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ORIGINAL ARTICLE

Chronic hyponatremia and association with osteoporosis among a large racially/ethnically diverse population

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Abstract

Summary Chronic hyponatremia may contribute to decreased bone density. We studied 341,003 men and women who underwent DXA testing and observed that individuals with chronic hyponatremia (sodium < 135 mEq/L) had an 11% greater likelihood of having osteoporosis. There was a dose-dependent effect with lower sodium and stronger association with osteoporosis.

Introduction Chronic hyponatremia has been associated with both neurologic deficits and increased risk of gait abnormalities leading to falls and resultant bone fractures. Whether chronic hyponatremia contributes to decreased bone density is uncertain. We evaluated whether chronic, mild hyponatremia based on serial sodium measurements was associated with increased risk of osteoporosis within a large, ethnically diverse population.

Methods This is a retrospective cohort study between January 1, 1998 and December 31, 2014 within Kaiser Permanente Southern California, an integrated healthcare delivery system. Men and women were aged ≥ 55 years with ≥ 2 serum sodium measurements prior to dual-energy X-ray absorptiometry (DXA) testing. Time-weighted (TW) mean sodium values were calculated by using the proportion of time (weight) elapsed between sodium measurements and defined as < 135 mEq/L. Osteoporosis defined as any T-score value ≤ − 2.5 of lumbar spine, femoral neck, or hip.

Results Among 341,003 individuals with 3,330,903 sodium measurements, 11,539 (3.4%) had chronic hyponatremia and 151,505 (44.4%) had osteoporosis. Chronic hyponatremic individuals had an osteoporosis RR (95% CI) of 1.11 (1.09, 1.13) compared to those with normonatremia. A TW mean sodium increase of 3 mEq/L was associated with a lower risk of osteoporosis [adjusted RR (95% CI) 0.95 (0.93, 0.96)]. A similar association was observed when the arithmetic mean sodium value was used for comparison.

Conclusions We observed a modest increase in risk for osteoporosis in people with chronic hyponatremia. There was also a graded association between higher TW mean sodium values and lower risk of osteoporosis. Our findings underscore the premise that chronic hyponatremia may lead to adverse physiological effects and responses which deserves better understanding.

Keywords Chronic hyponatremia · Diverse population · Osteoporosis

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Introduction

Hyponatremia is a common electrolyte disorder in both the inpatient and outpatient settings [1–4]. Among older adults, hyponatremia rates of 10–50% have been described in ambulatory and nursing home populations [5–8]. Acute hyponatremia is also known to induce cerebral edema and neurologic disturbances resulting in significant increase in morbidity and mortality [3, 9, 10].

Varying degrees of hyponatremia can contribute to adverse outcomes, such as neurologic deficits and increased risk of gait abnormalities leading to falls. Chronic hyponatremia has been associated with increased risk of fractures [11–14]. However, it is not clear if this increased risk of fractures is simply a result of increased fall risk or if chronic hyponatremia also contributes to decreased bone density. Animal models and human observations have suggested that chronic hyponatremia significantly diminishes bone mass and directly contributes to osteoporosis [15–17]. An association between hyponatremia and osteoporosis in humans have been described using relatively smaller populations and limited number of sodium measurements [18–20]. Capturing serial sodium measurements over a long duration would give a more reliable estimate of an individual's sodium status over time to better identify people with chronic hyponatremia.

Studying potential associations of chronic sodium states with osteoporosis among an older adult population within a real world clinical environment would provide valuable insights. Thus, we sought to determine whether chronic hyponatremia was associated with increased risk for osteoporosis based on time-weighted (TW) mean sodium values among a large, ethnically diverse population of men and women who underwent dual-energy X-ray absorptiometry (DXA) examinations.

Materials and methods

Study population

This retrospective cohort study included members of the Kaiser Permanente Southern California (KPSC) health system during the period January 1, 1998 through December 31, 2014. KPSC is an integrated health system providing comprehensive care to over 4.3 million members at 14 medical centers and > 200 satellite clinics throughout Southern California. The patient population is racially/ethnically and socioeconomically diverse, reflecting the general population of Southern California [21–23]. All KPSC members have similar benefits and access to healthcare services, clinic visits, procedures, and copays for medications. Healthcare encounters are tracked using an electronic health record (EHR) from which all study information was extracted. All data for this study were collected as part of routine clinical encounters in which healthcare providers determined the need for laboratory measurements, procedures, and medications. The study protocol was reviewed and approved by the KPSC Institutional Review Board.

Individuals aged ≥ 55 years with ≥ 2 serum sodium measurements on different dates but prior the date of a documented DXA bone mineral density (BMD) result were included in the study (Fig. 1). Sodium measurements that had a

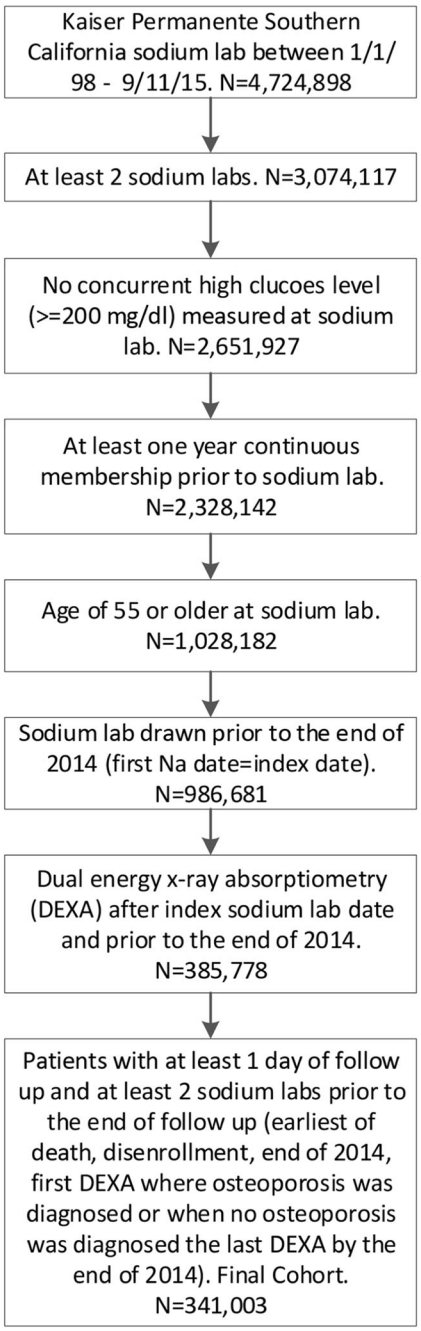

Fig. 1 Study population. Members of Kaiser Permanente Southern California (KPSC) health system during the period January 1, 1998 through December 31, 2014 who were age 55 years and older with two separate sodium measurements *prior* to DXA study

concurrently high glucose (≥ 200 mg/dL) value at the time of the sodium laboratory measurement were excluded because of the potential for pseudohyponatremia. Individuals were required to have 1 year of continuous membership in the health care plan prior to the first serum sodium measurement in order to comprehensively capture any comorbidities. The study population was observed until disenrollment from the healthcare plan, death, or until the end of the study period.

Sodium measurement and definition of hyponatremia

Serum sodium levels during the study period were measured using the Ion Selective Electrode (ISE). While the companies that have run the assays have changed twice during the observation window, the normal reference ranged including the low clinical reportable range of < 135 mEq/L has remained the same throughout KPSC during this period. For this study, hyponatremia was defined as serum sodium < 135 mEq/L. Hyponatremia was further categorized as mild with sodium level of 130–134 mEq/L and severe hyponatremia as < 130 mEq/L. For this study, all sodium states including hyponatremia were classified as chronic using the rationale that it was based on two separate serum sodium measurements obtained on different dates.

Descriptive information

Information on the following were extracted from the EHR and/or pharmacy records: demographics (age, sex, race, ethnicity), comorbidities (diabetes mellitus, cardiovascular disease, peripheral vascular disease, hypertension, hypothyroidism, and prior fracture), laboratory results (potassium, bicarbonate, chloride, blood urea nitrogen, creatinine, calcium, hemoglobin, thyrotropin (TSH), alkaline phosphatase, hemoglobin A1C, albumin, and estimated glomerular filtration rate (eGFR)), and medication usage (bisphosphonates, other osteoporosis medications, anti-hypertensive medications, anti-arrhythmia medications, anti-coagulation medications, anti-seizure medications, endocrine and hormonal therapies, corticosteroids, thiazide diuretics, benzodiazepines, anti-depressants, and proton-pump inhibitors). Baseline characteristics were ascertained within the year prior to the first sodium measurement. Comorbidities were identified using inpatient and outpatient ICD-9 diagnosis codes. With the exception of sodium which had to be prior to DXA, all other laboratory values that were closest to the DXA scan date were used. eGFR was calculated from serum creatinine levels using the Chronic Kidney Disease Epidemiology Collaboration Equation [24]. Information on hospitalizations and diagnoses that occurred outside the healthcare system were available through administrative billing and claim records. Information on pharmacy fills was retrieved from the KPSC pharmacy dispensing records. Individuals were considered to be on a medication if it was dispensed at least twice during the observation period.

Primary outcome—osteoporosis

DXA results were used to determine the presence of osteoporosis. BMD measurements were performed at the lumbar spine and both femoral necks using a Lunar Prodigy scanner (General Electric). Results were reported as T-scores indicative of the number of standard deviations by which the bone density value differs from a normal reference group. BMD results for men were referenced to young males and women were referenced to young females. Osteopenia was defined as a T-score of − 1.0 to > − 2.5 and osteoporosis as a T-score of ≤ − 2.5, consistent with the World Health Organization (WHO) definitions [25].

Statistical analysis

Individuals were categorized as having chronic hyponatremia and normonatremia. The TW mean sodium value is the weighted average of sodium lab values during an individual's entire sodium history between their sodium values. The proportion of the period between the sodium lab of interest and the next sodium lab, out of the entire history, is assigned to the sodium lab of interest as its weight. The last sodium was weighted by the measurement data and the earliest of the following dates: death, disenroll, DEXA scan, and end of 2014. Individuals were further categorized by their TW mean sodium values (Na ≥ 135 mEq/L, Na 130–134 mEq/L, and Na < 130 mEq/L). The demographic characteristics and by TW mean sodium values were compared. Chi-squared test was used for comparison of categorical variables and the two-sample Wilcoxon rank-sum test was used for continuous variables.

The primary analysis was to determine whether there was an association between hyponatremia and osteoporosis. Multivariable regression analyses were used to estimate relative risk (RR) and 95% confidence intervals (95% CI) for osteoporosis for (1) chronic hyponatremia versus normonatremia and (2) TW sodium value increases of 1 mEq/L, 3 mEq/L, and 5 mEq/L. All models were adjusted for demographics, comorbidities, laboratory results, and medication usage. Adjustments were made sequentially where the fully adjusted models accounted for age, gender, race, ethnicity, comorbidities, labs, and medications (bisphosphonates, other osteoporosis medications, anti-hypertensive medications, anti-arrhythmia medications, anti-coagulation medications, anti-seizure medications, endocrine and hormonal

therapies, corticosteroids, thiazide diuretics, benzodiazepines, anti-depressant medications, and proton-pump inhibitors).

Sensitivity analyses were conducted on the study population using arithmetic mean sodium values. Arithmetic mean sodium values were determined for each individual and multivariable regression modeling were used to estimate RR and 95% CI for osteoporosis for arithmetic mean sodium value increases of 1, 3, and 5 mEq/L. All models were adjusted for demographics, comorbidities, laboratory results, and medication usage. Sequential adjustments were made to estimate RR by adding selected variables.

All statistical analyses were conducted using SAS statistical software (version 9.2, SAS Institute Cary, NC).

Results

Cohort characteristics

The study cohort included 341,003 individuals that had a total of 3,330,903 sodium measurements with 302,003 (89%) individuals having had 3 or more measurements (Fig. 2). The median length of observation was 6.3 years. The median age of the study population was 63 years, and males comprised 33% of the cohort (Table 1). Osteoporosis (T-score ≤ -2.5) was present in 151,505 (44.4%) of the population. The osteoporotic population was older (66 versus 62 years), more likely white or Asian, and less likely to be black. They also had greater rates of comorbidities but lower blood pressure and body mass index (Supplemental Table 1). During the study period, 34.5% were prescribed osteoporosis medications and 0.3% were observed to have a history of prior hip fracture. The median eGFR was 73.0 mL/min/1.73 m^2 (Table 2). Ninety-four percent of the population had three or more sodium measurements for analysis (Fig. 2).

Chronic hyponatremia

A total of 11,539 (3.4%) individuals were identified as having chronic hyponatremia with 564 (0.2%) having a TW mean sodium value < 130 mEq/L (Table 1). Those with chronic hyponatremia were significantly older and less likely male compared to individuals with normonatremia. Individuals with chronic hyponatremia had a greater prevalence of comorbid conditions including hypertension, cardiovascular disease, and peripheral vascular disease ($p < 0.001$). There was greater use of medications of various classes including bisphosphonates, antihypertensive medications, corticosteroids, diuretics, and anti-depressants ($p < 0.001$) (Table 1). Osteoporosis was present in 59.7% of individuals with chronic hyponatremia compared to 43.9% with normonatremia ($p < 0.001$). In terms of laboratory findings, individuals

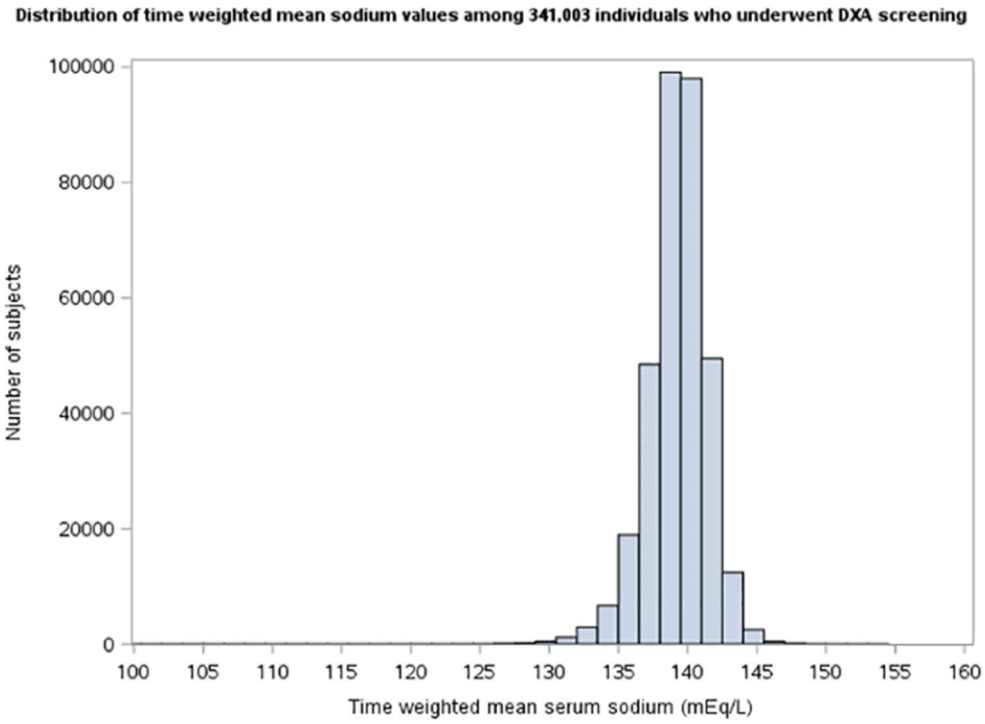

Fig. 2 Population distribution based on sodium measurement. A total 3,330,903 sodium measurements were resulted among of 341,003 individuals. Within the KPSC health system regional and local laboratories, the methodology for the sodium measurement has remained the same during (1998–2014). The Ion Selective Electrode (ISE) method has been used, and the low clinical reportable range of < 135 mEq/L has remained the same throughout this period

Table 1 Characteristics of the study cohort by sodium status using time-weighted mean sodium values

Characteristic	All	Time-weighted mean sodium ≥ 135 mEq/L	Time-weighted mean sodium 130–135 mEq/L	Time-weighted mean sodium < 130 mEq/L	*P* value
N (row %)	341,003 (100)	329,464 (96.6)	10,975 (3.2)	564 (0.2)	
Osteoporosis[a]					< 0.001
No	189,498 (55.6%)	184,851 (56.1%)	4491 (40.9%)	156 (27.7%)	
Yes	151,505 (44.4%)	144,613 (43.9%)	6484 (59.1%)	408 (72.3%)	
Age, median	63.3	63.1	67.3	68.6	< 0.001
Age (%)					< 0.001
55–64 years	195,949 (57.5%)	191,319 (58.1%)	4408 (40.2%)	222 (39.4%)	
65–74 years	107,751 (31.6%)	103,448 (31.4%)	4098 (37.3%)	205 (36.3%)	
75–84 years	34,120 (10%)	31,808 (9.7%)	2197 (20%)	115 (20.4%)	
85+ years	3183 (0.9%)	2889 (0.9%)	272 (2.5%)	22 (3.9%)	
Male (%)	112,546 (33%)	109,047 (33.1%)	3330 (30.3%)	169 (30%)	< 0.001
Race/ethnicity (%)					< 0.001
White	201,017 (58.9%)	193,148 (58.6%)	7451 (67.9%)	418 (74.1%)	
Black	34,260 (10%)	33,676 (10.2%)	562 (5.1%)	22 (3.9%)	
Asian/Pacific Islander	31,199 (9.1%)	30,409 (9.2%)	755 (6.9%)	35 (6.2%)	
Hispanic white	62,323 (18.3%)	60,400 (18.3%)	1856 (16.9%)	67 (11.9%)	
Other	12,204 (3.6)	11,831 (3.6)	351 (3.2)	22 (3.9)	
SBP, median	129	129	133	135	< 0.001
DBP, median	74	74	75	73	0.104
History of hip fracture (%)	1122 (0.3%)	1031 (0.3%)	83 (0.8%)	8 (1.4%)	< 0.001
Body mass index, median	27.3	27.3	25.9	25.1	< 0.001
Hypertension (%)	120,864 (35.4%)	115,779 (35.1%)	4820 (43.9%)	265 (47%)	< 0.001
Diabetes mellitus (%)	14,460 (4.2%)	13,979 (4.2%)	458 (4.2%)	23 (4.1%)	0.921
Cardiovascular disease (%)	35,929 (10.5%)	34,540 (10.5%)	1304 (11.9%)	85 (15.1%)	< 0.001
Peripheral vascular disease (%)	5361 (1.6%)	5053 (1.5%)	287 (2.6%)	21 (3.7%)	< 0.001
Hypothyroid (%)	23,136 (6.8%)	22,167 (6.7%)	910 (8.3%)	59 (10.5%)	< 0.001
Medication exposure (%)					
Bisphosphonates	102,995 (30.2%)	98,130 (29.8%)	4606 (42%)	259 (45.9%)	< 0.001
Other osteoporosis meds	14,772 (4.3%)	13,898 (4.2%)	819 (7.5%)	55 (9.8%)	< 0.001
Anti-hypertensive meds	225,889 (66.2%)	217,222 (65.9%)	8248 (75.2%)	419 (74.3%)	< 0.001
Anti-arrhythmia meds	7894 (2.3%)	7589 (2.3%)	287 (2.6%)	18 (3.2%)	0.039
Anti-coagulation meds	46,310 (13.6%)	44,426 (13.5%)	1797 (16.4%)	87 (15.4%)	< 0.001
Anti-seizure meds	41,598 (12.2%)	39,678 (12%)	1818 (16.6%)	102 (18.1%)	< 0.001
Endocrine/hormonal meds	78,731 (23.1%)	75,725 (23%)	2870 (26.2%)	136 (24.1%)	< 0.001
Corticosteroids	107,501 (31.5%)	103,612 (31.4%)	3680 (33.5%)	209 (37.1%)	< 0.001
Thiazide diuretics	118,289 (34.7%)	113,836 (34.6%)	4272 (38.9%)	181 (32.1%)	< 0.001
Benzodiazepines	92,107 (27%)	88,198 (26.8%)	3725 (33.9%)	184 (32.6%)	< 0.001
Anti-depressant meds	132,883 (39%)	127,625 (38.7%)	5013 (45.7%)	245 (43.4%)	< 0.001
Proton-pump inhibitors	107,326 (31.5%)	103,265 (31.3%)	3874 (35.3%)	187 (33.2%)	< 0.001

[a] Defined as any T-score value ≤ − 2.5 of lumbar spine or femoral neck on DXA study

with normonatremia had higher levels of calcium, PTH, albumin, uric acid, and hemoglobin compared to those with hyponatremia. They also were younger, had higher body mass index (BMI), had lower systolic blood pressure (SBP), and had fewer prior hip fractures (Table 2).

Regression analyses: osteoporosis risk

The fully adjusted RR (95% CI) for osteoporosis among individuals with chronic hyponatremia (< 135 meq/L) compared to individuals with normonatremia (≥ 135 mEq/L) was 1.11

Table 2 Laboratory and DXA results for the study cohort by time-weighted mean sodium values

Characteristic	All	Time-weighted mean sodium ≥ 135 mEq/L	Time-weighted mean sodium 130–134 mEq/L	Time-weighted mean sodium < 130 mEq/L	*P* value
N (%)	341,003 (100)	329,464 (96.6)	10,975 (3.2)	564 (0.2)	
BMD, lowest T-score (%)					< 0.001
> − 1.0	43,312 (12.7%)	42,363 (12.9%)	921 (8.4%)	28 (5%)	
− 1.0 to > − 2.5	146,082 (42.8%)	142,390 (43.2%)	3564 (32.5%)	128 (22.7%)	
≤ − 2.5	151,609 (44.5%)	144,711 (43.9%)	6490 (59.1%)	408 (72.3%)	
Sodium (mEq/L), median	139	140	135	132	< 0.001
Potassium (mEq/L), median	4.1	4.1	4.2	4.3	< 0.001
Bicarbonate (mEq/L), median	28	28	28	27	< 0.001
Chloride (mEq/L), median	104	104	100	97	< 0.001
BUN (mg/dL), median	15	15	14	13	< 0.001
Creatinine (mg/dL), median	0.9	0.9	0.9	0.8	< 0.001
eGFR (mL/min/1.73 m^2), median	73	72.9	74.9	80	< 0.001
Calcium (mg/dL), median	9.4	9.4	9.3	9.3	< 0.001
Phosphorus, median	3.4	3.4	3.5	3.6	< 0.001
Magnesium (mEq/L), median	1.9	1.9	1.8	1.8	< 0.001
TSH (uIU/mL), median	1.6	1.6	1.7	1.7	< 0.001
Uric acid (mg/dL), median	5.6	5.6	4.8	4.4	< 0.001
ALT (U/L), median	0.7	0.7	0.7	0.7	0.301
Alkaline phosphatase (U/L), median	68	68	69	70	0.015
PTH (pg/mL), median	49	49	43	41	< 0.001
Vitamin D (ng/mL), median	32	31	32	31	< 0.001
HgbA1C, median	5.8	5.8	5.8	5.7	< 0.001
Albumin (g/dL), median	3.9	3.9	3.8	3.8	< 0.001
White blood cell (cell/mcL), median	0.5	0.5	0.5	0.5	< 0.001
Hemoglobin (g/dL), median	13.6	13.6	13.2	13	< 0.001

(1.09, 1.13). Compared to individuals with sodium ≥ 135 mEq/L, the RR for osteoporosis was 1.10 (1.08, 1.12) and 1.25 (1.17, 1.34) for individuals with sodium 130–134 mEq/L and < 130 mEq/L, respectively. Higher TW mean sodium values were associated with lower adjusted RR for osteoporosis for all adjusted models (Table 3). In the fully adjusted model, TW mean sodium increases of 1, 3, and 5 mEq/L were associated with osteoporosis RR (95% CI) of 0.98 (0.98, 0.99), 0.95 (0.93, 0.96), and 0.91 (0.89, 0.93), respectively. Sensitivity analyses using arithmetic mean serum sodium levels also showed a similar association where sodium increases of 1, 3, and 5 mEq/L were associated with osteoporosis RR (95% CI) of 0.98 (0.98, 0.99), 0.95 (0.94, 0.96), and 0.92 (0.90, 0.94), respectively.

Discussion

Our study of over 340,000 racially/ethnically diverse men and women among a routine clinical practice environment demonstrated an increased risk for osteoporosis among individuals with chronic hyponatremia compared to those with normal sodium levels. We observed a graded association where people with incrementally higher serum sodium levels had lower risk for osteoporosis. Given our findings, hyponatremia may represent another modifiable risk factor for osteoporosis for which appropriate prevention and therapeutic measures could be warranted.

Osteoporosis remains a significant public health concern given its association with increased risk of serious fractures. Osteoporotic fractures have been shown to result in increased morbidity including physical disability and financial cost, and significantly increased mortality [26, 27].

Associations between hyponatremia and osteoporosis have also been described in the past observations [15, 18, 20]. Hyponatremia has also been described as a risk factor for falls and fractures [11–14, 28–30]. While mild, chronic hyponatremia is often assumed to be asymptomatic and harmless, even small and persistent changes in sodium levels can produce cognitive impairments leading to unsteady gait and falls [11, 12, 30, 31]. One study even described significant improvement in the timed up and go (TUG) test after correction

Table 3 Odds ratio (RR) and 95% confidence intervals (CI) for osteoporosis in crude and sequentially adjusted models

Model	Per 1 mEq/L sodium		Per 3 mEq/L sodium		Per 5 mEq/L sodium	
	Time-weighted mean sodium	Arithmetic mean sodium	Time-weighted mean sodium	Arithmetic mean sodium	Time-weighted mean sodium	Arithmetic mean sodium
Model 1[a]	0.98 (0.97, 0.98)	0.97 (0.96, 0.98)	0.94 (0.93, 0.95)	0.91 (0.88, 0.93)	0.85 (0.81, 0.89)	0.85 (0.81, 0.89)
Model 2[b]	0.98 (0.98, 0.99)	0.98 (0.97, 0.99)	0.95 (0.94, 0.97)	0.94 (0.92, 0.96)	0.90 (0.87, 0.93)	0.90 (0.87, 0.93)
Model 3[c]	0.98 (0.98, 0.99)	0.98 (0.97, 0.99)	0.95 (0.94, 0.97)	0.94 (0.92, 0.96)	0.90 (0.87, 0.93)	0.90 (0.87, 0.93)
Model 4[d]	0.98 (0.97, 0.98)	0.97 (0.97, 0.98)	0.93 (0.91, 0.95)	0.92 (0.91, 0.93)	0.89 (0.86, 0.92)	0.87 (0.85, 0.89)
Model 5[e]	0.98 (0.98, 0.99)	0.98 (0.98, 0.99)	0.95 (0.93, 0.96)	0.95 (0.94, 0.96)	0.91 (0.89, 0.93)	0.92 (0.90, 0.94)

[a] Unadjusted

[b] Adjusted for age, gender, race, and ethnicity

[c] Adjusted for age, gender, race, ethnicity, and comorbidities (diabetes mellitus, cardiovascular disease, peripheral vascular disease, hypertension, hypothyroidism, and prior fracture)

[d] Adjusted for age, gender, race, ethnicity, comorbidities, and labs (potassium, bicarbonate, chloride, BUN, creatinine, calcium, hemoglobin, TSH, alkaline phosphatase, HgbA1C, and albumin)

[e] Adjusted for age, gender, race, ethnicity, comorbidities, labs, and medication usage (bisphosphonates, other osteoporosis medications, anti-hypertensive medications, anti-arrhythmia medications, anti-coagulation medications, anti-seizure medications, endocrine and hormonal therapies, corticosteroids, thiazide diuretics, benzodiazepines, anti-depressant medications, and proton-pump inhibitors)

[f] Chronic hyponatremia was defined as a serum sodium level that remained < 135 mEq/L for > 1 consecutive day

of sodium in patients with mild to moderate hyponatremia [32]. Although acute trauma from falls can lead to fractures, bone frailty from decreased bone mineral density is of significant concern as it may predispose patients to both traumatic and non-traumatic fractures. Among our cohort, we also observed a higher association with falls and fractures in patients with hyponatremia (Supplemental Fig. 1). However, we feel that our data should be interpreted with some trepidation because our cross-sectional design could not establish a chronological relationship between the hyponatremia and events.

There is growing evidence to suggest that bone disease is more prevalent and thus may be a consequence of hyponatremia. One prior animal model found that rats who had hyponatremia induced for 3 months experienced a 30% reduction in BMD as measured by DXA, compared to non-hyponatremic rats [15]. Hyponatremia has been shown to increase osteoclastogenesis and bone resorbing activity [16]. This effect appears to be more specific to the low sodium rather than the low osmolar state associated with hyponatremia. Reports have also shown that prolonged hyponatremia induces the release of sodium from bone stores with resultant bone demineralization [16, 33]. An intermediary mechanism has also been suggested where arginine-vasopressin levels have been shown to rise with hyponatremia [17]. Arginine-vasopressin has differential effects on osteoclastic and osteoblastic activities. Another study showed that hyponatremia increases bone resorption by reducing ascorbic acid uptake and inducing oxidative stress and decreasing bone quality and density [7, 16]. A study of the NHANES III population found adjusted ORs of 2.87 (95% CI 1.03–7.66) for osteoporosis at the femoral neck and 2.85 (95% CI 1.41–5.81) for osteoporosis at the hip among subjects with mild hyponatremia (mean serum sodium of 133 mEq/L) [15]. The presumed mechanism for development of osteoporosis is the effect of chronic hyponatremia on bone modeling over time. Often these inferences are limited by the cross-sectional nature of epidemiological certain studies and specifically the lack of repeated sodium measurements. Our study findings using serial measurements where 89% of our study population had three or more sodium measurements results appear consistent with previous findings and also provide new insights into the potential cumulative burden of hyponatremia on bone modeling.

There are many different causes of hyponatremia and often the etiologies of hyponatremia in patients are multifactorial. Approximately 50% of chronic hyponatremia is due to the syndrome of inappropriate anti-diuretic hormone (SIADH) [15, 34]. Other causes include medications, hypothyroidism, end-stage renal disease, chronic kidney disease, hepatic cirrhosis, congestive heart failure, and endocrine deficiencies. We found that our chronic hyponatremic population had greater use of thiazide diuretics, antidepressant medications, and benzodiazepines. Ironically, thiazide diuretics have been shown to improve bone mineral density [35, 36]. While medication use may have been a contributor to hyponatremia among our study population, the increased risk for osteoporosis was sustained while controlling for these specific medication classes.

Compared to acute, symptomatic patients with hyponatremia, individuals with mild and chronic hyponatremia often go untreated because of the presumption that it is a benign state. However, it is becoming more evident that there is potential

harm with even mild hyponatremia. Correction of hyponatremia in these instances may prevent changes in BMD, ultimately reducing fracture risk and improving morbidity and mortality.

Limitations

There are several potential limitations that may affect the interpretation of our study findings. We identified our subjects by sodium values and BMD measurements but were unable to account for the causes of hyponatremia among the population. In addition, we were unable to evaluate or control for additional biomarkers and lifestyle modifications that may have affected sodium values and risk for osteoporosis. We were unable to control for some comorbidities, including undocumented comorbidities or malignancies, which are known to lead to hyponatremia. Given the retrospective, observational nature of this study, a causal relationship between serum sodium concentrations and osteoporosis cannot be established. Our study population also likely had different levels of physical activity, dietary salt intake, and tobacco abuse, which we could not measure or account for. Nevertheless, the association between chronic mild hyponatremia and osteoporosis remained significant after controlling for various potential confounders. Despite these limitations, our study was strengthened by the availability of detailed longitudinal data on comorbidities, procedures, laboratory tests, medications, utilizations, and clinical outcomes captured from the EHR and health system.

Conclusion

Among a large, ethnically diverse population with serial sodium values and BMD measurements, individuals with chronic hyponatremia were associated with an 11% higher risk for having osteoporosis. In addition, there was a dose-dependent association where a 3-mEq/L increase in TW mean sodium was associated with 7% lower risk of having osteoporosis. Our findings underscore the premise that chronic (even mild) hyponatremia may lead to adverse physiological effects and responses which deserves better understanding. More vigilant management of hyponatremia may be a preventative measure for osteoporosis.

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Compliance with ethical standards

Conflicts of interest A. Adams, B. Li, S. Bhandari, C. Rhee, K. Kalantar-Zadeh, S. Jacobsen, and J. Sim report no conflicts of interest relevant to this manuscript. H. Krasa, S. Kamat, and S. Sundar are employees of Otsuka Pharmaceutical Development & Commercialization, Inc., who has a treatment for hyponatremia.

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