy initiation) and mortality in incident HD patients has not been evaluated adequately. Mortality in end-stage renal disease is high¹² and has remained largely unchanged despite scientific advances. Therefore, identification of novel risk factors is critical to determining optimal management aimed at improving survival.

Emerging animal studies have demonstrated that chronic hyponatremia activates osteoclastic bone resorption and results in a high bone turnover state, as indicated by elevated bone-specific alkaline phosphatase levels.^{13,14} Bone turnover abnormalities are universal in incident HD patients¹⁵ and these abnormalities are important contributors to morbidity and mortality in end-stage renal disease.¹⁶ Although hyponatremia also is highly prevalent in this population,¹¹ associations between hyponatremia and mineral bone abnormalities have not been evaluated.

We designed the present study to investigate the associations between hyponatremia and mineral bone abnormalities at HD therapy initiation in incident maintenance HD patients. We also sought to determine whether hyponatremia is associated with increased mortality in incident maintenance HD patients and define how mineral bone abnormalities that are associated with hyponatremia affect the association between hyponatremia and mortality.

METHODS

Study Population

The study population for this nonconcurrent prospective cohort study was derived from the Accelerated Mortality on Renal Replacement (ArMORR) Study. ArMORR is a nationally representative prospective cohort of incident maintenance HD outpatients who began HD therapy between July 1, 2004, and July 30, 2005, at 1 of 1,056 dialysis centers in the United States operated by Fresenius Medical Care, North America (FMCNA).¹⁷ Patients who were previously maintained on HD therapy at a non-FMCNA facility who subsequently transferred to an FMCNA facility were excluded. The ArMORR data set contains a broad range of demographic and clinical data, including comorbid conditions, laboratory results, and medications. Clinical data were collected prospectively and entered uniformly into a central database by practitioners at the point of care. Blood samples collected for clinical care were shipped to and processed by Spectra East (Rockland, NJ). The ArMORR Study

was approved by the Institutional Review Board of the Massachusetts General Hospital and conducted in accordance with its ethical standards.

Study Data

The ArMORR cohort includes 10,044 patients. Laboratory data at the time of first outpatient HD session at one of the study facilities were recorded as baseline laboratory data at HD therapy initiation. Serum sodium data at the time of HD therapy initiation were available for 6,127 patients. Sodium values were corrected for serum glucose level using the following formula: corrected sodium=measured sodium+0.016 × (serum glucose−100).¹⁸ Based on corrected sodium values, we classified patients as hyponatremic if sodium level was <135 mEq/L (n = 775) and normonatremic if sodium level was 135–145 mEq/L (n = 5,278). Patients with sodium levels >145 mEq/L were excluded (n = 74). The predictor variable was hyponatremia. Outcome variables were abnormalities in mineral bone parameters (serum calcium, serum phosphorus, serum alkaline phosphatase, serum parathyroid hormone [PTH], and serum 25-hydroxyvitamin D) at the time of HD therapy initiation, rates of falls and/or fractures per 100 person-years, and 1-year mortality. Hypercalcemia was defined as albumin-corrected serum calcium level >10.5 mg/dL; hypocalcemia, as albumin-corrected serum calcium level <8.4 mg/dL; hyperphosphatemia, as serum phosphorus level >4.5 mg/dL; hypophosphatemia, as serum phosphorus level <2.6 mg/dL; elevated alkaline phosphatase, as serum alkaline phosphatase level >129 U/L; hypoparathyroidism, as serum intact PTH level <150 pg/mL; hyperparathyroidism, as PTH level >300 pg/mL; and hypovitaminosis D, as 25-hydroxyvitamin D level <30 ng/mL. Abnormalities in calcium, phosphorus, alkaline phosphatase, and 25-hydroxyvitamin D levels were defined according to laboratory normal ranges, whereas PTH level abnormalities were defined according to recommended goal ranges per the NKF-KDOQI (National Kidney Foundation–Kidney Disease Outcomes Quality Initiative) at the time of the study period.¹⁵

Statistical Analysis

Categorical variables were summarized by frequency, and continuous variables, by mean ± standard deviation. Characteristics of the study population were compared by baseline corrected sodium level using χ^2 and *t* tests, when applicable. Intact PTH level, which was highly right skewed, was summarized by median (interquartile range [IQR]) and compared between sodium groups using Mann-Whitney *U* test. Logistic regression models were developed to test the associations between sodium categories and predefined mineral bone abnormalities. Data for serum calcium, phosphorous, alkaline phosphatase, and PTH at baseline were available for 99.7%, 99.6%, 95.5%, and 88.1% of the cohort, respectively. Data for 25-hydroxyvitamin D levels at baseline were available for 778 patients (12.7% of cohort) who did not differ from the rest of the cohort in terms of age, sex, race, and comorbid conditions (data not shown).¹⁵ Rates of falls and/or fractures per 100 person-years were compared using Poisson regression analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) for 1-year mortality were calculated using Cox proportional hazard models. Covariate selections for the regression and proportional hazard models were based on significance in univariate analysis and clinical reasoning. Multivariable logistic regression model 1 was adjusted for age, race, and sex. Multivariable logistic regression model 2 was adjusted for age, race, sex, comorbid conditions (diabetes mellitus, hypertension, and coronary artery disease), catheter access, body mass index, serum albumin level, serum bicarbonate level, and medications that affect mineral bone parameters (cinacalcet, phosphate binders, and active vitamin D). Cox proportional hazard model 1 for mortality was adjusted for age, race, and sex; model 2 was adjusted for age, race, sex, diabetes mellitus, hypertension, coronary artery disease, catheter access, facility mortality statistic, body mass index, serum albumin level, and serum bicarbonate level.

We also conducted propensity score analyses (univariate and multivariable) for mineral bone abnormalities and mortality by frequency matching the low and normal sodium level groups based on propensity score predicting sodium status from age, systolic blood pressure, body mass index, congestive heart failure, liver disease, and malignancy ($n = 769$ in each group). Covariate selections for multivariable models for propensity score analyses were similar to multivariable models for Cox proportional hazards and logistic regression models as described earlier.

A 2-sided $P < 0.05$ was considered significant. All analyses were performed using SAS (version 9.2; SAS Institute Inc).

RESULTS

Study Participants

Mean age of the study cohort ($n = 6,053$) was 62.5 years, 54.4% were men, and 58.9% were white (Table 1). At baseline, mean, minimum, and maximum sodium values were 138.2 ± 3.4 (SD), 116, and 145 mEq/L, respectively (Fig 1). Most patients with hyponatremia had mild hyponatremia (89.2%) with sodium levels of 130–134 mEq/L. A history of congestive heart failure was present in 12.3% of the cohort, whereas 26.9% had diabetes mellitus, 2.7% had liver disease, 2.8% had malignancy, and 2.0% had chronic obstructive lung disease. Most patients (62.9%) had HD therapy initiation using a catheter vascular access.

Clinical and demographic characteristics comparing hyponatremic and normonatremic patients are listed in Table 1. Patients with hyponatremia ($n = 775$) were older, had lower body mass index, had lower blood pressure, and were more likely to have HD therapy initiation using a catheter vascular access compared with patients with normonatremia ($n = 5,278$). Lower prevalences of diabetes mellitus, hypertension, and coronary artery disease were noted in hyponatremic patients. Mean serum bicarbonate and serum albumin levels were lower in hyponatremic patients (Table 1). Baseline sodium levels measured at dialysis therapy initiation showed positive correlation with levels at 90 days ($r = 0.45$).

Mineral Bone Disease Abnormalities

At the time of dialysis therapy initiation, patients with hyponatremia were noted to have higher prevalences of hypercalcemia (2.2% vs 1.2%; $P = 0.02$), elevated alkaline phosphatase levels (20.3% vs 15.7%; $P = 0.002$), and hypoparathyroidism (27.5% vs 20.9%; $P < 0.001$) compared with normonatremic patients (Table 1). Mean serum calcium level was higher in hyponatremic patients (8.94 ± 0.79 vs 8.86 ± 0.75 mg/dL; $P = 0.008$). Mean serum alkaline phosphatase level also was higher in hyponatremic patients (107.8 ± 89.1 vs 99.0 ± 68.3 U/L; $P = 0.01$), whereas PTH levels were lower in hyponatremic patients (181.0 [IQR, 90.3–308.7] vs 210.0 [IQR, 116.0–335.0] pg/mL; $P < 0.001$). There were no differences in serum phosphorus and serum 25-hydroxyvitamin D levels between hyponatremic and normonatremic patients.

In univariate logistic regression analyses, hyponatremia was associated with higher odds of hypercalcemia (odds ratio [OR], 1.92; 95% CI, 1.11–3.30), elevated alkaline phosphatase level (OR, 1.36; 95% CI, 1.12–1.66), and hypoparathyroidism (OR, 1.40; 95% CI, 1.18–1.65). Similar relationships were observed in multivariable models adjusted for age, race, sex, comorbid conditions, and medications that may affect mineral bone parameters (Table 2; Fig 2).

The presence of hypercalcemia was associated with hypoparathyroidism: in patients with hypercalcemia, 77.6% were noted to have hypoparathyroidism ($P < 0.001$). Similarly, in patients with hypocalcemia, 54.1% had hyperparathyroidism ($P < 0.001$). No statistically

significant associations were noted between calcium level abnormalities and elevated alkaline phosphatase level and between PTH level abnormalities and elevated alkaline phosphatase level.

In univariate and minimally adjusted multivariable propensity score-matched analyses, hyponatremia was associated significantly with hypoparathyroidism (ORs of 1.28 [95% CI, 1.03–1.60] and 1.29 [95% CI, 1.03–1.62], respectively). The association between hyponatremia and hypoparathyroidism in fully adjusted multivariable propensity score-matched analyses was attenuated (OR, 1.29; 95% CI, 0.95–1.74). Other associations, including those between hyponatremia and hypercalcemia (univariate: OR, 1.43 [95% CI, 0.68–3.01]; multivariable model 1: OR, 1.40 [95% CI, 0.66–2.96]; multivariable model 2: OR, 1.44 [95% CI, 0.64–3.25]) and hyponatremia and elevated alkaline phosphatase level (univariate: OR, 1.14 [95% CI, 0.88–1.48]; multivariable model 1: OR, 1.15 [95% CI, 0.89–1.50]; multivariable model 2: OR, 1.10 [95% CI, 0.83–1.46]) also were attenuated, possibly due to limited sample size, and did not reach statistical significance.

Falls and Fractures

There were 137 patients who experienced at least one fall and/or fracture during the 1-year follow up. Rates of falls and/or fractures were 4 events per 100 person-years and 3 events per 100 person-years for hyponatremic and normonatremic patients, respectively ($P=0.3$). Due to limited numbers of events, we could not perform multivariable-adjusted analyses for this outcome.

Mortality

At the 1-year follow-up, 965 (15.8%) patients had died. In univariate analysis, patients with hyponatremia had a significantly higher risk of 1-year mortality compared with normonatremic patients (HR, 1.59; 95% CI, 1.34–1.87; Fig 3). In multivariable analyses, hyponatremic patients continued to have a higher risk of 1-year mortality (model 1: HR, 1.48 [95% CI, 1.26–1.75]; model 2: HR, 1.42 [95% CI, 1.19–1.69]). Considered as a continuous predictor, each 3-mEq/L decrease in sodium level (the observed standard deviation in our cohort) was associated with the following hazards for 1-year mortality: univariate model: HR, 1.18 [95% CI, 1.11–1.23]; multivariable model 1: HR, 1.15 [95% CI, 1.10–1.22]; multivariable model 2: HR, 1.14 [95% CI, 1.08–1.20].

In propensity score-matched analyses, hyponatremia was associated with higher 1-year mortality in both univariate (HR, 1.41; 95% CI, 1.12–1.78) and multivariable analyses (model 1: HR, 1.41 [95% CI, 1.12–1.78]; model 2: HR, 1.31 [95% CI, 1.02–1.67]). Most deaths were attributable to cardiovascular causes (57%) and hyponatremia was associated with increased cardiovascular mortality in univariate (HR, 1.37; 95% CI, 1.09–1.72) and multivariable analyses (model 1: HR, 1.28 [95% CI, 1.02–1.61]; model 2: HR, 1.29 [95% CI, 1.02–1.64]).

The mineral bone abnormalities that were associated with hyponatremia, namely hypercalcemia, elevated alkaline phosphatase level, and hypoparathyroidism, were all associated with 1-year mortality ($P<0.001$). In analyses adjusted for these abnormalities, the association between hyponatremia and mortality was unaltered (HR, 1.54; 95% CI, 1.28–1.85).

DISCUSSION

In a large prospective cohort of incident HD patients, we found that hyponatremic patients at HD therapy initiation have notable differences in mineral bone metabolism, including higher

prevalences of hypercalcemia, elevated alkaline phosphatase levels, and hypoparathyroidism, compared with normonatremic patients. In an experimental rat model, hyponatremia has been shown to increase osteoclastogenesis and osteoclast activity and lead to a reduction in bone mineral density, lower bone volume, and lower cortical and trabecular thickness.^{13,14} A sodium concentration-dependent reduction in the activity of the sodium-dependent ascorbic acid transporter has been shown to mediate the altered bone metabolism observed in hyponatremia.¹⁹ Corresponding data for humans about this are unknown. Increased bone formation may manifest with increased serum alkaline phosphatase levels and increased bone resorption may manifest with increased serum calcium levels.^{20,21} Thus, the associations that we observe may suggest that hyponatremia is an important independent determinant of bone turnover state in incident HD patients.

Although the exact sequence of events describing hyponatremia leading to mineral bone abnormalities is unknown, we speculate that associations between hyponatremia and these mineral abnormalities are derived from the direct actions of hyponatremia on bone. Hyponatremia may directly stimulate osteoclastic activity, increasing calcium levels and consequently suppressing PTH. The elevation in serum alkaline phosphatase levels noted in our study suggests that hyponatremia also may have direct stimulatory effects on osteoblasts. Osteoporosis increasingly is recognized as a process associated with increased bone resorption and bone formation markers.²² The associations between hyponatremia and markers of bone turnover observed in our study raise the possibility that hyponatremia may contribute to osteoporosis in this population. However, our interpretations regarding these associations are hypotheses and cannot be proved by an observational study such as this one. Biological studies are needed to better define cause-and-effect relationships.

Mineral bone abnormalities associated with hyponatremia in this study are established risk factors for mortality in HD patients,^{23,24} and our study found significant associations with mortality for hypercalcemia, elevated alkaline phosphatase levels, and hypo-parathyroidism. These parameters also are taken into account to guide therapies such as active vitamin D administration that has been associated with reduced mortality in prior observational studies in an incident HD population.^{25,26} In our study, hyponatremia at HD therapy initiation was associated with reduced active vitamin D administration at 90 days (data not shown), which most likely is a reflection of mineral bone abnormalities associated with hyponatremia, and emphasizes the significance of further investigating associations between hyponatremia and mineral bone disease parameters. However, the relationship between hyponatremia and mortality was unaltered even after adjusting for mineral bone abnormalities, indicating that additional mechanisms may be at play simultaneously. Although such mechanisms are not entirely characterized, possible candidates include effects of hyponatremia on cardiac contractility,²⁷ nerve impulse transmission,²⁸ and inflammation.^{29,30}

Waikar et al⁹ previously described hyponatremia as an independent risk factor for mortality in a prevalent HD population, and our study establishes hyponatremia as an independent risk factor for all-cause and cardiovascular mortality in incident HD patients. Although some significant differences in baseline characteristics were noted between hyponatremic and normonatremic patients, in analyses adjusted for those covariates, hyponatremia remained as a significant predictor of mortality. We used cutoff values based on clinical thresholds, rather than quartiles that may differ by only 1–2 mEq/L. An association from cohort studies does not imply causality because one cannot entirely rule out residual confounding. In this regard, lack of availability of data for residual urine output, diuretic use, fluid intake, and interdialytic weight gain can limit the interpretation of our findings. However, confounding by dialysis-related practice patterns, dialysate sodium concentration, and interdialytic weight gain is less likely in our study because we assessed baseline sodium levels at HD therapy initiation. Also, baseline sodium levels measured at dialysis therapy initiation correlated

with those at 90 days, suggesting that hyponatremia persists beyond the peri-initiation period. Thus, our study findings are more likely to represent a possible causal link between hyponatremia and mortality rather than one that reflects differences in dialysis management. A randomized controlled clinical trial to test whether correcting hyponatremia improves survival is needed.

In experimental studies of chronic hyponatremia by Verbalis et al,¹³ hyponatremic rats developed lower 25-hydroxyvitamin D levels.¹⁴ Possible explanations for this phenomenon may include insufficient intake, altered gastrointestinal absorption, or increased catabolism of vitamin D. In hyponatremic rats, 25-hydroxyvitamin D levels were uncorrected despite a significant increase in vitamin D₃ intake, suggesting that changes in absorption or metabolism may be at play. We did not observe an association between hyponatremia and 25-hydroxyvitamin D levels, indicating that serum sodium levels do not predict 25-hydroxyvitamin D deficiency in incident HD patients. However, there are other differences in vitamin D metabolism between humans and rats (eg, rats are nocturnal and have reduced sun exposure compared with humans) that may explain some of the discrepant findings. In addition, the nature of bone disorders in the dialysis population is likely to be complex compared with experimental settings of chronic hyponatremia induced by liquid diet and desmopressin.^{13,14}

We acknowledge the following additional limitations of our study. In the ArMORR cohort, the first set of laboratory values was obtained from the first-ever outpatient HD session. We used these data as baseline because we did not have information for laboratory data from prior HD sessions that patients may have had during hospitalization for HD therapy initiation. We also did not have data for dialysis prescriptions for HD sessions that may have been conducted prior to the first outpatient HD session at an FMCNA facility. Data for sodium level at baseline were not available for the entire cohort; however, patients with available data did not differ from those who did not have available data in terms of demographics and comorbid conditions. Catheter HD access was more common in hyponatremic patients. Although reasons for higher catheter HD access use in the hyponatremic group are not clear, we believe it is unlikely to reflect differences in the cause of kidney failure (acute vs chronic) because all patients in the ArMORR cohort were long-term maintenance HD patients and recovery of kidney function leading to discontinuation of HD therapy (as may be seen more commonly with acute kidney injury) was very rare in the ArMORR cohort. Furthermore, in multivariable models adjusted for catheter access, associations of hyponatremia with mineral bone abnormalities and mortality continued to be significant. Although elevated serum alkaline phosphatase level has been reported to be the only biochemical parameter associated with reduced bone mineral density in the HD population,³¹ the low rate of falls and/or fractures in this cohort and lack of data for bone density limit our ability to translate effects of elevated alkaline phosphatase levels on clinical outcomes. Fall and fracture data were ascertained from inpatient discharge summaries; thus, the possibility of ascertainment bias cannot be excluded. Due to limited study follow-up duration, associations between hyponatremia and long-term outcomes could not be assessed. We could not assess associations between hyponatremia and other mineral bone parameters, including ionized calcium, fibroblast growth factor 23 (FGF-23), and bone alkaline phosphatase, because these data were not available. Future larger studies with longer follow-up should investigate associations between hyponatremia and bone mineral density and risk of falls and fractures. Future studies also should investigate associations between hyponatremia and other mineral bone parameters, such as levels of FGF-23 and bone alkaline phosphatase, markers previously established to predict mortality in this population.^{32,33}

In conclusion, in incident HD patients, hyponatremia at the initiation of maintenance HD therapy is associated with mineral bone abnormalities and increased mortality. More thorough assessment of bone disease likely will be needed to better understand the effects of sodium on bone metabolism. Future prospective studies will be needed to examine whether altering serum sodium level affects mineral bone abnormalities and mortality in these patients.

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Figure 1. Histogram shows the distribution of baseline serum sodium levels. Black vertical lines show groupings of hyponatremia and normonatremia (included in the analysis), as well as the hypernatremic group (excluded from the analysis).

Figure 2.
Multivariable adjusted odds of mineral bone abnormalities for hyponatremic patients.

Figure 3.
Kaplan-Meier curves for 1-year all-cause mortality by sodium category.

Table 1

Baseline Characteristics and Prevalence of Mineral Bone Abnormalities According to Sodium Categories

	All (N = 6,053)	Hyponatremic ^a (n = 775)	Normonatremic ^a (n = 5,278)	P
Characteristic				
Age (y)	62.5 ± 15.2	65.1 ± 14.0	62.2 ± 15.4	<0.001 ^b
Male sex	54.4	52.5	54.7	0.3
Race				0.09
White	58.9	57.7	59.0	
Black	33.7	32.9	33.8	
Other	7.5	9.4	7.2	
Congestive heart failure	12.3	12.3	12.3	0.9
Diabetes mellitus	26.9	20.1	27.9	<0.001 ^b
Hypertension	38.4	30.6	39.5	<0.001 ^b
Coronary artery disease	9.8	6.8	10.2	0.004 ^b
Liver disease	2.7	3.2	2.6	0.3
Malignancy	2.8	2.8	2.8	0.9
Chronic obstructive lung disease	2.0	1.8	2.0	0.7
Catheter vascular access	62.9	70.0	61.9	<0.001 ^b
Body mass index (kg/m ²)	27.9 ± 9.1	26.5 ± 7.6	28.2 ± 9.3	<0.001 ^b
Systolic BP (mm Hg)	145.1 ± 23.2	139.8 ± 25.6	145.9 ± 22.7	<0.001 ^b
Diastolic BP (mm Hg)	74.3 ± 14.2	72.1 ± 17.0	74.6 ± 13.7	<0.001 ^b
Estimated Kt/V	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	0.2
Urea reduction ratio	69.8 ± 7.9	70.1 ± 8.0	69.8 ± 7.8	0.3
Serum glucose (mg/dL)	153.3 ± 81.5	141.3 ± 74.4	155.1 ± 82.3	<0.001 ^b
Serum albumin (g/dL)	3.4 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	0.01 ^b
Serum creatinine (mg/dL)	6.3 ± 2.7	6.5 ± 2.8	6.3 ± 2.7	0.01 ^b
eGFR (mL/min/1.73 m ²)	10.5 ± 6.2	10.0 ± 5.4	10.6 ± 6.3	0.01 ^b
Serum bicarbonate (mEq/L)	23.2 ± 4.1	22.2 ± 3.8	23.3 ± 4.1	<0.001 ^b
Hemoglobin (g/dL)	10.3 ± 1.4	10.3 ± 1.3	10.3 ± 1.4	0.7
Mineral bone abnormality ^c				
Hypocalcemia	20.4	18.4	20.8	0.1
Hypercalcemia	1.3	2.2	1.2	0.02 ^b
Hypophosphatemia	5.5	6.1	5.4	0.4
Hyperphosphatemia	48.3	49.2	48.1	0.6
Elevated alkaline phosphatase	16.3	20.3	15.7	0.002 ^b
Hypoparathyroidism	21.8	27.5	20.9	<0.001 ^b
Hyperparathyroidism	31.5	26.0	32.3	0.001 ^b
Hypovitaminosis D	80.7	85.2	80.1	0.3

Note: Values for categorical variables are given as percentages; values for continuous variables, as mean $\pm$ standard deviation. Conversion factors for units: creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; glucose in mg/dL to mmol/L, $\times 0.05551$.

Abbreviations: BP, blood pressure; Ca, calcium; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone.

^aHyponatremic (sodium, <135 mEq/L) or normonatremic (sodium, 135–145 mEq/L) based on glucose-corrected sodium level at the time of dialysis therapy initiation.

^bSignificant at $P < 0.05$.

^cHypocalcemia defined as Ca <8.4 mg/dL; hypercalcemia, Ca >10.5 mg/dL; hypophosphatemia, serum phosphorus <2.6 mg/dL; hyperphosphatemia, serum phosphorus >4.5 mg/dL; elevated alkaline phosphatase, serum alkaline phosphatase >129 U/L; hypoparathyroidism, as PTH <150 pg/mL; hyperparathyroidism, as PTH >300 pg/mL; hypovitaminosis D, as 25-hydroxyvitamin D <30 ng/mL.

Cox Proportional Hazard and Logistic Regression Models of Associations of Hyponatremia With Mortality and Mineral Bone Abnormalities

Table 2

Outcome	Unadjusted			Multivariable Model 1 ^a			Multivariable Model 2 ^b		
	HR/OR	(95% CI)	P	HR/OR	(95% CI)	P	HR/OR	(95% CI)	P
HR for mortality	1.59	(1.34–1.87)	<0.001 ^c	1.48	(1.26–1.75)	<0.001 ^c	1.42	(1.19–1.69)	<0.001 ^c
OR for mineral bone abnormalities ^d									
Hypocalcemia	0.86	(0.71–1.04)	0.1	0.88	(0.73–1.07)	0.2	0.80	(0.65–0.99)	0.04 ^c
Hypercalcemia	1.92	(1.11–3.30)	0.02 ^c	1.84	(1.06–3.17)	0.03 ^c	2.03	(1.14–3.59)	0.02 ^c
Hypophosphatemia	1.14	(0.83–1.57)	0.4	1.05	(0.76–1.45)	0.8	1.28	(0.91–1.82)	0.2
Hyperphosphatemia	1.04	(0.90–1.21)	0.6	1.15	(0.99–1.35)	0.08	1.02	(0.86–1.20)	0.9
Elevated alkaline phosphatase	1.36	(1.12–1.66)	0.002 ^c	1.40	(1.15–1.70)	0.001 ^c	1.33	(1.08–1.63)	0.008 ^c
Hypoparathyroidism	1.40	(1.18–1.65)	<0.001 ^c	1.39	(1.17–1.65)	<0.001 ^c	1.29	(1.04–1.60)	0.02 ^c
Hyperparathyroidism	0.74	(0.61–0.89)	0.001 ^c	0.75	(0.62–0.90)	0.002 ^c	0.82	(0.67–1.01)	0.07
Hypovitaminosis D	1.43	(0.77–2.66)	0.3	1.41	(0.75–2.64)	0.3	1.27	(0.66–2.44)	0.5

Note: ORs and 95% CIs are for low sodium compared to normal sodium levels for each outcome listed.

Abbreviations: Ca, calcium; CI, confidence interval; HR, hazard ratio; OR, odds ratio; PTH, parathyroid hormone.

^a Multivariable model 1 is adjusted for age, sex, and race.

^b Multivariable model 2 for Cox proportional hazard analysis adjusted for age, sex, race, facility mortality statistic, diabetes mellitus, hypertension, coronary artery disease, catheter access, body mass index, serum albumin level, and serum bicarbonate level. Multivariable model 2 for logistic regression analysis is adjusted for age, sex, race, diabetes mellitus, hypertension, coronary artery disease, catheter access, body mass index, serum albumin level, serum bicarbonate level, phosphate-binder use, cinacalcet use, and active vitamin D use.

^c Significant at $P < 0.05$.

^d Hypocalcemia defined as Ca <8.4 mg/dL; hypercalcemia, Ca >10.5 mg/dL; hypophosphatemia, serum phosphorus <2.6 mg/dL; hyperphosphatemia, serum phosphorus >4.5 mg/dL; elevated alkaline phosphatase, serum alkaline phosphatase >129 U/L; hypoparathyroidism, PTH <150 pg/mL; hyperparathyroidism, PTH >300 pg/mL; hypovitaminosis D, 25-hydroxyvitamin D <30 ng/mL.