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# Chronic prolonged hyponatremia and risk of hip fracture in elderly patients with chronic kidney disease

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ABSTRACT

*Background:* Chronic prolonged hyponatremia (CPH) is a risk factor for hip fracture in the general population. Whether CPH increases hip fracture risk in chronic kidney disease (CKD) patients is unknown.

*Methods:* Case-control study in patients over 60 years of age with stage 3 or greater CKD. Patients who had a hip fracture were referred to as cases ($n$ = 1236) and controls had no hip fracture ($n$ = 4515). Patients were classified as having CPH if serum sodium was < 135 mEq/L on at least two occasions separated by a minimum of 90 days prior to the diagnosis of hip fracture (cases) or at any time during the study period (controls). Conditional logistic regression models were used to test the association between CPH and hip fracture. Analyses were conducted for patients with and without osteoporosis and falls and for patients with age > 70 years versus ≤70 years.

*Results:* CPH was present in 21% of cases and 10% of controls ($p$ < 0.001; sodium level: 131–134 mEq/L). In univariate logistic regression analysis, CPH was associated with higher odds of hip fracture (odds ratio [OR] 2.44, (95% [CI] 2.07–2.89). In a multivariate model adjusted for comorbidities, medications and laboratory parameters CPH association with higher odds of Hip fracture was attenuated but remained significant (OR 1.36, 95% CI 1.04–1.78). The association between CPH and risk of hip fracture was consistent in patients with or without osteoporosis and falls and across the age strata.

*Conclusion:* Chronic prolonged hyponatremia is a risk factor for hip fracture in CKD patients older than 60 years of age.

## 1. Introduction

In patients over 60 years of age, the prevalence of chronic kidney disease (CKD) is increasing with estimates ranging from 23% to 36% [1]. In these patients, a skeletal fracture, particularly a hip fracture, is associated with an increased risk of recurrent fractures, increased morbidity, increased mortality and high economic costs [2–4]. Compared to people with normal kidney function, patients with moderate to severe CKD have 1.5- to 3-fold higher risk of fracture [5–8]. This heightened fracture risk is attributed primarily to CKD induced changes in bone and mineral metabolism, without a clear evidence. Moreover, this risk is present even in early stages of CKD in which biochemical parameters are normal. Though the exact pathogenesis remains uncertain, yet, the higher hip fracture risk among patients with CKD compared to those without CKD suggests the role of additional factors other than mineral bone parameters [9].

Hyponatremia is prevalent in patients with CKD [10]. There is mounting evidence to indicate hyponatremia as a risk factor for bone disease in the general population [11–13]. Among patients who fall, those with hyponatremia have a further higher risk of bone fracture [14]. We recently reported that mild chronic prolonged hyponatremia is a significant risk factor for hip fractures in elderly patients without CKD, independent of the Fracture Risk Assessment Tool (FRAX) clinical risk factors [15]. However, whether chronic prolonged hyponatremia

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increases hip fracture risk in elderly patients with CKD, a population with high fracture rate and high prevalence of hyponatremia, is unknown. In this case-control study, we assessed the role of chronic prolonged hyponatremia (defined as serum sodium < 135 mEq/L on at least two occasions separated by at least 90 days) as a risk factor for hip fracture in elderly patients (age > 60 years) with CKD.

## 2. Methods

### 2.1. Setting and period

Patients were identified from the Partners Research Patient Data Registry during the study period extending from January 1, 2006 to December 31, 2013. This registry is a relational database containing clinical and administrative information on millions of patients seen within the Partners Healthcare System [16]. Partners Healthcare is a not-for-profit, integrated health care system in Boston, Massachusetts that provides care for roughly 50% of the population in the Boston metropolitan area. Partners Healthcare includes community and specialty hospitals, a managed care organization, a physician network, community health centers, home care and other health related services. The registry contains information on patient demographics, diagnoses, laboratory data, and procedures derived from a combination of claims submitted for billing purposes and electronic medical records. The Clinical Quality Group mandates protocols and audits incoming information to ensure data are accurately documented. The study was approved by the Institutional Review Board of the Partners Healthcare System and conducted in accordance with its ethical standards. A waiver of informed consent was obtained due to the retrospective nature of the study.

### 2.2. Study design and sample

In this matched case-control study we identified patients older than 60 years of age with CKD defined as at least two measurements of estimated glomerular filtration rate (eGFR) calculated by applying chronic kidney disease-epidemiology formula [17] below 60 ml/min/1.73m$^2$ separated by at least 90 days, excluding patients with end-stage renal disease treated with dialysis or transplantation.

We excluded individuals with billing claims and electronic medical record diagnoses of pathologic hip fractures (e.g., due to bony metastasis) and those with hip fracture due to polytrauma. The remaining patients with CKD who had a hip fracture due to minor trauma during the study period (after establishing the CKD status) were categorized as cases ($n$ = 1236). CKD patients older than 60 years of age who had no hip fracture during the study period were identified from the Partners Research Patient Data Registry and those who matched to cases for age ( ± 5 years), sex, and race were included as controls ($n$ = 4515). We included only patients with at least two serum sodium levels separated by at least 90 days during the study period for both cases (prior to fracture event) and controls. The study subject selection scheme is outlined in Fig. 1.

### 2.3. Study data on hyponatremia

Serum sodium levels were corrected for serum glucose using the following formula: corrected sodium (mEq/L) = measured sodium (mEq/L) + 0.016 * (Serum glucose [mg/dL] – 100). Based on corrected sodium values, cases were classified as having chronic prolonged hyponatremia if the serum sodium was < 135 mEq/L on at least two occasions separated by at least 90 days prior to the diagnosis of hip fracture (cases) or at any time during the study period (controls).

### 2.4. Covariates

Comorbidities (diabetes mellitus, hypertension, obesity, coronary artery disease, congestive heart failure, cerebrovascular disease, liver cirrhosis, dementia, chronic obstructive pulmonary disease, lung cancer, thyroid disorder, and osteoporosis) and medications (calcium supplements, vitamin D supplements, bisphosphonates, diuretic therapy, antidepressant therapy, antipsychotic therapy, corticosteroids and non-steroidal anti-inflammatory agents) were recorded. Laboratory data regarding parameters of mineral metabolism, glucose, bicarbonate and C reactive protein were abstracted from the electronic medical records. The most proximal laboratory value recorded within one year preceding fracture was used for cases and the last recorded value was used for controls.

### 2.5. Statistical analysis

Frequency (for categorical variables), mean and standard deviation values (for normally distributed variables), and median and interquartile range values (for non-normally distributed variables) were reported. Categorical variables were compared between cases and controls using a Chi-squared test. Continuous variables were compared using independent samples $t$-test (normally distributed data) or Mann–Whitney $U$ test (non-normally distributed data).

The primary predictor variable was chronic prolonged hyponatremia. To test the association between chronic prolonged hyponatremia and hip fracture, conditional logistic regression models were applied to compute odds ratios (OR) and 95% confidence intervals (CI). Model 1 adjusted for all comorbidities and medications. Model 2 adjusted for all covariates in the primary model and laboratory parameters that were statistically different between cases and controls. Stratified analyses were conducted by stratifying patients by a) osteoporosis as a baseline comorbidity, b) falls as a baseline comorbidity, and c) age > 70 years versus equal to or < 70 years. Exploratory univariate and multivariable-adjusted analyses were conducted using only one episode of hyponatremia as a predictor variable and using two episodes of hyponatremia but separated by at least 180 days. Additionally, sensitivity analyses were conducted by adding matching criteria (age, sex, and race) to model 2 and by restricting to patients with the available data for body mass index (BMI).

A two-sided $p$-value < 0.05 was considered significant. All the analyses were performed using SAS version 9.4 (Cary, NC).

### 2.6. Star methods

| Resource | Source | Identifier |
|---|---|---|
| Antibody | | |
| Anti-inflammatory | | |
| Chemical | | |
| Bicarbonate | | |
| Bisphosphonates | | |
| Calcium | | |
| Sodium | | |

## 3. Results

### 3.1. Baseline characteristics

The demographic and clinical characteristics of cases and controls are summarized in Table 1. The mean age of cases and controls was 84 ± 9 and 83 ± 9 years, respectively. Most patients were white (87%) and were predominantly female (61%). Eighty four percent of study participants had stage 3 CKD, 12% had stage 4, and 4% had stage 5 CKD. The mean eGFR was 40 ml/min/1.73 m$^2$ (interquartile range: 28–52) in cases versus 43 ml/min/1.73 m$^2$ (interquartile range: 32–56)

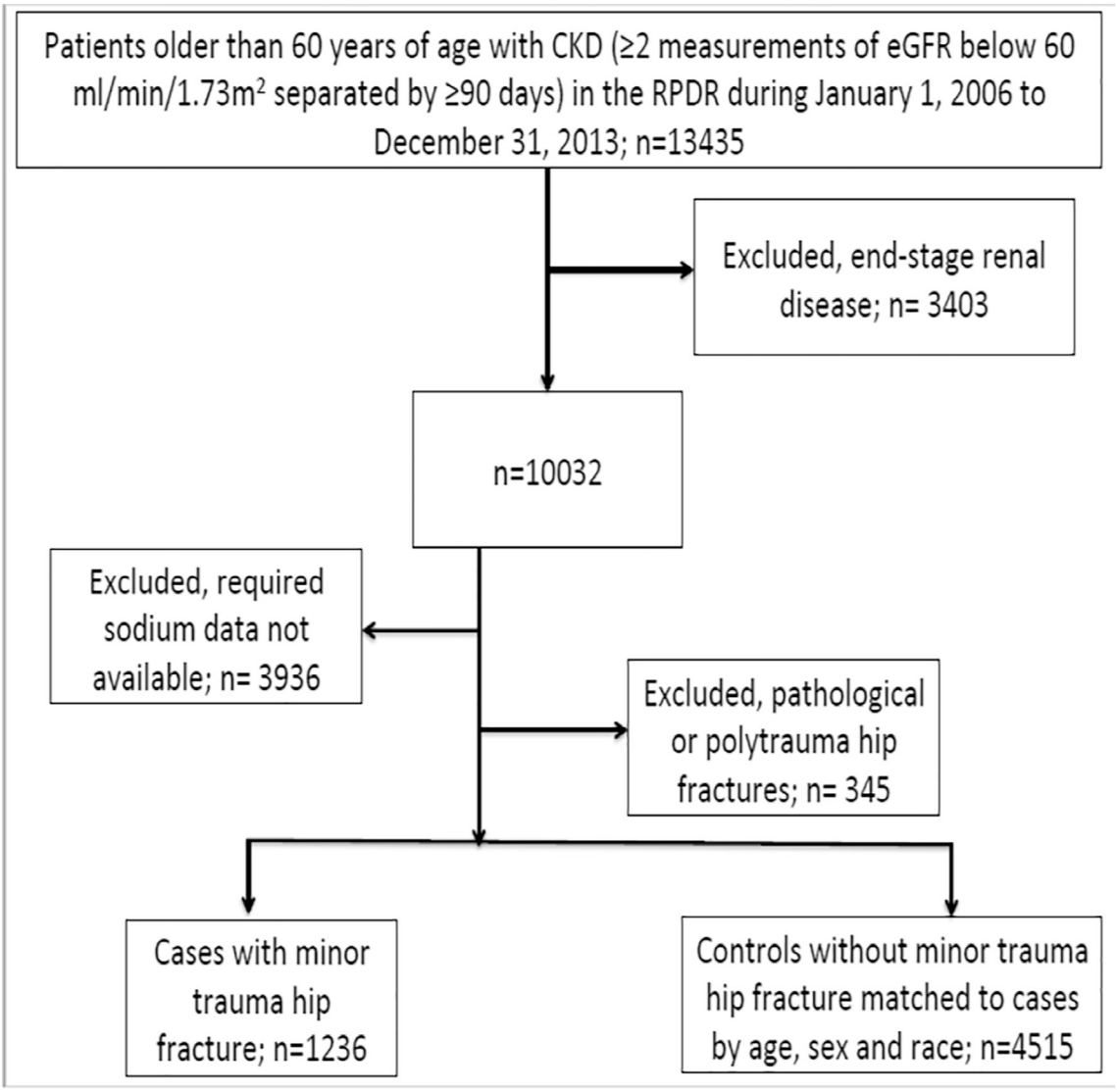


**Fig. 1.** Flow diagram outlining patient selection.

in controls ($p < 0.001$). The prevalence of several comorbidities including congestive heart failure, hypothyroidism, chronic obstructive pulmonary disease, and diabetes mellitus was higher in cases. The use of diuretic therapy, corticosteroids, antidepressant therapy, antiepileptic, proton pump inhibitors, antipsychotic therapy, calcium and vitamin D supplements was more common in cases whereas the use of non-steroidal anti-inflammatory agents was comparable between cases and controls. Among patients with the available data for body mass index, cases had a lower mean BMI than controls (496 cases: 26.4 ± 5.4 kg/m$^2$, 1368 controls: 28.8 ± 6.1 kg/m$^2$, $p < 0.001$).

Among patients with available data, median levels of calcium (cases: 9.2 mg/dL [8.9, 9.6], controls: 9.3 mg/dL [8.9, 9.7], $p = 0.55$), phosphorous (cases: 3.4 mg/dL [3.0, 3.9], controls: 3.3 mg/dL [2.9, 3.9], $p = 0.13$), parathyroid hormone (cases: 96 pg/ml [58, 190], controls: 82 pg/ml [50, 150], $p = 0.15$), 25-hydroxyvitamin D (cases: 30 ng/ml [19, 40], controls: 27 ng/ml [17,38], $p = 0.05$), magnesium (cases: 1.8 mg/dL [1.6, 2.0], controls: 1.6 mg/dL [1.4, 1.8], $p = 0.16$), and C-reactive protein (cases: 10.7 mg/L [2.4, 56.9], controls: 11.3 mg/L [2.3, 60.8], $p = 0.84$) were comparable between cases and controls whereas alkaline phosphatase was higher in cases (cases: 84 U/L (67, 110), controls: 78 U/L [63, 99], $p < 0.001$) while serum bicarbonate (cases: 26.3 mmol/L [24.0, 29.0], controls: 27.0 mmol/L [24.7, 29.0], $p < 0.001$) was lower.

### 3.2. Hyponatremia

Chronic prolonged hyponatremia was present in 21% of cases and 10% of controls ($p < 0.001$). Most cases (77%) and controls (79%) had mild hyponatremia (serum sodium level: 131–134 mEq/L). For patients who had multiple sodium measurements during the study period, the first sodium level demonstrated a strong positive correlation with subsequent levels ($r = 0.65$, $p < 0.0001$).

The demographic and clinical characteristics of patients with and without chronic prolonged hyponatremia are shown in Table 2.

Fifty three percent of cases and 41% of controls had at least one episode of hyponatremia ($p < 0.001$). Sixteen percent of cases and 7% of controls had chronic prolonged hyponatremia of at least 180 days ($p < 0.001$).

### 3.3. Hyponatremia and risk of hip fracture (Table 3)

In univariate logistic regression analysis, chronic prolonged hyponatremia was associated with higher odds of hip fracture (OR 2.44, 95% CI 2.07–2.89). This association was attenuated but remained significant in a multivariate model adjusted for comorbidities and medications (model 1; OR 1.31, 95% CI 1.01–1.70). A similar increased odds ratio for hip fracture was observed in multivariate models adjusted for all

**Table 1**
Baseline characteristics of cases and controls.

| | Cases (n = 1236) | Controls (*n* = 4515) | *P* value |
|---|---|---|---|
| Demographics | | | |
| Age (years) | 84 ± 9 | 83 ± 9 | |
| Male gender (%) | 487 (39.4) | 1780 (39.4) | |
| Race (%) | | | |
| White | 1075 (87.0) | 3942 (87.3) | |
| Black | 45 (3.6) | 158 (3.5) | |
| Asian | 18 (1.5) | 86 (1.9) | |
| Hispanic | 22 (1.3) | 79 (1.8) | |
| Other | 16 (4.9) | 37 (0.8) | |
| Comorbidities | | | |
| Congestive heart failure (%) | 580 (46.9) | 1451 (32.1) | < 0.001 |
| Hypothyroidism (%) | 216 (17.5) | 587 (13.0) | < 0.001 |
| Cirrhosis (%) | 27 (2.2) | 66 (1.5) | 0.07 |
| Addison's disease (%) | 12 (1.0) | 14 (0.3) | 0.002 |
| Falls (%) | 951 (76.9) | 358 (7.9) | < 0.001 |
| Previous hip fracture (%) | 94 (7.6) | 10 (0.2) | < 0.001 |
| Dementia (%) | 120 (9.7) | 130 (2.9) | < 0.001 |
| Tobacco use (%) | 69 (5.6) | 142 (3.2) | < 0.001 |
| Alcohol use (%) | 44 (3.6) | 95 (2.1) | 0.003 |
| Chronic obstructive pulmonary disease (%) | 332 (26.9) | 809 (17.9) | < 0.001 |
| Osteoporosis (%) | 263 (21.3) | 393 (8.7) | < 0.001 |
| Hypertension (%) | 981 (79.4) | 3001 (66.5) | < 0.001 |
| Diabetes mellitus (%) | 479 (38.8) | 1385 (30.7) | < 0.001 |
| Inflammatory bowel disease (%) | 41 (3.3) | 131 (2.9) | 0.45 |
| Rheumatoid arthritis (%) | 38 (3.1) | 87 (1.9) | 0.01 |
| Medications | | | |
| Antidepressant (%) | 378 (30.6) | 771 (17.1) | < 0.001 |
| Anxiolytic (%) | 125 (10.1) | 438 (9.7) | 0.67 |
| Antipsychotic (%) | 139 (11.3) | 286 (6.3) | < 0.001 |
| Antiepileptic (%) | 17 (1.4) | 17 (0.4) | < 0.001 |
| Anti-Parkinson (%) | 0 (0.0) | 1 (0.1) | 0.60 |
| Proton pump inhibitor (%) | 569 (46.0) | 1806 (40.0) | < 0.001 |
| Angiotensin converting enzyme inhibitor (%) | 434 (35.1) | 1481 (32.8) | 0.13 |
| Angiotensin II receptor blocker (%) | 174 (14.1) | 573 (12.7) | 0.20 |
| Calcium (%) | 482 (39.0) | 1202 (26.6) | < 0.001 |
| Vitamin D (%) | 369 (29.9) | 597 (13.2) | < 0.001 |
| Estrogen (%) | 12 (1.0) | 31 (0.7) | 0.30 |
| Bisphosphonate (%) | 366 (29.6) | 819 (18.1) | < 0.001 |
| Anti-arrhythmic (%) | 114 (9.2) | 291 (6.5) | < 0.001 |
| Nonsteroidal anti-inflammatory (%) | 165 (13.4) | 517 (11.5) | 0.07 |
| Analgesic, other than non-steroidal anti-inflammatory (%) | 726 (58.7) | 1554 (34.4) | < 0.001 |
| Inhaled and oral Corticosteroids (%) | 289 (23.4) | 714 (15.8) | < 0.001 |
| Diuretic (%) | 700 (56.6) | 2308 (51.1) | < 0.001 |

Table shows mean ± standard deviation or number (percentage).
*Race data were missing for 60 cases and 213 controls.

**Table 2**
Baseline characteristics of patients with and without chronic prolonged hyponatremia.

| | Chronic prolonged hyponatremia | | P value |
|---|---|---|---|
| | Yes (*n* = 710) | No (*n* = 5041) | |
| Demographics | | | |
| Age (years) | 81 ± 10 | 84 ± 9 | < 0.001 |
| Male gender (%) | 277 (39.0) | 1990 (39.5) | 0.81 |
| Race (%)* | | | 0.01 |
| White | 591 (83.2) | 4426 (87.8) | |
| Black | 39 (5.5) | 164 (3.3) | |
| Asian | 16 (2.3) | 88 (1.8) | |
| Hispanic | 14 (2.0) | 87 (1.7) | |
| Other | 7 (1.0) | 46 (0.9) | |
| Comorbidities | | | |
| Congestive heart failure (%) | 384 (54.1.9) | 1647 (32.7) | < 0.001 |
| Hypothyroidism (%) | 139 (19.6) | 664 (13.2) | < 0.001 |
| Cirrhosis (%) | 35 (4.9) | 58 (1.2) | < 0.001 |
| Addison's disease (%) | 12 (1.7) | 14 (0.3) | < 0.001 |
| Falls (%) | 275 (38.7) | 1034 (20.5) | < 0.001 |
| Previous hip fracture (%) | 30 (4.2) | 74 (1.5) | < 0.001 |
| Dementia (%) | 41 (5.8) | 209 (4.2) | 0.05 |
| Tobacco use (%) | 55 (7.8) | 156 (3.1) | < 0.001 |
| Alcohol use (%) | 32 (4.5) | 107 (2.1) | < 0.001 |
| Chronic obstructive pulmonary disease (%) | 216 (30.4) | 925 (18.4) | < 0.001 |
| Osteoporosis (%) | 106 (14.9) | 550 (10.9) | 0.002 |
| Hypertension (%) | 583 (82.1) | 3399 (67.4) | < 0.001 |
| Diabetes mellitus (%) | 333 (46.9) | 1531 (30.4) | < 0.001 |
| Inflammatory bowel disease (%) | 33 (4.7) | 139 (2.8) | 0.006 |
| Rheumatoid arthritis (%) | 25 (3.5) | 100 (2.0) | 0.009 |
| Medications | | | |
| Antidepressant (%) | 258 (36.3) | 891 (17.7) | < 0.001 |
| Anxiolytic (%) | 155 (21.8) | 408 (8.1) | < 0.001 |
| Antipsychotic (%) | 91 (12.8) | 334 (6.6) | < 0.001 |
| Antiepileptic (%) | 7 (1.0) | 27 (0.5) | 0.14 |
| Anti-Parkinson (%) | 0 (0.0) | 1 (0.02) | 0.70 |
| Proton pump inhibitor (%) | 434 (61.1) | 1941 (38.5) | < 0.001 |
| Angiotensin converting enzyme inhibitor (%) | 303 (42.7) | 1612 (32.0) | < 0.001 |
| Angiotensin II receptor blocker (%) | 122 (17.2) | 625 (12.4) | < 0.001 |
| Calcium (%) | 341 (48.0) | 1343 (26.6) | < 0.001 |
| Vitamin D (%) | 205 (28.9) | 761 (15.1) | < 0.001 |
| Estrogen (%) | 9 (1.3) | 34 (0.7) | 0.09 |
| Bisphosphonate (%) | 233 (32.8) | 952 (18.9) | < 0.001 |
| Anti-arrhythmic (%) | 106 (14.9) | 299 (5.9) | < 0.001 |
| Nonsteroidal anti-inflammatory (%) | 124 (17.5) | 558 (11.1) | < 0.001 |
| Analgesic, other than non-steroidal anti-inflammatory (%) | 408 (57.5) | 1872 (37.1) | < 0.001 |
| inhaled and oral corticosteroids (%) | 234 (33.0) | 769 (15.3) | < 0.001 |
| Diuretic (%) | 481(67.8) | 2527 (50.1) | < 0.001 |

covariates in model 1 and laboratory parameters that were statistically different between cases and controls (model 2; OR 1.36, 95% CI 1.04–1.78).

The association between chronic prolonged hyponatremia and hip fracture was consistent in patients with (OR: 2.45, 95% CI: 1.60–3.74) and without osteoporosis (OR: 2.38, 95% CI: 1.98–2.87), with (OR: 1.57, 95% CI: 1.14–2.16) and without falls (OR: 1.76, 95% CI: 1.25–2.47), and across the age strata of > 70 years (OR: 2.24, 95% CI: 1.86–2.70) and equal to or < 70 years (OR: 4.02, 95% CI: 2.66–6.09).

In sensitivity analyses conducted by adding matching criteria (age, sex, and race) to model 2, the association between chronic prolonged hyponatremia and hip fracture persisted (OR: 1.33, 95% CI: 1.01–1.74). The association also remained significant after adjusting for BMI (OR: 1.99, 95% CI: 1.55–2.56).

To evaluate the impact of severity of hyponatremia on the risk of fractures, we categorized the lowest serum sodium into tertiles as follows: tertile 1: serum sodium > 133 but mEq/L, tertile 2: serum sodium 130 to 133 mEq/L and tertile 3: serum sodium < 130 mEq/L and applied logistic regression analyses. Compared to patients in tertile 3 (most severe hyponatremia), patients in tertile 2 (OR: 0.88, 95% CI: 0.55–1.39) and tertile 1 (OR: 0.69, 95% CI: 0.45–1.04) had no statistical differences for the risk of fracture indicating that severe hyponatremia is not a pre-requisite for fracture risk and rather relatively milder degree of hyponatremia may attribute significant fracture risk.

### 3.4. Exploratory analyses (Table 3)

In univariate logistic regression analysis, chronic prolonged hyponatremia of at least 180 days was associated with higher odds of hip fracture (OR 2.65, 95% CI 2.18–3.22). In a multivariate model adjusted for comorbidities and medications, chronic prolonged hyponatremia of at least 180 days remained associated with higher odds of hip fracture

**Table 3**
Association between hyponatremia[a] and risk of hip fracture.

| | n | Odds ratio | 95% Confidence intervals |
|---|---|---|---|
| Unadjusted analyses | | | |
| At least 1 occurrence | 5751 | 1.60 | 1.41, 1.81 |
| At least 2 occurrences ≥90 days apart | 5751 | 2.44 | 2.07, 2.89 |
| At least 2 occurrences ≥6 months apart | 5751 | 2.65 | 2.18, 3.22 |
| Adjusted analyses | | | |
| Model 1[b] | | | |
| At least 1 occurrence | 5751 | 1.08 | 0.89, 1.30 |
| At least 2 occurrences ≥90 days apart | 5751 | 1.31 | 1.01, 1.70 |
| At least 2 occurrences ≥6 months apart | 5751 | 1.45 | 1.08, 1.95 |
| Model 2[c] | | | |
| At least 1 occurrence | 4968 | 1.03 | 0.84, 1.30 |
| At least 2 occurrences ≥90 days apart | 4968 | 1.36 | 1.04, 1.78 |
| At least 2 occurrences ≥6 months apart | 4968 | 1.51 | 1.11, 2.05 |
| Stratified analyses | | | |
| Osteoporosis, present | | | |
| At least 1 occurrence | 656 | 2.37 | 1.73,3.27 |
| At least 2 occurrences ≥90 days apart | 656 | 2.45 | 1.60,3.74 |
| At least 2 occurrences ≥6 months apart | 656 | 2.33 | 1.44,3.77 |
| Osteoporosis, absent | | | |
| At least 1 occurrence | 5095 | 1.47 | 1.28, 1.69 |
| At least 2 occurrences ≥90 days apart | 5095 | 2.38 | 1.98, 2.87 |
| At least 2 occurrences ≥6 months apart | 5095 | 2.63 | 2.12,3.23 |
| Falls, present | | | |
| At least 1 occurrence | 1309 | 1.02 | 0.80, 1.30 |
| At least 2 occurrences ≥90 days apart | 1309 | 1.57 | 1.14, 2.16 |
| At least 2 occurrences ≥6 months apart | 1309 | 2.01 | 1.37, 2.96 |
| Falls, absent | | | |
| At least 1 occurrence | 4442 | 1.55 | 1.22,1.97 |
| At least 2 occurrences ≥90 days apart | 4442 | 1.76 | 1.25, 2.47 |
| At least 2 occurrences ≥6 months apart | 4442 | 1.64 | 1.13, 2.39 |
| Age, ≤ 70 years | | | |
| At least 1 occurrence | 655 | 2.84 | 1.86, 4.33 |
| At least 2 occurrences ≥90 days apart | 655 | 4.02 | 2.66, 6.09 |
| At least 2 occurrences ≥6 months apart | 655 | 4.06 | 2.59, 6.37 |
| Age, > 70 years | | | |
| At least 1 occurrence | 5096 | 1.51 | 1.32, 1.73 |
| At least 2 occurrences ≥90 days apart | 5096 | 2.24 | 1.86, 2.70 |
| At least 2 occurrences ≥6 months apart | 5096 | 2.44 | 1.96, 3.03 |

[a] Defined as ≤135 mmol/L.
[b] Model 1- adjusted for comorbidities and medications listed in Table 1.
[c] Model 2- adjusted for comorbidities and medications listed in Table 1 and for laboratory parameters that were statistically different between cases and controls.

(OR 1.45, 95% CI 1.08–1.95). A single episode of hyponatremia was associated with higher odds of hip fracture in univariate analysis (OR 1.60, 95% CI 1.41–1.81); however, the association was not significant in a multivariate model adjusted for comorbidities and medications (OR 1.08, 95% CI 0.89–1.30).

## 4. Discussion

This study suggests that chronic prolonged hyponatremia is a potential novel risk factor for hip fracture in elderly patients with CKD, after adjustment for comorbidities, medications and laboratory parameters. The chronicity of hyponatremia appears to be a key factor in determining fracture risk, as a single episode of hyponatremia was not associated with increased fracture risk in a multivariate adjusted model. Hip fracture risk in patients with chronic prolonged hyponatremia was increased in stratified analysis of patients both with and without osteoporosis. Similarly, chronic prolonged hyponatremia remained as a significant risk factor for hip fracture in stratified analysis of patients with and without a history of falls. More importantly, the association between chronic prolonged hyponatremia and hip fracture was consistent across the age strata of > 70 years (OR: 2.24, 95% CI: 1.86–2.70) and equal to or < 70 years (OR: 4.02, 95% CI: 2.66–6.09) supporting the potential impact of hyponatremia on bone health independent of age groups. As elderly patients are particularly predisposed to chronic hyponatremia and complications from chronic hyponatremia, we believe that our findings have direct conceivable relevance to clinical care of these patients. It is also notable that majority of patients had mild hyponatremia, an abnormality that may not typically receive attention in the current clinical practice.

Hyponatremia is the most common electrolyte disorder encountered in clinical practice [18], and it is more frequent in the elderly [19]. Mild chronic hyponatremia has traditionally been regarded as a benign asymptomatic condition. However, data from large population and animal studies have linked mild chronic hyponatremia to increased risk of osteoporosis and fractures [20–22]. A recent meta-analysis of 12 studies found a statistically significant association between hyponatremia fracture risk and osteoporosis [23]. Prior studies have found increased risk of major osteoporotic fractures despite controlling for potential confounders including osteoporosis and medications [24,25]. In a recent paper, proton pump inhibitors (PPIs) were associated with hip fracture events, in patients with ESKD on hemodialysis [26]. In the present study, use of PPI was higher among cases than controls, yet hyponatremia continued to be a significant risk factor for hip fractures after adjustment. Furthermore, in patients with normal renal function, we found that mild chronic hyponatremia was also associated with hip fractures in adjusted models [15]. The present study confirms this finding and advances the concept of chronic prolonged hyponatremia as a novel risk factor in patients with CKD.

Falls are common especially in elderly CKD patients [27], which is very likely to be one of the major causes of increased hip fracture risk in this population. Muscle wasting [28], frailty [29], and dementia [30] are potential contributors to the elevated risk of falling among CKD patients. We noted elderly CKD patients with hip fractures had 10 times more falls than those without fractures and chronic prolonged hyponatremia was also significantly more frequent in cases than controls (21% versus 10%). Recent data have now revealed that mild chronic hyponatremia is associated with unsteady gait and falls. Renneboog, et al. [31] evaluated the incidence of falls among elderly patients admitted to the emergency department with asymptomatic chronic hyponatremia compared to matched controls with normonatremia. The incidence of falls was 21.3% in the hyponatremic group compared to 5.3% in the controls, with an adjusted OR of falls in patients with hyponatremia of 67 (95% CI: 7.5–607). The authors also evaluated the mechanism of falls in hyponatremic patients, by performing several attention and gait tests in adults with chronic asymptomatic hyponatremia and tested them again following the correction of hyponatremia. The hyponatremic group demonstrated more severe unstable gait and attention impairment compared to those with moderate alcohol consumption. The attention and gait abnormalities completely reversed following the correction of hyponatremia.

A possible mechanism to explain the added risk of fracture with chronic hyponatremia is perturbed bone quality due to chronically low sodium concentration. Bone quality can be understood as an umbrella term that describes the set of characteristics that influence bone strength [32]. Osteocytes have emerged as key regulators of bone strength. The lacunar-canalicular network of bone contains osteocytes and their dendritic extensions, which form an interconnected network which allow for intercellular communication and are believed to serve as the mechano-sensors that coordinate the processes of bone modeling and remodeling as they are also connected with osteoblast-like cells at the matrix surface [33]. In an animal model of aging, age-related bone changes analogous to those in humans were observed [34]. These bone changes were associated with a dramatic reduction in osteocyte dendrite number and cell density. Reduced dendricity preceded decreased osteocyte number, suggesting dendrite loss may trigger loss of viability. Patients and mice with CKD show impaired osteocyte maturation, and osteocyte differentiation is needed for the formation of a full osteocyte dendritic network [35,36]. CKD has been suggested as a model of accelerated aging [37] and chronic hyponatremia has been shown to exacerbate multiple manifestations of senescence in rats [38]. Thus, we postulate that chronic hyponatremia, through a process similar to aging, could exacerbate the reduction in osteocyte dendrite number and cell density reducing bone quality.

Our study has several limitations. As an observational study of clinical practice, our study is susceptible to residual confounding as we relied on the information of the database to identify potential confounders. Data to calculate BMI was not frequently registered in the database. Most of the CKD patients in this study had stage 3 CKD (84%), with little representation of patients in more advanced stages. In the future, studies to investigate fracture risk and effects of chronic hyponatremia in patients with more advanced CKD, including those dependent on dialysis are needed. Data regarding osteoporosis severity or number of falls were not available, limiting assessments across the spectrum of patients with different intensities of these co-morbidities.

In conclusion, chronic prolonged hyponatremia is a risk factor for hip fracture in elderly patients with CKD. Thus, prevention and treatment of hyponatremia presents as opportunity as an unaddressed, potentially modifiable risk factor in this population. Future studies that examine whether hip fracture rates can be attenuated by correction of hyponatremia in elderly patients with CKD are needed.

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## Contribution of each author to the manuscript

S.U.N. and J.C.A. designed the study; S.U.N., A.L.N., D.B. and J.C.A. analyzed the data; S.U.N., A.L.N. and J.C.A. made the figure and tables; S.U.N. A.L.N. and J.C.A. drafted the paper; all authors made contributions during the writing and revision of the manuscript; all the authors approved the final version of the manuscript.

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