Mild Chronic Hyponatremia and Risk of Hip Fracture in the Elderly

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Introduction

- Hyponatremia is a common disorder in the elderly (10%-20%)(1). The brain is the main target of symptomatic hyponatremia, which is associated with significant morbidity and mortality (2,3). Subjects at high risk for hyponatremia include premenopausal women, children, postoperative patients, and patients with hypoxia or central nervous system disease (2,4,5).
- Hyponatremia can also affect organs other than the brain. Bone abnormalities have also been associated with hyponatremia (8). For example, in 1999 our group noted that orthopedic injury was a presenting manifestation of chronic symptomatic severe hyponatremia (9). This association has since been confirmed by multiple epidemiological studies, which show an increased prevalence of hyponatremia in patients admitted for fractures (10-17). In these studies different types of fracture were noted, and the duration of hyponatremia was not known.
Introduction

• Hip fractures are among the most serious types of bone fracture in the elderly population, with more than 70% of all hip fractures experienced by women older than 65 years (18).
• Despite the evidence of an association between hyponatremia and bone fractures, it is unclear whether chronic hyponatremia is an independent risk factor for fractures or a surrogate marker of another condition.
• We recently hypothesized that chronic hyponatremia is a risk factor for hip fracture in the elderly (19).
Our objective in this study was to determine whether there is an independent association between chronic hyponatremia and hip fracture in the elderly.
Materials and Methods

Setting and Period
This study was performed at the Italian Hospital of Buenos Aires, Argentina from January 1, 2005 to December 1, 2012.
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.

Study Sample and Design
We designed a cohort study that included all patients at the Italian Hospital Medical Care Program >60 years of age who had more than two measurements of plasma sodium level during the study period.
Materials and Methods

• We defined *chronic hyponatremia* as two or more consecutive plasma sodium values <135 mmol/L over a period of more than 90 days.
• Patients were classified as *normonatremic* if they never had plasma sodium values <135 mmol/L (Figure 1).
• Plasma sodium was measured using the ion-selective electrode method (normal range 135–145 mmol/L).
• Using the electronic medical records we also identified all patients who had an emergency admission diagnosis (or diagnosis at discharge following emergency admission) coded as hip fracture.
• Follow-up continued until the time of hip fracture or the end date of the study period.
We identified the following variables associated with increased risk for chronic hyponatremia: age, gender, congestive heart failure, chronic kidney disease (estimated glomerular filtration rate <60 mL/min, using the MDRD), liver failure, and use of antidepressant medications (selective serotonin reuptake inhibitors, tricyclic antidepressants), anticonvulsants, or thiazides. We constructed a propensity score for hyponatremia to adjust for the effect of such confounding factors (20).

Clinical risk factors included in the Fracture Risk Assessment Tool (FRAX®), which was developed by the World Health Organization (21,22), were also evaluated.

Patient electronic medical records were used to determine use of anticonvulsants, antidepressants, diuretics, and corticosteroids, as patients had access to these drugs only from the Medic Care Health pharmacy.
Statistical Analysis: Descriptive and association

• Continuous variables are expressed as mean and standard deviation or median and interquartile range (IQR), depending on their distribution. Continuous variables were compared between groups by t test or Mann–Whitney test. Categorical variables are expressed as absolute frequency and percentage and were compared by chi-squared or Fisher exact test.

• We evaluated the relationship between chronic hyponatremia and hip fracture using several approaches. First, the unadjusted incidence rate (IR) of hip fracture, with the associated 95% confidence interval (CI), was calculated for patients with or without chronic hyponatremia. We also evaluated the IR according to age and gender, and calculated the incidence rate ratio and associated 95% CI.
We used logistic regression to estimate the propensity score for the likelihood of having chronic hyponatremia. The variables included were age; gender; history of congestive heart failure, chronic kidney disease, or liver disease; and use of antidepressants, anticonvulsants, or thiazides. This model was used to determine each patient’s individual risk and was used with other potential risk factors to calculate the adjusted hazard ratio.

We then analyzed the relationship between chronic hyponatremia and hip fracture using the univariate Cox–Mantel test. Multivariate Cox regression analysis was used to determine the risk for hip fracture associated with chronic hyponatremia after adjusting for the hyponatremia propensity score and risk factors included in the FRAX score.
1-We adjusted for age, gender, diabetes, comorbidities and medications included in the propensity score model, and comorbidities included in the FRAX score using multivariate Cox regression.

2- We conducted separate sensitivity analyses to test the effect of hyponatremia severity and number of plasma sodium measurements <135 mmol/L.

3-Then we ran the same Cox model with plasma sodium as a continuous variable to determine how the hazard ratio of hip fracture was affected by each 1-mmol or 10-mmol change in plasma sodium concentration.

We performed a subanalysis to assess interaction of covariates on the association of interest. We included other subgroups like age (>80 years, ≤80 years) and body mass index (BMI <25 or ≥25).

A p-value <0.05 was considered significant. All estimators and hazard ratios (unadjusted and adjusted) were reported with 95% CIs. Statistical analyses were performed with SPSS 19.0 software.
Cohort study sample

Members of Italian Hospital Medical Care Program 2005-2012
n=155,000

Patients with sodium determinations n=133,135

Older than 60 years n=63,858 (48%)

Was consistently hyponatremic or normonatremic throughout the study period.
n=43,279 (67.8%)

Sample study population n=31,527 (73%)

Chronic hyponatremia n=228

“Normonatremia” n=31,299

Plasma sodium measurements =958,403
- Error or empty n=5,005
- >200mmol/l n=6
- < 80 mmol/l n=21

Excluded < 60 years n=69,277 (52%)

“Excluded patients with plasma sodium fluctuations above or below 135 mmol/L”
n=20,579 (32.2%)

Excluded because they had less than two plasma sodium measurements n=11,752 (27%)
- Mean follow-up from hyponatremia to hip fracture was 506 days (IQR 968) for patients with chronic hyponatremia, and 1408 days (IQR 1463) for normonatremic patients.
- The median number of plasma sodium measurements was 3 (IQR 1) for hyponatremic patients, and 2 (IQR 4) for normonatremic patients.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Chronic hyponatremia (n=228)</th>
<th>Normonatremia (n=31,299)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
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<td></td>
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<tr>
<td>Natremia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>7 (3)</td>
<td>411 (1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female sex</td>
<td>163 (71.5)</td>
<td>21347 (88)</td>
<td>0.30</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>28 (12.3)</td>
<td>3243 (10.4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>28 (12)</td>
<td>3043 (10)</td>
<td>0.20</td>
</tr>
<tr>
<td>Liver failure</td>
<td>0</td>
<td>74 (0.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide use</td>
<td>9 (4)</td>
<td>914 (3)</td>
<td>0.50</td>
</tr>
<tr>
<td>Anticonvulsant use</td>
<td>48 (21)</td>
<td>7778 (25)</td>
<td>0.20</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>0</td>
<td>182 (0.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>68 (30)</td>
<td>8500 (27)</td>
<td>0.40</td>
</tr>
<tr>
<td>Chronic corticoid use</td>
<td>3 (1.3)</td>
<td>678 (2.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Previous fractures</td>
<td>39 (17)</td>
<td>3732 (12)</td>
<td>0.01</td>
</tr>
<tr>
<td>Active smoker</td>
<td>21 (9)</td>
<td>4575 (15)</td>
<td>0.02</td>
</tr>
<tr>
<td>Alcohol use</td>
<td></td>
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</tbody>
</table>

*Mean and interquartile interval
*Absolute frequency and percentage
*Inhibitors of serotonin and tricyclic receptors
• The Rate ratio was 2.14 (95% CI, 1.26–3.94).
• Among women, the IR for hip fracture was 811.16 for chronic hyponatremia (95% CI, 451.99–1473.77) and 457.17 for normonatremia (95% CI, 414.24–504.56).
• The IR for hip fracture was lower among men but showed the same trend: 677.27 for chronic hyponatremia (95% CI, 218.43–2099.97) and 159.89 for normonatremia (95% CI, 124.66–205.08).
Main Analysis

Figure 3. Cumulative risk of hip fracture among normonatremic and hyponatremic patients.
Figure 4. Risk of hip fracture according to FRAX clinical risk factors and presence of chronic hyponatremia.

- **Age**: HR 1.14 (95% CI 1.12 - 1.15)
- **Female**: HR 2.23 (95% CI 1.66 - 2.99)
- **BMI**: HR 0.93 (95% CI 0.91 - 0.96)
- **Active smoker**: HR 1.08 (95% CI 0.81 - 1.45)
- **Alcohol Use**: HR 1.72 (95% CI 0.76 - 3.89)
- **Corticosteroid use**: HR 2.89 (95% CI 2.05 - 4.07)
- **Previous fractures**: HR 13.87 (95% CI 11.25 - 17.11)
- **Arthritis Reumatoidea**: HR 0.94 (95% CI 0.23 - 3.78)
- **Hyponatremic crude**: HR 6.76 (95% CI 3.2 - 14.29)
- **Hyponatremic Adjusted**: HR 4.52 (95% CI 2.13 - 9.58)
- **Diabetes**: HR 0.85 (95% CI 0.6 - 1.19)
# Table 2. Main analysis and sensitivity analysis of hip fracture risk for patients with hyponatremia.

<table>
<thead>
<tr>
<th>Sensitivity Analysis</th>
<th>Unadjusted HR</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with ≥2 plasma sodium measurements for &gt;90 days (n=31,527)</td>
<td>6.7 (95% CI, 3.2–14.2)</td>
<td>4.52 (95% CI, 2.14–9.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity Analysis</th>
<th>Unadjusted HR</th>
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<tbody>
<tr>
<td><strong>Sensitivity Analysis</strong></td>
<td></td>
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</tr>
<tr>
<td>Patients with ≥2 plasma sodium measurements for &gt;90 days (n=31,527)</td>
<td>5.1 (95% CI, 2.35–11)</td>
<td>3.25 (95% CI, 1.18–8.9)</td>
</tr>
</tbody>
</table>

According to severity of hyponatremia (n=31,527):

<table>
<thead>
<tr>
<th>Plasma sodium &lt;130 mmol/L (n=91)</th>
<th>9.3 (95% CI, 3–29)</th>
<th>7.81 (95% CI, 2.8–20.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma sodium 130–135 mmol/L (n=137)</td>
<td>3.7 (95% CI, 1.3–9.9)</td>
<td>2.9 (95% CI, 0.9–9)</td>
</tr>
</tbody>
</table>

According to number of plasma sodium values <135 mmol/L (n=53,716):

<table>
<thead>
<tr>
<th>One measurement (n=20,912)</th>
<th>4.4 (95% CI, 3.9–4.8)</th>
<th>2.35 (95% CI, 2.11–2.62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two measurements (n=13,506)</td>
<td>4.03 (95% CI, 3.7–4.4)</td>
<td>2 (95% CI, 1.8–2.2)</td>
</tr>
<tr>
<td>Three or more measurements (n=10,267)</td>
<td>3.74 (95% CI, 3.4–4.1)</td>
<td>1.77 (95% CI, 1.6–1.95)</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, hyponatremia propensity score, diabetes, and FRAX clinical risk factors
* Adjusted for comorbidities, age, gender, diabetes, medications associated with hyponatremia, and FRAX clinical risk factors
* Adjusted for propensity score for hyponatremia and FRAX clinical risk factors plus median 1-mmol/L change in plasma sodium
* Adjusted for hyponatremia propensity score and FRAX clinical risk factors plus median 10-mmol/L change in plasma sodium
Figure 5. Proportion of hip fractures in patients with chronic hyponatremia and patients with only one plasma sodium measurement <135 mmol/L.

*Chronic hyponatremia: ≥2 plasma sodium measurements <135 mmol/L in the 90 days before hip fracture. One determination: any plasma sodium value <135 mmol/L before hip fracture.
Figure 6. Forest plot of covariate interactions
In this study we found that elderly subjects with mild chronic hyponatremia had a higher risk for hip fracture than normonatremic subjects.

Results of sensitivity analysis evaluating plasma sodium as a continuous variable showed that hyponatremia severity and number of hyponatremic episodes had little effect on hip fracture risk.

Taken together, our results demonstrate that mild chronic hyponatremia is an independent risk factor for hip fracture in the elderly.

*These findings are consistent with previous studies. Several retrospective, case-controlled, or cross-sectional studies (10-17) have reported that mild hyponatremia is associated with fractures due to falling or decreased bone mineral density (11,14). However, none of these previous studies had evaluated the role of chronic hyponatremia or adjusted for the hyponatremia propensity score and FRAX clinical risk factors.*
Discussion

• In this study we found that elderly subjects with mild chronic hyponatremia had a higher risk for hip fracture than normonatremic subjects.
• After adjusting for age, gender, hyponatremia propensity score, diabetes, and FRAX clinical risk factors, the only FRAX risk factor that produced a greater HR than chronic hyponatremia was history of previous fracture.
• Results of sensitivity analysis evaluating plasma sodium as a continuous variable showed that hyponatremia severity and number of hyponatremic episodes had little effect on hip fracture risk.

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Discussion

The relationship between hyponatremia and osteoporosis in humans is not well understood. In our study hyponatremia was not associated with osteoporosis, which is in agreement with two previous studies (15,16). However, a study analyzing data from the Third National Health and Nutrition Examination Survey (NHANES III) reported an association between hyponatremia and osteoporosis (14).

Hip fractures in the elderly are usually caused by a simple fall, often produced by gait disturbances, which are associated with chronic hyponatremia. One study reported that patients with chronic hyponatremia have gait abnormalities similar to or worse than those produced by alcohol intoxication (11). In the present study, all hip fractures appeared to be caused by a fall, suggesting abnormal gait. The brain adapts to chronic hyponatremia with the loss of osmolytes, such as glutamate (26, 27), which is a neurotransmitter involved in gait function (28,29). Thus, loss of glutamate may play a role in gait abnormalities that lead to falls in patients with chronic hyponatremia.

Taken together, these results indicate that hyponatremia may contribute to bone fractures in the elderly by at least two separate mechanisms. Our study was strengthened by the large cohort and systematic follow-up until the time of hip fracture. We used strict inclusion criteria for the primary cohort analysis, applied a propensity score method for hyponatremia to address possible selection bias, and adjusted for FRAX clinical risk factors that predict hip fractures.
Nevertheless, our study has several limitations. As an observational study of clinical practice, our study is susceptible to residual confounding. The population was ethnically homogeneous (white). Thus, future studies are needed to determine the relationship between hyponatremia and hip fracture in other populations. Finally, we did not evaluate whether treatment for hyponatremia could prevent hip fracture.

subjects who were white.
References


