Published in final edited form as:

Osteoporos Int. 2015 September ; 26(9): 2291–2298. doi:10.1007/s00198-015-3108-z.

Hyponatremia and osteoporosis: reappraisal of a novel association

F. Afshinnia¹, B. Sundaram², R. J. Ackermann³, and K. K. Wong^{3,4}

F. Afshinnia: fafshin@med.umich.edu

¹Division of Nephrology, Department of Internal Medicine, University of Michigan, 3914 Taubman Center, 1500 E. Medical Center Dr., SPC 5364, Ann Arbor, MI 48109, USA

²Division of Radiology, Thomas Jefferson University, Philadelphia, PA, USA

³Department of Nuclear Medicine/Radiology, University of Michigan, Ann Arbor, MI, USA

⁴VA Ann Arbor Healthcare System, Ann Arbor, MI, USA

Abstract

Summary—Age was a modifier of the independent association between hyponatremia and osteoporosis (OP). Risk of OP was the highest in the youngest age group as compared to older patients. A longer duration of hyponatremia revealed a similar association with OP in all anatomical sites.

Introduction—Epidemiologic studies provide conflicting results on the relationship between hyponatremia and OP. Our aim is to test the modification effect of age on the relationship between hyponatremia and OP at various anatomical sites in a large patient population.

Methods—This is a cross-sectional observation of consecutive patients with available bone densitometry, demographic, clinical, and laboratory data from 2001 to 2013 at a single center. OP was defined as a bone mineral density of ≥ 2.5 standard deviations below the mean peak bone mass of young, healthy adults. Hyponatremia was defined as serum sodium ≤ 135 mmol/L. Multiple logistic regressions were used to calculate adjusted odds ratio (OR).

Results—Overall, 24,784 patients were included. There were 4549 males (18.4 %). Hyponatremia was present in 703 patients (2.8 %), femoral neck OP in 2603 (10.5 %), total hip OP in 1885 (7.5 %), and lumbar OP in 4830 (19.5 %). Total hip OP occurred in 17.6 % ($n=124$) of patients with hyponatremia as compared to 6.6 % ($n=880$) of patients with sodium level of “140–145” mmol/L ($P<0.001$). After multivariable adjustments, hyponatremia was associated with 2.46-fold higher odds of total hip OP (95 % CI, 1.36 to 4.46) in age <55 years, 1.96-fold (1.13 to 3.41) in age 55 to 67 years, and 1.55-fold (1.13 to 2.12) in age >67 years (age-sodium category interaction P value=0.002).

Correspondence to: F. Afshinnia, fafshin@med.umich.edu.

Conflicts of interest None.

Electronic supplementary material The online version of this article (doi:10.1007/s00198-015-3108-z) contains supplementary material, which is available to authorized users.

Conclusions—Age appeared as a modifier of the independent association between hyponatremia and OP. Risk of OP was the highest in the youngest age group as compared to older patients.

Keywords

Bone density; Fracture; Hyponatremia; Osteoporosis

Introduction

Hyponatremia is one of the most common electrolyte abnormalities in ambulatory elderly patients as well as in the inpatient setting [1, 2]. It is linked to a higher rate of mortality in hospitalized patients. Chronic mild hyponatremia, previously believed to be asymptomatic, is now recognized to contribute to a flurry of neurocognitive symptoms [3, 4] and to increase the risk of fall and fractures [5–11]. Apart from its detrimental impact on neurocognition, emerging data in model systems suggest that hyponatremia may also have a direct adverse impact on integrity and metabolism of bone leading to a higher rate of osteoporosis (OP) [12, 13]. However, results from epidemiologic studies are conflicting [13–15]. While two studies have reported a higher rate of OP [13, 15], another found no difference in bone mineral density (BMD) of patients with and without hyponatremia [14]. Obviously, there is considerable heterogeneity in the design, study population, and patients' characteristics in these studies, therefore requiring further investigations to better understand how these observations in model systems would translate to clinically meaningful findings. We hypothesize that the risk of hyponatremia-associated OP is age dependent, with age acting as a modifier of the association between hyponatremia and OP. In this study, our aims were (a) to explore the association of hyponatremia with OP at different anatomical sites of the hip and lumbar spine by categories of age and (b) to explore the relationship between observed duration of hyponatremia with OP at these sites by age categories.

Materials and methods

This study is a cross-sectional observation. Institutional review board approval was obtained (HUM00075043). The study population comprises patients who have undergone bone densitometry at the outpatient units of the University of Michigan from August 2001 to October 2013. Inclusion criteria are availability of key demographic, clinical, and laboratory data including serum sodium at or prior to the date of bone densitometry. Exclusion criteria are age less than 18 years and serum creatinine greater than 2 mg/dL to minimize likelihood of including patients with renal osteodystrophy. All the consecutive eligible patients who met the selection criteria were enrolled. Data on bone densitometry were obtained from the data archive of the bone densitometry unit. Demographic variables including age, gender, and race; clinical data including anthropometric measures such as weight and height; history of comorbidities known to impact bone mineral density using ICD9 codes (Supplement Table 1); medications known to impact serum sodium or bone mineral density (Supplement Table 2); and laboratory variables including serum sodium, calcium, random plasma glucose, serum albumin, and serum creatinine were obtained from the data electronic health records of the University of Michigan Health Services and merged with the corresponding

bone densitometry data. Hyponatremia was defined as a serum sodium < 135 mmol/L. Hyponatremic interval was defined as an interval between two hyponatremic values. Observed duration of hyponatremia as a surrogate marker of the actual duration of hyponatremia was calculated by summation of hyponatremic intervals within the 2 years prior to the date of densitometry. Time-averaged serum sodium was calculated from sodium measurements in the past 2 years prior to the date of densitometry. Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula [16]. Osteoporosis was defined according to the World Health Organization (WHO) definition as a bone mineral density of < 2.5 standard deviations (SD) below the mean peak bone mass of young, healthy adults [17], and this was applied to all age groups. Densitometry studies were performed using General Electric Lunar iDXA densitometers. Intraobserver coefficients of variation at the hip and lumbar areas were 1.65 and 2.39 %, respectively.

Statistical analysis

Age categories are defined by tertiles of age. Mean and SD are used for description of normally distributed variables. Median and interquartile range (IQR) are applied for description of skewed variables. Chi-square is used to test the association of categorical variables with different subgroups of serum sodium. Analysis of variance is used to compare the mean values of continuous variables across different subgroups, using post hoc Bonferroni correction for multiple comparisons. Multiple logistic regression analysis adjusting for covariates is used to calculate odds ratio of osteoporosis across different categories of serum sodium compared with the reference category. Three series of models with increased level of adjustment have been applied and included case-mix unadjusted model (model 1); adjustments for age, sex, and race (model 2); and the fully adjusted model (model 3) which consists of model 2 plus BMI, serum albumin, glucose, calcium, medications, and comorbidities which had a significantly different distribution by categories of serum sodium. In addition to using time-averaged serum sodium, the analyses are replicated using a single value of serum sodium closest to the date of bone densitometry as well. As all the results are similar, we are presenting the findings by the time-averaged serum sodium. The study has 82 and 95 % power to detect an odds ratio of 1.4 assuming the osteoporosis rate in the hyponatremic category to be 10 and 20 %, respectively, at an alpha level of 0.05 using a two-sided test.

Results

Baseline

Overall, 24,784 patients were included in the final analysis. Mean age was 61 years (SD=14). There were 4549 males (18.4 %) and 1843 black patients (7.4 %). Data on serum sodium was obtained from 210,425 measurements within 2 years prior to the date of bone densitometry. The median number of sodium measurements per patient was 3 (IQR of 1 to 6). The median interval between the last sodium measurement and date of bone densitometry was 61 days (IQR 19 to 193 days). Mean of time-averaged serum sodium was 140.2 mmol/L (SD=2.3, Fig. 1). There were 703 patients (2.8 %) with hyponatremia based on time-averaged sodium. Table 1 shows the distribution of patients' characteristics by categories of serum sodium. Accordingly, there is a "U"-shape association between age and categories of

serum sodium with the youngest patients observed in the “136–140” range as compared to the hyponatremic group ($P<0.001$). Similarly, hyponatremic patients had lower BMI, serum calcium, and serum albumin but a higher mean glucose as compared to the “141–145” category ($P<0.001$). There was also an increasing linear trend in female gender, African-American ethnicity, and use of vitamin D supplement by increasing category of serum sodium ($P<0.01$). On the other hand, there appeared to be a decreasing trend in the use of calcium supplements, bisphosphonates, steroids, antiepileptics, thiazides, and loop diuretics as well as medical conditions including history of bariatric surgery, solid organ transplantation, and liver cirrhosis by increasing category of serum sodium ($P<0.01$).

Rate of osteoporosis at different anatomical sites

There were 2603 patients (10.5 %) with femoral neck OP, 1827 (7.4 %) with total hip OP, and 4830 (19.5 %) with lumbar OP. Figure 2 represents the percentage of patients with OP at different anatomical sites by categories of serum sodium. Accordingly, OP was most prevalent in patients with serum sodium of 135 mmol/L in all anatomical sites as compared to other categories of serum sodium ($P<0.001$). OP declined from 28.4 % (200 patients) to 19.9 % (2643 patients) at the lumbar spine site, from 19.5 % (137 patients) to 10.0 % (1329 patients) at the femoral neck, and from 17.6 % (124 patients) to 6.6 % (880 patients) at the total hip site from the hyponatremic subgroup compared to the “141–145” subgroup ($P<0.001$).

Figure 3 illustrates the rate of OP within and between each category of serum sodium by different age groups at different anatomical sites. Accordingly, within each category of serum sodium, there is a significant increasing linear trend in the rate of OP by age in all anatomical sites ($P=0.001$), except in the hyponatremic group at the lumbar spine where the increasing trend did not reach statistical significance. Between each category of serum sodium, there is a significant decreasing linear trend in the rate of OP at the hip and femoral neck within different age groups ($P=0.001$), except at the lumbar spine where the decreasing trend did not reach statistical significance. Strikingly, the rate of OP in young hyponatremic patients (age <55 years) was comparable and not significantly different with the rate of OP in normonatremic patients aged over 67 years.

Risk of osteoporosis by categories of time-averaged sodium

Figure 4 and Supplement Table 3 demonstrate the odds ratio (OR) of OP associated with hyponatremia in unadjusted (models 1) to fully adjusted models (models 3), by categories of age. Accordingly, the OR of OP associated with hyponatremia as compared to the reference category (“141–145” subgroup) was the highest at the youngest age group (<55 years) with a trend toward null in the older age groups in all anatomical sites in unadjusted models (model 1, age-sodium interaction P value <0.001). Similar patterns of higher OR at the youngest age group with attenuation of OR in the older age groups were also noted in model 2 as well as model 3, the fully adjusted model (age-sodium interaction P values = 0.015).

Risk of osteoporosis by observed duration of hyponatremia

A relevant argument is that an acute change in serum sodium should not be expected to impact bone mineral density. Therefore, in a separate approach, we are testing the

association of observed duration of hyponatremia with osteoporosis. To do so, we have additionally identified the patients who have had at least one hyponatremic interval in the past 2 years prior to the date of densitometry, irrespective of their mean time-averaged serum sodium. As can be expected, the number of such patients exceeded the number of patients whose mean time-averaged serum sodium was ≥ 135 mmol/L. The reason is that a patient with normal-appearing mean serum sodium might have had a few episodes of hyponatremia, but because of having had more measures within normal limit, the mean value has fallen within the normal limit. As such, we identified 1930 patients with at least one hyponatremic interval prior to the date of densitometry. We then classified these patients with at least one hyponatremic interval into four subgroups by the quartiles of the observed duration of hyponatremia (25th, 50th, and 75th percentiles at 3, 19, and 105 days, respectively). Accordingly, there were 504 patients in the highest quartile, 503 in the third, 488 in the second, and the rest of all other patients in the first quartile. Patients with no hyponatremic interval were aggregated into the first quartile. The median intervals between the date of the first sodium measurement to the date of densitometry were not clinically significant by quartiles of hyponatremic intervals with the corresponding values of 16.9, 15.4, 15.8, and 16.3 months from the first to the fourth quartiles, respectively, suggesting an equally distributed observation period in all four groups. Figure 5 and Supplement Table 4 show that as compared to the first category, the longest duration of observed hyponatremia was associated with the highest risk of OP in the youngest age group in the lumbar anatomical site (age <55 , age-hyponatremia interval interaction P value <0.001). Similarly, OR of OP trended toward null at the femoral neck and total hip in the older age groups (age-hyponatremia interval interaction P value = 0.029).

Discussion

In this study, we found a significantly higher rate of OP in all anatomical sites studied in patients with hyponatremia. Within each category of sodium, the rate of OP increased by age. The odds of hyponatremia-associated OP was the highest in patients aged less than 55 years with attenuation toward null in the older age groups. Full adjustment by relevant covariates did not change the associations. In a novel observation, we showed that not only the presence of hyponatremia but also the observed duration of hyponatremia was associated with OP more so in the younger age group as compared to the elderly patients, so that the highest odds of OP belonged to the longest observed duration of hyponatremia in the youngest age group declining toward no increased risk of OP in the older groups. These findings are consistent with our hypotheses that the association between OP and hyponatremia is age dependent and that age acts as a modifier of this association.

Several reports have shown increased rate of fractures in association with hyponatremia [14, 15, 18–20]. A detrimental effect of hyponatremia on the central nervous system (CNS) with subsequent unsteadiness and attention deficit leading to increased rate of falls may partially explain the increase in fractures [3, 21–23]. However, more recent studies suggest that hyponatremia itself can have a direct negative impact on metabolism and integrity of bone. In a study of a rat model of syndrome of inappropriate antidiuretic hormone (SIADH), Verbalis et al. reported a reduction of BMD by 30 % after 3 months of induced hyponatremia, along with a significant reduction in both trabecular and cortical bone and an

increase in osteoclast numbers on histomorphometric analysis when compared with controls [13]. To provide clinical context to their observations, they examined the data from the third National Health and Nutrition Examination Survey (NHANES)-III and reported an OR of 2.85 for the association of hyponatremia and hip OP after multivariable adjustments [13]. In a study of 1408 consecutive females, Kinsella et al. showed that participants with a serum sodium level of <135 mmol/L had a lower bone density and a significantly higher rate of OP than normonatremic patients (8.7 versus 3.2 %, $P<0.001$) [15]. Contrary to these findings, the Rotterdam study, an observation of 5208 elderly participants, found an association between hyponatremia and nonvertebral fractures, though there was no statistically significant difference in femoral neck and lumbar spine BMD of the patients with and without hyponatremia [14]. We suggest that our study can be considered as reconciling the seemingly contradictory results of the Rotterdam study with other studies. The observed OR at different anatomical sites in the younger subgroup in our study is comparable and aligned with the analysis of the NHANES dataset, while the OR observed in the older subgroup is attenuated toward null comparable with the findings of the Rotterdam study. The lack of significant difference in the Rotterdam study is likely explained by the dominance of elderly patients in that cohort, while the significant associations observed in the NHANES dataset are likely driven by relatively younger individuals in that cohort as compared to the Rotterdam study. We postulate that the attenuation of the risk in elderly patients is likely a reflection of aging being a competing risk factor offsetting the risk of hyponatremia by increasing the numbers of patients with OP in the normonatremic group at old age comparable to the OP rate of young hyponatremic patients (as evident in Fig. 3), besides the possibilities for the presence of other competing comorbidities with a similar net effect.

Up to one third of body sodium is stored in bone. It is hypothesized that in hyponatremia, increased bone resorption occurs in an attempt to preserve the homeostasis of sodium at the expense of bone structural integrity [13]. Increased osteoclast activity and number in parallel with decreased serum level of osteocalcin (a marker of bone formation) observed in model systems [12, 13], reduced intracellular calcium [12], alteration in metabolism of vitamin D and steroid-containing hormones, and alteration in oxidative stress [24–26] are viewed as possible mechanistic links between hyponatremia and OP. Increased osteoclastic activity may be mediated by increased expression level of vasopressin receptors AVPr1alpha and AVPr2alpha triggering Erk (kinase) signaling pathway in favor of suppressing bone formation and stimulating bone resorption [27]. Another mechanism for activation of osteoclasts could be via voltage-gated sodium channels which are highly expressed in bone and are sensitive to changes in extracellular tonicity and, therefore, may mediate the activation of osteoclasts in chronic hyponatremia [13, 18, 28–30].

This study has several strengths. To our knowledge, this is the largest study of the association of hyponatremia with OP. This has allowed us to implement testing of several multivariable models in subgroups yet with a reasonable power. There are numerous established risk factors which may potentially impact the rate of osteoporosis including age, female sex, ethnicity, inactivity, medications, and certain comorbidities [31–33]. In our study, we adjusted for such covariates in multivariable models as much as they were available to us. The large sample size has allowed not only applying the multivariable adjustments but also providing the opportunity to test the modification effect of age. In this

study, we used both the last measured serum sodium as a single value and time-averaged sodium in the analysis. As the results were not significantly different, we chose to report the results using time-averaged serum sodium. A novel aspect of this study is the availability of multiple measurements of serum sodium which has provided a unique opportunity to test for the first time the impact of observed duration of hyponatremia on OP, a dose-response relationship, in addition to just the presence of hyponatremia in young patients. We believe that the surrogate marker of observed duration of hyponatremia is a valid surrogate of the actual duration of hyponatremia as the between-test intervals were similar by quartiles of hyponatremic intervals. There are also participants from both genders. This study also has limitations. Although by design this is an observational study that does not allow inferring a causal relationship, the causality has already been established in model systems [13]; therefore, these findings may have an important clinical impact. Although we cannot rule out the possibility of residual confounders in the analyses, the similarity of our results with and without adjustments with what is observed in model systems suggests that such residual confounders might have a negligible impact on the overall results. Although this study is highly powered, the results may not be extrapolated to other patient populations with different characteristics. As sicker patients are more likely to have more frequent lab measurements, there is a potential for ascertainment bias. We believe that the potential for ascertainment bias is likely offset by the large number of participants with normonatremia increasing the likelihood of detecting extra cases of OP that would have been detected by increased health-care utilization otherwise.

Clinical implications

These findings have very important clinical and public health implications. The rate of OP in hyponatremia at a young age comparable to what was seen in the elderly individuals without hyponatremia suggests that chronic hyponatremia may translate to early aging of the bone in young individuals. This finding would necessitate further research to assess the impact of correction of hyponatremia on important outcome measures of OP and fractures. The role of routine prescription of densitometry in patients with hyponatremia also requires assessment of cost and benefit in further research. Verification of mechanistic pathways underpinning the association of hyponatremia and OP will be valuable and may disclose new targets for antiresorptive treatments.

Conclusion

Age was a modifier of the independent association between hyponatremia and OP. The risk of OP-associated hyponatremia was the highest in the youngest age group as compared to older patients. A longer duration of hyponatremia revealed a similar association with OP in all anatomical sites.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

F.A. received support from 5T32DK7378-34 NIH grant. The authors thank Lalitha Natarajan at the Medical Center Information Technology of the University of Michigan for data transfer.

References

- Adroge HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000; 342(21):1581–1589.10.1056/NEJM200005253422107 [PubMed: 10824078]
- Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*. 2006; 119(7 Suppl 1):S30–35.10.1016/j.amjmed.2006.05.005 [PubMed: 16843082]
- Gunathilake R, Oldmeadow C, McEvoy M, Kelly B, Inder K, Schofield P, Attia J. Mild hyponatremia is associated with impaired cognition and falls in community-dwelling older persons. *J Am Geriatr Soc*. 2013; 61(10):1838–1839.10.1111/jgs.12468 [PubMed: 24117308]
- Widdess-Walsh P, Sabharwal V, Demirjian S, DeGeorgia M. Neurologic effects of hyponatremia and its treatment. *Cleve Clin J Med*. 2007; 74(5):377–383. [PubMed: 17506243]
- Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med*. 2010; 170(3):294–302.10.1001/archinternmed.2009.513 [PubMed: 20142578]
- Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med*. 2009; 122(9):857–865.10.1016/j.amjmed.2009.01.027 [PubMed: 19699382]
- Zilberberg MD, Exuzides A, Spalding J, Foreman A, Jones AG, Colby C, Shorr AF. Epidemiology, clinical and economic outcomes of admission hyponatremia among hospitalized patients. *Curr Med Res Opin*. 2008; 24(6):1601–1608.10.1185/03007990802081675 [PubMed: 18426691]
- Gill G, Huda B, Boyd A, Skagen K, Wile D, Watson I, van Heyningen C. Characteristics and mortality of severe hyponatraemia—a hospital-based study. *Clin Endocrinol*. 2006; 65(2):246–249.10.1111/j.1365-2265.2006.02583.x
- Clayton JA, Le Jeune IR, Hall IP. Severe hyponatraemia in medical in-patients: aetiology, assessment and outcome. *QJM: Monthly J Assoc Phys*. 2006; 99(8):505–511.10.1093/qjmed/hcl071
- Tierney WM, Martin DK, Greenlee MC, Zerby RL, McDonald CJ. The prognosis of hyponatremia at hospital admission. *J Gen Intern Med*. 1986; 1(6):380–385. [PubMed: 3794837]
- Anderson RJ, Chung HM, Kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. *Ann Intern Med*. 1985; 102(2):164–168. [PubMed: 3966753]
- Barsony J, Sugimura Y, Verbalis JG. Osteoclast response to low extracellular sodium and the mechanism of hyponatremia-induced bone loss. *J Biol Chem*. 2011; 286(12):10864–10875.10.1074/jbc.M110.155002 [PubMed: 21135109]
- Verbalis JG, Barsony J, Sugimura Y, Tian Y, Adams DJ, Carter EA, Resnick HE. Hyponatremia-induced osteoporosis. *J Bone Mineral Res: Off J Am Soc Bone Mineral Res*. 2010; 25(3):554–563.10.1359/jbmr.090827
- Hoorn EJ, Rivadeneira F, van Meurs JB, Zieme G, Stricker BH, Hofman A, Pols HA, Zietse R, Uitterlinden AG, Zillikens MC. Mild hyponatremia as a risk factor for fractures: the Rotterdam study. *J Bone Mineral Res: Off J Am Soc Bone Mineral Res*. 2011; 26(8):1822–1828.10.1002/jbmr.380
- Kinsella S, Moran S, Sullivan MO, Molloy MG, Eustace JA. Hyponatremia independent of osteoporosis is associated with fracture occurrence. *Clin J Am Soc Nephrol: CJASN*. 2010; 5(2):275–280.10.2215/CJN.06120809 [PubMed: 20056759]
- Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd EPI. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150(9):604–612. [PubMed: 19414839]
- Report of a WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organization technical report series. 1994; 843:1–129. [PubMed: 7941614]

18. Ayus JC, Negri AL, Kalantar-Zadeh K, Moritz ML. Is chronic hyponatremia a novel risk factor for hip fracture in the elderly? *Nephrol, Dialysis, Transplant: Off Publication of the European Dialysis and Transplant Assoc - Eur Renal Assoc.* 2012; 27(10):3725–3731.10.1093/ndt/gfs412
19. Sandhu HS, Gilles E, DeVita MV, Panagopoulos G, Michelis MF. Hyponatremia associated with large-bone fracture in elderly patients. *Int Urol Nephrol.* 2009; 41(3):733–737.10.1007/s11255-009-9585-2 [PubMed: 19472069]
20. Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G. Mild hyponatremia and risk of fracture in the ambulatory elderly. *QJM: Monthly J Assoc Phys.* 2008; 101(7):583–588.10.1093/qjmed/hcn061
21. Zaino CJ, Maheshwari AV, Goldfarb DS. Impact of mild chronic hyponatremia on falls, fractures, osteoporosis, and death. *Am J Orthop.* 2013; 42(11):522–527. [PubMed: 24340324]
22. Bun S, Serby MJ, Friedmann P. Psychotropic medication use, hyponatremia, and falls in an inpatient population: a retrospective study. *J Clin Psychopharmacol.* 2011; 31(3):395–397.10.1097/JCP.0b013e318218f446 [PubMed: 21532373]
23. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med.* 2006; 119(1):71. e71–78.10.1016/j.amjmed.2005.09.026 [PubMed: 16431193]
24. Yilmaz N, Eren E. Homocysteine oxidative stress and relation to bone mineral density in post-menopausal osteoporosis. *Aging Clin Exp Res.* 2009; 21(4–5):353–357. [PubMed: 19959926]
25. Ostman B, Michaelsson K, Helmersson J, Byberg L, Gedeberg R, Melhus H, Basu S. Oxidative stress and bone mineral density in elderly men: antioxidant activity of alpha-tocopherol. *Free Radic Biol Med.* 2009; 47(5):668–673.10.1016/j.freeradbiomed.2009.05.031 [PubMed: 19500667]
26. Basu S, Michaelsson K, Olofsson H, Johansson S, Melhus H. Association between oxidative stress and bone mineral density. *Biochem Biophys Res Commun.* 2001; 288(1):275–279.10.1006/bbrc.2001.5747 [PubMed: 11594785]
27. Tamma R, Sun L, Cuscito C, Lu P, Corcelli M, Li J, Colaianni G, Moonga SS, Di Benedetto A, Grano M, Colucci S, Yuen T, New MI, Zallone A, Zaidi M. Regulation of bone remodeling by vasopressin explains the bone loss in hyponatremia. *Proc Natl Acad Sci U S A.* 2013; 110(46):18644–18649.10.1073/pnas.1318257110 [PubMed: 24167258]
28. Hoorn EJ, Lianis G, Zietse R, Zillikens MC. Hyponatremia and bone: an emerging relationship. *Nat Rev Endocrinol.* 2012; 8(1):33–39.10.1038/nrendo.2011.173 [PubMed: 22024973]
29. Tseng AS, Beane WS, Lemire JM, Masi A, Levin M. Induction of vertebrate regeneration by a transient sodium current. *J Neurosci Off J Soc Neurosci.* 2010; 30(39):13192–13200.10.1523/JNEUROSCI.3315-10.2010
30. Komarova SV, Dixon SJ, Sims SM. Osteoclast ion channels: potential targets for antiresorptive drugs. *Curr Pharm Des.* 2001; 7(8):637–654. [PubMed: 11375773]
31. Prevention and management of osteoporosis: report of a WHO scientific group. WHO Scientific Group on the Prevention and Management of Osteoporosis. *World Health Organ Tech Rep Ser.* 2003
32. Arampatzis S, Gaetcke LM, Funk GC, Schwarz C, Mohaupt M, Zimmermann H, Exadaktylos AK, Lindner G. Diuretic-induced hyponatremia and osteoporotic fractures in patients admitted to the emergency department. *Maturitas.* 2013; 75(1):81–86.10.1016/j.maturitas.2013.02.007 [PubMed: 23489552]
33. Cowen LE, Hodak SP, Verbalis JG. Age-associated abnormalities of water homeostasis. *Endocrinol Metab Clin N Am.* 2013; 42(2):349–370.10.1016/j.ecl.2013.02.005

Fig. 1.
Distribution of time-averaged serum sodium in the study population

Fig. 2. Percentage with osteoporosis by categories of time-averaged serum sodium at different anatomical sites. **P*value <0.001 compared with the category of “141–145.” Bars are percentage plus standard error

Fig. 3.

Comparison of the rate of OP within and between each category of serum sodium by different age groups at different anatomical sites. Linear trend of osteoporosis within each category of sodium by age: P values 0.001 in all anatomical sites and all sodium categories except for $\text{Na} \leq 135$ at the lumbar spine where increased trend by age did not reach statistical significance. Linear trend of osteoporosis between different categories of sodium in different age groups at the femoral neck and total hip: P values 0.001. Rate of osteoporosis at “age ≤ 55 years and $\text{Na} \leq 135$ mmol/L” compared with the rate of osteoporosis at “age >67 at other categories of sodium” in all anatomical sites is not different ($P = 0.2$). Bars are percentages plus standard error

Fig. 4.

Odds of osteoporosis by categories of time-averaged serum sodium and age categories at different anatomical sites in unadjusted to fully adjusted models. Model 1: unadjusted case-mix (age-sodium interaction P value <0.001); model 2: adjusted for age, sex, and race (age-sodium interaction P value <0.001); model 3: model 2 plus further adjusting with BMI, serum albumin, glucose, calcium, medications, and comorbidities (age-sodium interaction P value 0.015). Odds ratio (OR) $\pm 95\%$ confidence interval is presented

Fig. 5. Odds of osteoporosis by categories of observed duration of hyponatremia and age at different anatomical sites in fully adjusted models

Table 1

Characteristics of the study population by subgroups of time-averaged serum sodium

Variables	135	136–140	141–145	>145
<i>N</i>	703	10,626	13,295	160
Age (years)	67±15	60±15 ***	62±13 ***	64±11
Female gender (%) [‡]	75.5 %	78.7 %	84.2 %	88.1 %
Height (m)	1.6±0.1	1.7±0.1	1.6±0.1	1.6±0.1
Weight (kg)	69±17	75±19 ***	75±18 ***	74±17
BMI (kg/m ²)	25.7±5.4	27.5±6.4 ***	27.5±6.2 ***	27.6±6.3 **
Ethnicity [‡]				
Caucasian (%)	88.8 %	85.2 %	82.8 %	78.1 %
Asian (%)	5.0 %	4.7 %	6.5 %	5.6 %
African-American (%)	4.1 %	7.0 %	7.9 %	11.9 %
Others (%)	2.1 %	3.1 %	2.8 %	4.4 %
Medications				
Calcium (%) [‡]	4.0 %	3.6 %	3.1 %	1.3 %
Vitamin D (%) [‡]	1.1 %	1.3 %	1.7 %	1.3 %
Bisphosphonates (%) [‡]	14.8 %	11.1 %	12.1 %	8.1 %
Steroids (%) [‡]	24.9 %	28.1 %	25.0 %	14.4 %
Thiazides (%) [‡]	22.3 %	15.5 %	15.6 %	11.9 %
Loop diuretics (%) [‡]	8.4 %	6.1 %	4.8 %	3.8 %
Antiepileptics [‡]	14.2 %	12.2 %	11.3 %	4.4 %
Medical history				
Bariatric surgery (%) [‡]	6.3 %	7.2 %	6.1 %	4.4 %
Solid organ transplant (%) [‡]	5.3 %	5.1 %	4.0 %	2.5 %
Liver cirrhosis (%) [‡]	5.3 %	5.4 %	4.5 %	2.5 %
Plasma glucose (mmol/L)	6.16±3.05	5.88±2.11 ***	5.55±1.39 ***	5.44±1.00 ***
Calcium (mmol/L)	2.35±0.15	2.38±0.13 ***	2.38±0.13 ***	2.38±0.13
Creatinine (μmol/L)	79.6±26.5	79.6±17.7	79.6±17.7	79.6±17.7
Albumin (g/L)	42±5	42±4 ***	43±3 ***	42±3
GFR (mL/min/1.73 m ²)	79±21	81±22	78±19	76±19
Lumbar L1–L4 BMD (g/cm ²)	1.12±0.21	1.15±0.20 ***	1.14±0.19	1.12±0.20
Femoral neck BMD (g/cm ²)	0.83±0.14	0.89±0.15 ***	0.87±0.14 ***	0.87±0.12 ***
Trochanteric BMD (g/cm ²)	0.70±0.15	0.75±0.15 ***	0.74±0.14 ***	0.74±0.13 ***
Total hip BMD (g/cm ²)	0.87±0.16	0.93±0.16 ***	0.92±0.15 ***	0.92±0.13 ***

Values are mean±SD, percentage, or median [interquartile range]

BMD bone mineral density**
P 0.01 compared to “ 135”;

 P 0.001 compared to “ 135”;

$\dagger P$ 0.05 linear trend;

$\dagger P$ 0.001 linear trend

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript