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Journal
Nephrology Dialysis Transplantation, 31(10)

ISSN
0931-0509

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Publication Date
2016-10-01

DOI
10.1093/ndt/gfw029

Nephrol Dial Transplant (2016) 31: 1662–1669
doi: 10.1093/ndt/gfw029
Advance Access publication 23 March 2016

ORIGINAL ARTICLE

Mild prolonged chronic hyponatremia and risk of hip fracture in the elderly

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ABSTRACT

Background. Hip fractures are among the most serious bone fractures in the elderly, producing significant morbidity and mortality. Several observational studies have found that mild hyponatremia can adversely affect bone, with fractures occurring as a potential complication. We examined if there is an independent association between prolonged chronic hyponatremia (>90 days duration) and risk of hip fracture in the elderly.

Methods. We performed a retrospective cohort study in adults >60 years of age from a prepaid health maintenance organization who had two or more measurements of plasma sodium between 2005 and 2012. The incidence of hip fractures was assessed in a very restrictive population: subjects with prolonged chronic hyponatremia, defined as plasma sodium values <135 mmol/L, lasting >90 days. Multivariable Cox regression was performed to determine the hazard ratio (HR) for hip fracture risk associated with prolonged chronic hyponatremia after adjustment for the propensity to have hyponatremia, fracture risk factors and relevant baseline characteristics.

Results. Among 31 527 eligible patients, only 228 (0.9%) had prolonged chronic hyponatremia. Mean plasma sodium was 132 ± 5 mmol/L in hyponatremic patients and 139 ± 3 mmol/L in normonatremic patients ($P < 0.001$). The absolute risk for hip fracture was 7/282 in patients with prolonged chronic hyponatremia and 411/313 299 in normonatremic patients. Hyponatremic patients had a substantially elevated rate of hip fracture [adjusted HR 4.52 (95% CI 2.14–9.6)], which was even higher in those with moderate hyponatremia (<130 mmol/L) [adjusted HR 7.61 (95% CI 2.8–20.5)].

Conclusion. Mild prolonged chronic hyponatremia is independently associated with hip fracture risk in the elderly population, although the absolute risk is low. However, proof that

correcting hyponatremia will result in a reduction of hip fractures is lacking.

Keywords: bone, falls, hip fracture, hyponatremia, osteoporosis

INTRODUCTION

Hyponatremia, typically defined as a serum sodium level <135 mmol/L, is a clinical feature in 15–20% of emergency admissions to hospital [1]. In a population-based, cross-sectional study of 14 697 adults ≥18 years of age who participated in the nationally representative National Health and Nutrition Examination Survey for 1999–2000, the prevalence of hyponatremia in the US population in a weighted analysis was 1.72%. The prevalence of hyponatremia was significantly higher in women (2.09%) and increased with age [2]. This electrolyte disorder occurs frequently in the elderly, affecting ∼10% of elderly individuals living at home and 20% of those living in nursing homes [3]. The most serious complication of hyponatremia is hyponatremic encephalopathy, which is associated with significant morbidity and mortality [4–7]. In addition to the neurologic manifestations of hyponatremic encephalopathy, it can be associated with respiratory failure and noncardiogenic pulmonary edema [8, 9].

Novel associated features of hyponatremia are bone abnormalities [10]. In 1999, our group noted that orthopedic injury was a presenting manifestation of chronic symptomatic severe hyponatremia [11]. It has subsequently been demonstrated that mild and asymptomatic hyponatremia is associated with bone abnormalities, with numerous studies been demonstrating an increased prevalence of hyponatremia in patients admitted for fractures [10, 12–19]. Hip fractures are among the most serious types of fracture in the elderly and are associated with high mortality (14–36%) during the first year postfracture [20]. Furthermore, death from any cause in the first 3 months after a hip fracture is 5.75-fold higher in women and 8-fold higher in men compared with age-matched controls [21]. Postfracture morbidity is also significant, with many patients experiencing a marked decline in functional capabilities and the need for long-term care.

There are two proposed mechanisms by which hyponatremia contributes to bone fractures: (i) by causing subtle neurologic impairment, with gait abnormalities and falls and (ii) by directly contributing to osteoporosis and increased bone fragility [22]. Animal studies have demonstrated that prolonged chronic hyponatremia of 3-months duration leads to abnormal bone histomorphology and reduced bone mineral density (BMD) [16]. No human studies have evaluated whether the duration of hyponatremia is a contributing factor to bone abnormalities. Our hypothesis was that prolonged hyponatremia of >90 days duration, similar to what has been reported in animal studies [16, 22], would be a significant risk factor for hip fractures in the elderly. We therefore examined whether prolonged hyponatremia of >90 days duration was independently associated with hip fractures in a diverse elderly population.

MATERIALS AND METHODS

Setting and period

This study was performed among patients treated within the Italian Hospital Medical Care Program (IHMCP) from 1 January 2005 to 1 December 2012. The Italian Hospital of Buenos Aires (IHBA) is a general tertiary-level hospital offering comprehensive medical services to a population of 155 000 beneficiaries of the IHMCP, a prepaid health maintenance organization (HMO) of the city of Buenos Aires in Argentina. All medical care interventions for the beneficiaries are registered centrally in a computerized data repository, with only one electronic health record (EHR) per person.

The study was approved by the hospital's institutional review board and was carried out in compliance with the principles outlined in the Declaration of Helsinki. A waiver of informed consent was obtained due to the retrospective nature of the study.

Study design and sample

We conducted a retrospective cohort study among all IHMCP members >60 years of age who had a plasma sodium level identified in laboratory databases during the study period. For the primary analysis we compared patients with prolonged chronic hyponatremia, defined as two or more consecutive plasma sodium values <135 mmol/L for >90 days, to normonatremic patients, defined as two or more serum sodium values for >90 days who never had a sodium value <135 mmol. Patients with only one sodium value <135 mmol/L or fluctuations in their serum sodium were excluded from the primary analysis but were included in a secondary analysis to assess the effect of one low serum sodium (Figure 1). Normonatremic patients and patients with prolonged hyponatremia were assigned a median sodium value that was obtained from all its determinations. Plasma sodium was measured using the ion-selective electrode method (normal range 135–145 mmol/L).

Follow-up and identification of hip fracture

Follow-up began when the patient met the inclusion criteria. Patients were followed up to 31 December 2012 or until the occurrence of hip fracture, death or disenrollment from IHMCP, whichever occurred first. A traumatic hip fracture was assessed using relevant Systematized Nomenclature of Medicine—Clinical Terms (SNOMED-CT) codes from the emergency department diagnosis or hospital primary discharge diagnosis found in the integrated IHMCP electronic health records. A trained physician evaluated patient medical records for all potential hip fractures to confirm the presence of a hip fracture and to detect and exclude pathologic hip fractures, such as bone metastasis or hip fracture due to polytrauma.

Covariates

All patient comorbidities were identified using data from the EHR. The EHR is a unique information system for each patient that integrates clinical diagnoses and procedures, clinical measurements, laboratory results, medications and imaging results,

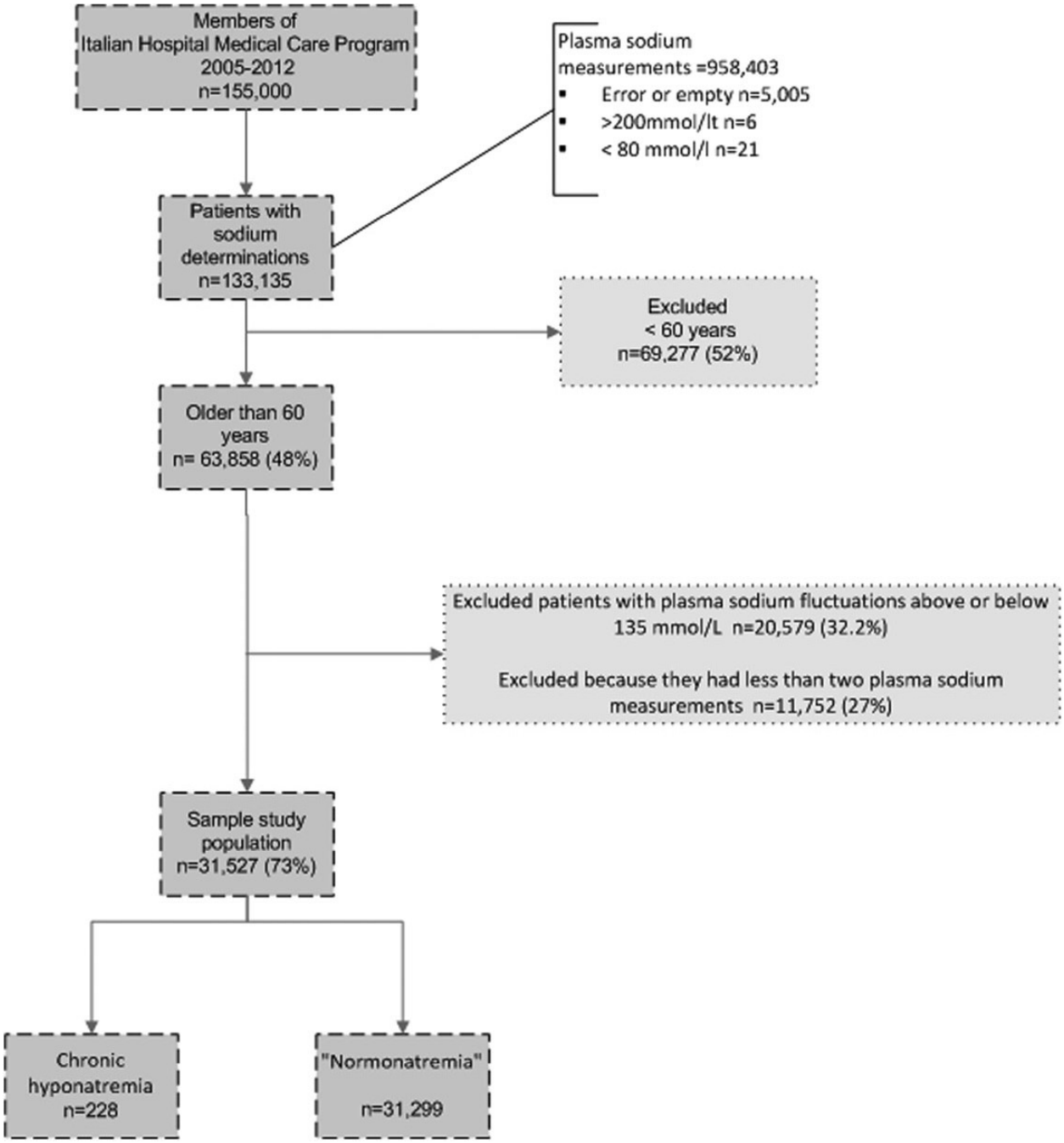

FIGURE 1: Cohort assembly of elderly subjects with and without chronic hyponatremia between 2005 and 2012.

stores these in a common data repository and encoded by terminology referenced to SNOMED-CT. This system is able to generate mirrored databases of deidentified information to ensure privacy and confidentiality of data and make possible the secondary analysis of information. The accuracy of each diagnosis is improved through various processes, such as the integration of problem lists in a single repository that promotes communication and allows for continuity of care as well as the sharing of information between records and preventing loss and duplication of data.

Covariates associated with an increased risk of hyponatremia were assessed using specific SNOMED-CT codes in the EHR, including age, gender, congestive heart failure, chronic kidney disease (defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease Study equation), liver failure, chronic use of antidepressant medications (selective serotonin reuptake inhibitors, tricyclic antidepressants), anticonvulsants and thiazide diuretics. The presence of diabetes mellitus was also assessed as a risk factor for hip fracture.

Components of the Fracture Risk Assessment Tool (FRAX) were assessed. The FRAX was developed by the World Health Organization [23, 24] in order to calculate a predicted probability of fracture based on the history of

previous fractures, smoking, alcohol use, rheumatoid arthritis, long-term corticosteroid use and BMD at the femoral, neck based on data from the EHR. A family history of hip fracture was not included in the assessment, as it was not possible to accurately assess this from the EHR. All other FRAX components using SNOMED-CT codes from the EHR we assessed. BMD at the femoral neck were assessed when available in order to improve the accuracy of assessing the presence of osteoporosis.

The Anatomical Therapeutic Chemical (ATC) Classification System was used to identify patients with chronic use of anticonvulsants, antidepressants, diuretics and corticosteroids during the 90-day period before the date of the first plasma sodium measurement during the study period. All prescriptions from the pharmacy database were assessed. This database includes every prescribed and dispensed medication in the IHMCP. Long-term corticosteroid use was defined as more than three separate purchases of corticosteroids during a period of >90 days. The patient's daily corticosteroid dose could not be evaluated through the pharmacy database.

Statistical analysis

All statistical analyses were performed with SPSS 19.0 software and a two-sided P-value <0.05 was considered significant. Continuous variables were expressed as means and standard deviations (SDs) or medians and interquartile ranges (IQRs), and results were compared between groups using the *t*-test or Mann–Whitney *U*-test if there were nonnormal distributions. Categorical variables were expressed as frequencies and proportions and were compared using χ^2 or Fisher exact tests, as appropriate.

The association between prolonged chronic hyponatremia and hip fracture was assessed using several approaches. Crude unadjusted incidence rates (IRs) (per 100 000 person-years) of hip fracture with associated 95% CIs were calculated for patients with and without prolonged hyponatremia.

An analysis of time to the event between patients with and without prolonged hyponatremia was calculated using Kaplan–Meyer survival curves. The relationship between prolonged hyponatremia and hip fracture occurrence was assessed using the univariate Cox–Mantel test. The crude HR with 95% CI for developing a hip fracture was calculated in patients with and without prolonged hyponatremia.

In order to reduce the effect of possible selection bias, a propensity score [25] for hyponatremia was constructed using logistic regression that included the following variables: age; gender; history of congestive heart failure, chronic kidney disease or liver failure; and use of antidepressants, anticonvulsants or thiazide diuretics. The c-statistic of the propensity score model was 0.73.

A multivariable Cox proportional hazard regression was then calculated to evaluate the independent association between prolonged hyponatremia and the risk for hip fracture after adjustment for the hyponatremia propensity score as a continuous variable and also for each available clinical risk factor included in the FRAX tool (smoking, alcohol use, rheumatoid arthritis, corticosteroid use and osteoporosis). There was no evidence of a violation of the proportional hazard assumption assessed through visual inspection and graphing the log [−log (survival)] versus log of survival time. In order to maintain parsimony of the final model, it was assumed that 10 hip fracture events per covariate would be required.

To further evaluate the robustness of the estimates, models were performed that adjusted for age, gender, diabetes, comorbidities and medications included in the propensity score model and individual risk factors included in the FRAX tool, given that these variables may provide additional prognostic information and improve control of confounding beyond their inclusion in integrated risk scores. Additional sensitivity analyses were performed to examine the association of hyponatremia severity. The plasma sodium concentration was evaluated as a continuous variable; given the nonnormal distribution of plasma sodium, the median plasma sodium levels were used for each patient in this analysis.

A series of sensitivity analyses were performed to evaluate if the severity or frequency of hyponatremia had an impact on fracture occurrence. The median serum sodium concentration, the severity of hyponatremia (<130 mmol/L or 130–135 mmol/L) and the sodium concentration as a continuous variable were assessed in patients with chronic hyponatremia and a sensitivity analysis was performed. A separate sensitivity analysis, looking at all patients >60 years of age with only one low serum sodium (Figure 1), was calculated to assess the impact of hyponatremia of a short duration on hip fracture occurrence.

RESULTS

Baseline characteristics

Among 31 527 eligible adults identified during the study period, 228 (0.9%) met the criteria for prolonged chronic hyponatremia (Figure 1). The mean plasma sodium level was 132 ± 5 mmol/L in the prolonged hyponatremia group and 139 ± 3 mmol/L in the normonatremic group (P < 0.001) (Table 1). The median number of plasma sodium measurements was 3 (IQR 1) for the hyponatremic group and 2 (IQR 4) for the normonatremic group. The median follow-up time for the hyponatremic group was 510 days (range 93–2820 days) and for the normonatremic group was 1421 days (range 90–2888 days) (Figure 2).

In Table 1 we evaluated multiple baseline factors, including those known to influence the development of hyponatremia and hip fracture occurrence. Patients in the hyponatremic group were on average 8 years older and had a lower BMI. The only identified increased risk factor for hyponatremia in the hyponatremic group was heart failure (Table 1). Patients in the hyponatremic group had a higher incidence of previous fractures and alcohol use, both known to increase fracture occurrence.

Crude rates of hip fracture by hyponatremia status

All hip fractures were caused by mechanical falls. The absolute number of hip fractures in patients with prolonged chronic hyponatremia was 7 (1 in males, 6 in females) and 411 in those without hyponatremia (55 in men and 356 in females) (Table 1). The crude incidence rate of hip fracture was higher in the hyponatremic group [781.8 per 100 000 person-years (95% CI

Table 1. Baseline characteristics in hyponatremic and normonatremic patients

	Chronic hyponatremia ($n = 228$)	Normonatremia ($n = 31\,299$)	P-value
Baseline characteristics			
Plasma sodium, mean (SD), mmol/L	132 (5)	139 (3)	<0.001
Age, mean (SD), years	78 (12)	70 (12)	<0.001
Female, *n* (%)	163 (71.5)	21 347 (68.0)	0.30
Body mass index, mean (SD)	26 (6)	28 (6)	<0.001
Diabetes mellitus, *n* (%)	28 (12.3)	3243 (10.4)	0.34
Risk factors associated with hyponatremia, *n* (%)			
Heart failure	18 (8)	910 (3)	<0.001
Chronic kidney disease	28 (12)	3043 (10)	0.20
Liver failure	0	74 (0.2)	0.50
Antidepressant use	58 (25)	12 026 (38)	<0.001
Thiazide use	9 (4)	914 (3)	0.50
Anticonvulsant use	48 (21)	7778 (25)	0.20
FRAX clinical risk factors associated with hip fracture, *n* (%)			
Rheumatoid arthritis	0	182 (0.6)	0.74
Osteoporosis	68 (30)	8500 (27)	0.40
Chronic corticosteroid use	3 (1.3)	676 (2.2)	0.40
Previous fractures	39 (17)	3732 (12)	0.01
Active smoker	21 (9)	4575 (15)	0.02
Alcohol use	6 (2.6)	254 (0.8)	0.002
Total number of hip fracture events during the follow-up period, *n* (%)	7 (3)	411 (1)	0.02

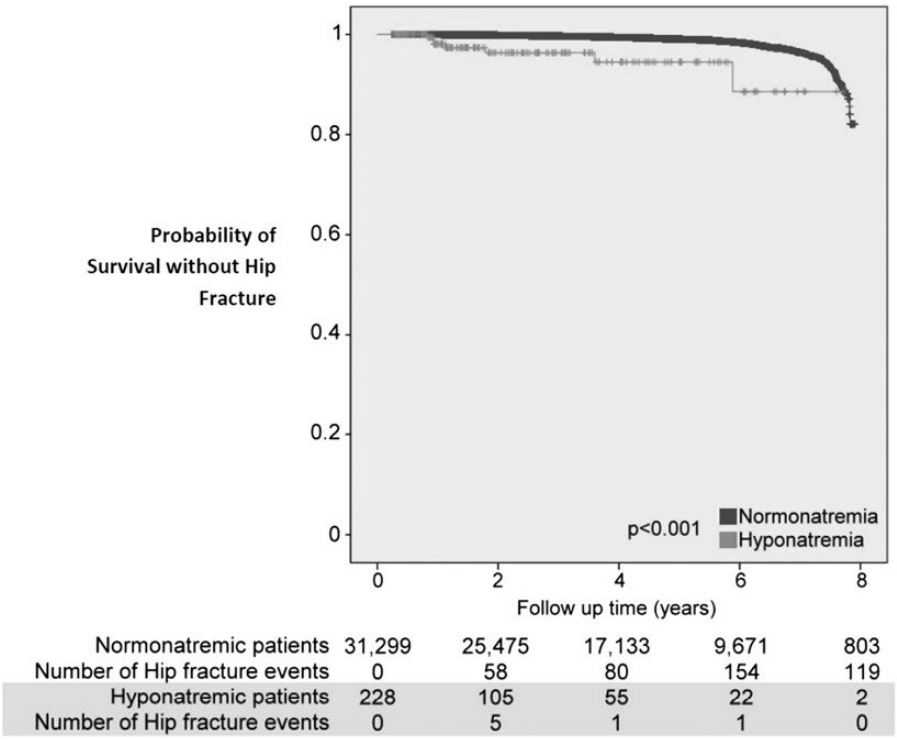

FIGURE 2: Cumulative risk of hip fracture among normonatremic and hyponatremic elderly subjects.

463.0–1320.1)] than the normonatremic group [365.8 per 100 000 person-years (95% CI 333.1–400.14); P < 0.001], with an incidence rate ratio of 2.14 (95% CI 1.26–3.94). Hyponatremic females had the highest incidence rate for hip fracture of 811.2 per 100 000 person-years (95% CI 452.0–1473.8) compared with 457.2 per 100 000 person-years for normonatremic females (95% CI 414.2–504.6) (P < 0.001). Hyponatremic men also had a higher hip fracture rate [677.3 per 100 000 person-years (95% CI 218.4–2010.0)] than normonatremic men [159.9 per 100 000 person-years (95% CI 124.7–205.1)] (P < 0.001).

Association between hyponatremia and hip fracture

In the primary analysis, after adjustment for the propensity for hyponatremia, age, gender, diabetes and FRAX clinical

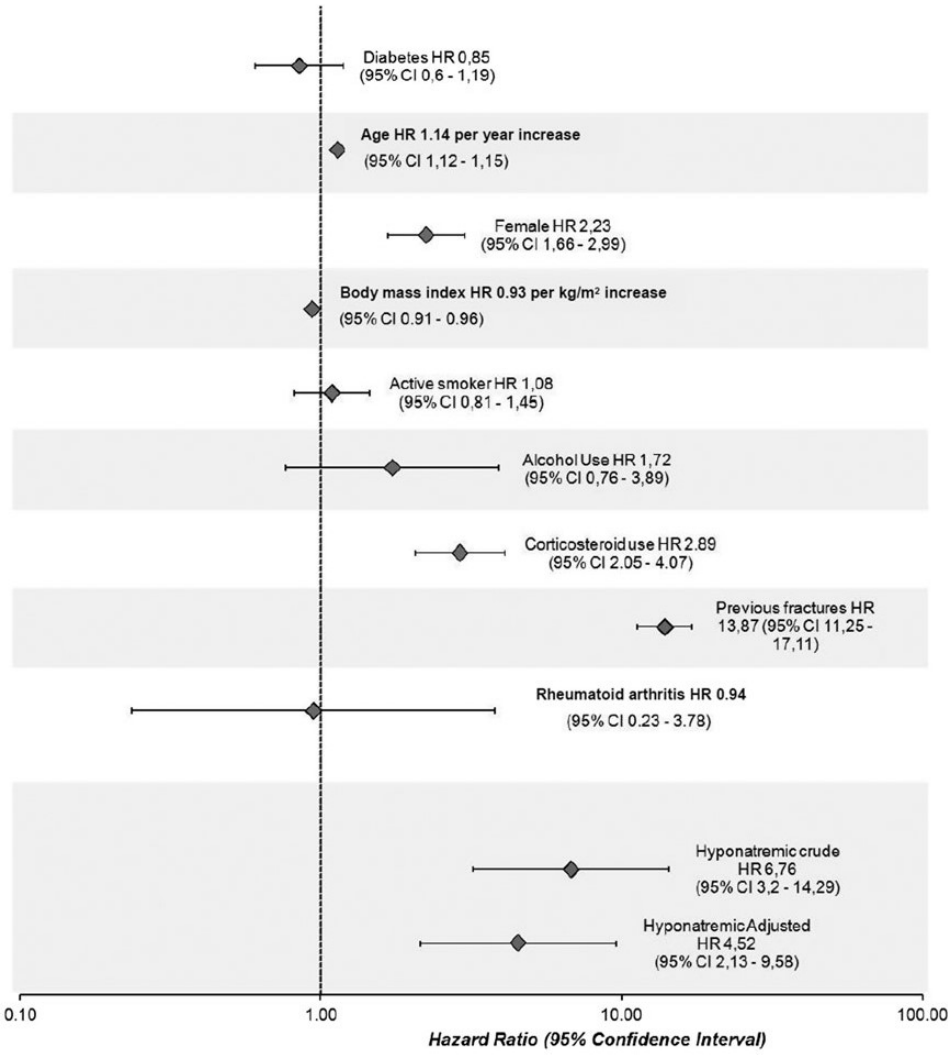

FIGURE 3: Multivariable associations of prolonged hyponatremia and other potential risk factors for hip fracture in elderly adults.

risk factors, the adjusted hazard ratio (HR) for hip fracture was 4.52 (95% CI 2.13–9.58). The adjusted HR for hip fracture was higher for chronic prolonged hyponatremia than any of the known risk factors for fracture present in FRAX, except for having a previous fracture (Figure 3).

The first sensitivity analysis performed adjusted for baseline characteristics, comorbidities and individual FRAX clinical risk factors (age, gender, BMI, congestive heart failure, chronic kidney disease, liver failure, rheumatoid arthritis, long-term corticosteroid use, current smoking, alcohol consumption and use of antidepressants, anticonvulsants or thiazides). After adjustment for these potential confounders, the risk of hip fracture in the hyponatremic group was similar to that of the first model [adjusted HR 5.10 (95% CI 2.35–11.00)]. A subsequent sensitivity analysis adjusted for the median plasma sodium for each patient as a continuous variable (in mmol/L), along with adjustments for the hyponatremia propensity score and FRAX clinical risk factors, and found that the risk for hip fracture remained high [HR 3.25 (95% CI 1.18–8.9)]. A sensitivity analysis was performed adjusting for the severity of hyponatremia as a risk factor for hip fracture and found an increased risk of hip fracture for hyponatremic patients with plasma sodium level <130 mmol/L compared with 130–135 mmol/L [adjusted HR 7.61 (95% CI 2.8–20.5) versus HR 2.9 (95% CI 0.9–9.0)].

A sensitivity analysis was performed looking at patients who only had one episode of hyponatremia ($n = 20\,912$). These patients were excluded from the primary analysis (Figure 1). This analysis was performed to assess if patients with prolonged hyponatremia (those with two or more plasma sodium measurements <135 mmol/L for >90 days) had a greater rate of fracture than those with short durations of hyponatremia (only one plasma sodium measurement <135 mmol/L). The absolute risk for hip fracture was 7/282 in patients with prolonged chronic hyponatremia and 1540/20 912 in patients with only one episode of hyponatremia. Patients with prolonged hyponatremia had a higher adjusted HR for hip fracture than those with only one episode of hyponatremia [4.52 (95% CI 2.14–9.60) versus 2.35 (95% CI 2.11–2.62)].

DISCUSSION

In this study, prolonged chronic hyponatremia of >90 days (mean plasma sodium level 132 mmol/L) in elderly patients

was independently associated with a >4-fold adjusted rate of subsequent hip fracture compared with normonatremic subjects (Figure 3), although the absolute risk was very low (7/228 subjects). Hyponatremia detected once was independently associated with an increased rate of hip fracture, but not as much as prolonged hyponatremia. Collectively, this study suggests that mild prolonged chronic hyponatremia is independently associated with hip fracture risk in the elderly population.

Several retrospective, case–control, or cross-sectional studies [10, 12–19] have reported that mild hyponatremia is associated with fractures due to falling or reduced BMD [13–16]. However, none of these previous studies evaluated the role of the duration of hyponatremia or adjusted for the hyponatremia propensity score and FRAX clinical risk factors. Only one of the previous studies used a prospective design and suggested that mild hyponatremia was associated with an increased risk for incident and prevalent nonvertebral fractures but not incident vertebral fractures [18]. The study serum sodium was measured only at baseline, which precluded evaluation of the chronicity of hyponatremia [18]. The fact that a single hyponatremic measurement was associated with fracture risk suggests that the relationship is strong. In a recent cross-sectional and longitudinal analysis using data from the Osteoporotic Fractures in Men Study (MrOS), which enrolled 5122 community dwelling men ≥65 years followed for fractures for up to 9 years, Jamal *et al.* [26] found that hyponatremic men were at increased risk for hip fracture [HR 3.04 (95% CI 1.37–6.75)]. This was also a very restricted study, with a small number of exposed subjects (64 males) and a small number of events (9 hip fractures). Yet they found a strong association between hyponatremia and a risk for hip fracture in men.

The present study focused on patients with prolonged chronic hyponatremia with two or more consecutive plasma sodium measurements <135 mmol/L during a period >90 days. This was based on animal studies showing that prolonged hyponatremia for 90 days resulted in considerable loss of bone mass [16]. It found that hip fracture was strongly associated with prolonged hyponatremia. It also found that patients with prolonged chronic hyponatremia were at greater risk for hip fracture than those with just one low serum sodium (adjusted HR 4.52 versus 2.35). This suggests that the duration of hyponatremia is an additional risk for hip fracture. In our study, six of the seven fractures in the chronic hyponatremia group were observed in females.

Animal models suggest that chronic hyponatremia leads to bone fracture through direct effects on bone quantity. One study demonstrated that chronic hyponatremia increased bone resorption and decreased bone formation, resulting in osteoporosis [16]. A recent study reported that two arginine vasopressin receptors coupled to extracellular signal-regulated kinases are expressed in osteoblasts and osteoclasts [27]. These findings are supported by older studies showing that one-third of total body sodium resides in the skeleton [28, 29] and, of this, 40% is exchangeable with plasma sodium, indicating that chronic sodium depletion leads to sodium mobilization from bone with resultant bone demineralization.

Hip fractures in the elderly are frequently caused by a simple mechanical fall, often produced by gait disturbances, which are also known to be associated with chronic hyponatremia and can be similar to or worse than those produced by alcohol intoxication [11, 13]. In the present study, all hip fractures were caused by a mechanical fall, suggesting abnormal gait was present in these subjects. The brain adapts to chronic hyponatremia with the loss of osmolytes, such as glutamate [29, 30], which is a neurotransmitter involved in gait function [31, 32]. Thus, loss of glutamate may play a role in gait abnormalities that lead to falls in patients with chronic hyponatremia. Taken together, these results suggest that hyponatremia may contribute to bone fractures in the elderly by at least two separate mechanisms: neurological effects leading to unsteady gait and falls, as well as direct alternations in bone metabolism resulting in osteoporosis.

A strength of this study was that it analyzed a large retrospective cohort using multiple design and analytic approaches. It applied strict inclusion criteria for the main analysis to minimize the possibility of including pseudohyponatremia (e.g. related to hyperglycemia) and applied propensity score methods to address possible selection bias attributable to differential risk of hyponatremia in the elderly population based on relevant patient characteristics and prescription drug use. It further adjusted for validated FRAX clinical risk factors for hip fractures and performed several sensitivity analyses that yielded consistent results. This study also did not suffer from the problem of time bias, as other studies have [33], as patients were followed from the time they were eligible until the occurrence of hip fracture, death, disenrollment or the end of the study period. Patients with hyponatremia should have had a higher risk of death associated with a greater comorbidity burden that is not related to hip fracture, as it is known that hyponatremia is a marker of mortality in patients with cirrhosis or heart failure [34], so the estimates of prolonged hyponatremia and hip fracture may be conservative. Nevertheless, this study has several limitations, among them, the low number of patients exposed to prolonged chronic hyponatremia and the low number of events (7/288). This is the result of the very restrictive design we used. As an observational study of clinical practice, this study is susceptible to residual confounding, as it relied on information from an electronic medical record to identify potential confounders and did not include all possible characteristics, such as the use of certain over-the-counter medications (e.g. NSAIDS, proton pump inhibitors), that may be associated with the development of chronic hyponatremia but were not systematically available. In addition, results from the study sample may also not be fully generalizable to all populations, given the limited racial/ethnic diversity. Thus, future studies are needed in other populations to confirm our finding of a higher risk of hip fracture with chronic hyponatremia.

In summary, this study found that mild chronic hyponatremia of >90 days (mean plasma sodium level 132 mmol/L) in elderly patients was independently associated with hip fracture risk. This suggests that the duration of hyponatremia is an additional risk for hip fracture. Although the present study cannot establish a causal relationship, the results raise questions about the current indication for the treatment of mild hyponatremia in older patients and suggest the need for interventional studies to evaluate whether systematic surveillance and active

correction of mild hyponatremia could help to reduce hip fractures in the elderly.

CONFLICT OF INTEREST STATEMENT

We confirm that all co-authors have no conflicts of interest to declare. We declare that the results presented in this paper have not been published previously in whole or part, except in abstract format.

(See related article by Zietse and Van Biesen. Cum grano salis. *Nephrol Dial Transplant* 2016; 31: 1556–1558)

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Received for publication: 19.1.2016; Accepted in revised form: 29.1.2016