Association between Serum Calcium Level and Fracture Risk among Hospitalized Adults: A Case Control Study

Jen-Tzer Gau1,2*, Osman Perez1, Masato Nakazawa2,3, Brian C Clark1,2, Tzu-Cheg Kao4

1Department of Geriatric Medicine/Gerontology, Ohio University Heritage College of Osteopathic Medicine, USA
2Department of Biomedical Science, Ohio University Heritage College of Osteopathic Medicine, USA
3Office of Research and Grant, Ohio University Heritage College of Osteopathic Medicine, USA
4Department of Preventive Medicine and Biometrics, Uniformed Services University of the Health Sciences, USA

Abstract

Objectives: It is unclear whether the association between lower serum calcium and fracture risk is confounded by lower serum albumin. The purpose of this study is to determine the association between serum calcium levels and fracture risk in the consideration of potential confounders including albumin levels.

Methods: A case-control study of hospitalized adults aged 50 years or older was conducted in a community hospital of Southeast Ohio between 2006 and 2012. Patients were excluded if they had keto acidosis, bicarbonate <16 mmol/L, calcium levels ≥11.0 mg/dL, creatinine ≥3.5 mg/dL, and fractures related to motor vehicle accidents. Cases (N=335: hip fractures=148, non-hip fractures=187) were those diagnosed with fracture(s) as identified by radiography. Controls (N=1,036) were patients without the diagnosis of new fracture, but admitted to the hospital during 2008.

Results: Case and control groups had similar mean serum calcium levels (8.83±0.49 vs. 8.85±0.51 mg/dL). However, higher serum calcium level emerged as a significant negative risk factor for fractures of all types (adjusted odds ratio [OR] =0.58, 95% CI=0.40-0.85) when potential confounders (including albumin) were adjusted for. Higher calcium level remained significantly associated with a lower risk for hip fracture (adjusted OR=0.50, 95% CI=0.31-0.83), but was not significantly associated with non-hip fracture (adjusted OR=0.65, 95% CI=0.42-1.03) with adjustment of confounders.

Conclusions: This case-control study suggested that lower serum calcium level was significantly associated with a higher risk for fractures of all types as well as for hip fractures independently of serum albumin levels after adjusting for other confounders among hospitalized adult patients.

ABBREVIATIONS

CHF: Congestive Heart Failure; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; GI: Gastrointestinal; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; PPI: Proton Pump Inhibitor; OR: Odds Ratio.

INTRODUCTION

Calcium is important for bone health as it is one of the main building blocks for bone [1]. Inadequate dietary calcium intake is associated with osteoporosis and increased fracture risk [2], and calcium supplementation helps to maintain bone mineral density (BMD) and reduces bone resorption [3-6]. However, it is uncertain whether calcium supplementation alone reduces fracture risk [3,5-8].

Patients with fractures often have a poor nutritional status. More specifically, case-control studies have shown that patients with hip fractures are often malnourished [9], have lower concentrations of serum calcium [10,11], 25-hydroxy (OH)
vitamin D [10-13], and albumin [9-12], [14,15], and often have evidence of secondary hyperparathyroidism [10,11]. However, whether calcitriotropic hormones are associated with hip and non-spine fractures in older adults is still controversial [16].

Serum calcium measurement is often one of the steps in assessing an individual’s calcium homeostasis [17]. Approximately 50% of total calcium is bound ionically to negatively charged proteins (predominately albumin and immunoglobulins); therefore, clinicians often use serum albumin in adjusting total calcium concentration to determine whether a patient has hypocalcaemia in clinical practice [17]. It is presently unclear whether the association between lower serum calcium levels and fracture risk is confounded by serum albumin levels [10,11] as previous studies that have shown that fractured patients had lower mean serum calcium levels did not explore further whether the association was confounded by lower serum albumin level [10,11]. Accordingly, the purpose of this study was to investigate the association between serum calcium levels and fracture risk in the consideration of adjusting for serum albumin levels among other risk factors in adult patients who were hospitalized for either surgical or medical management of new fractures. We hypothesized that lower serum calcium levels are independently associated with higher fracture risk among middle-aged and older adults.

METHODS

Patients and setting

Data were retrieved from a community hospital in Athens, Ohio, which is located in Southeast Ohio. This hospital is the largest in respective county and provides ~ 85,000 residents first-line access to an emergency department (ED) and hospitalization services. Because this hospital is not a trauma center, the majority of moderate to severe motor-vehicle-related fractures are referred out. This study was approved by the Ohio University Institutional Review Board.

Inclusion and exclusion criteria

Adults aged 50 years or older were all eligible for medical record screening. Patients with the following conditions were excluded from data analysis: metabolic disorders such as ketoacidosis, bicarbonate levels less than 16 mmol/L, and advanced renal failure (creatinine levels ≥ 3.5 mg/dL) as the above conditions impose an acidic blood environment that may alter serum calcium homeostasis; calcium levels ≥11.0 mg/dL, and those who suffered a fracture related to a motor vehicle accident (MVA) or pathological fracture (due to bone or metastatic cancers), death during the hospital stay, ventilator dependent respiratory failure, and incomplete medical record. Those patients who were re-admitted during the same year were reviewed once.

Identification of fracture cases and control subjects

For fracture cases, data were retrieved from medical records between January 1, 2006 and June 30, 2012. Eligible patients who were hospitalized for at least 24 hours were initially identified by the diagnostic codes of fractures of all sites (800 to 829) by International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM)). Three hundred seventy nine newly diagnosed fracture cases were identified and confirmed by radiographic studies on admission, and 44 patients were excluded as they met the exclusion criteria (MVA [n=30]; metabolic disorders [n=8]; advanced renal disease [n=6]). Thus, 335 patients (hip fracture cases N=148; non-hip fracture N=187) were included in the final statistical analysis. Patients with both hip and non-hip fracture diagnoses (n=4) were analyzed as hip fracture cases. The diagnosis of vertebral fractures (n=35) was based on discharge diagnosis along with the radiographic report while the acuity of its nature for each case was not confirmed. The remaining non-hip fractures were long bone (n=139) and short/flat bone fractures (n=13).

For the controls, data were obtained from a dataset of those patients aged 50 years or older who were hospitalized without the newly diagnosed fracture(s) between January 1, 2008 and December 31, 2008 [18]. Briefly, the control group was selected as follows: all hospitalized patients aged 50 or older was initially selected by all diagnostic codes (from 0 to 9999 of ICD-9-CM). After excluding those who met the exclusion criteria and newly fracture diagnosis, 1,036 patients were grouped as the control group.

Data Collection and Measurement

All data were recorded on standardized paper forms and all medical records under study were reviewed and verified for accuracy. The following variables were recorded: age, sex, education, smoking status, medical diagnosis, medication use prior to admission, discharge diagnosis, and admission blood test results (i.e., serum albumin, creatinine, calcium levels, electrolytes) obtained on the first set of blood tests. All blood tests were performed by standardized procedures for routine laboratory tests at the hospital. Total serum calcium concentration was measured by the SYNCHRON® System(s) by indirect potentiometry utilizing a calcium ion selective electrode in conjunction with a sodium reference electrode. The analyzer used during the study time period was a Beckman Coulter instrument. Total serum calcium concentration (normal range: 8.4 to 10.5) was reported as mg/dL by the laboratory.

Medication use prior to admission was based on the medication reconciliation forms and physician’s notes (use vs. non-use). Vitamin B12 supplementation was recorded as “yes” if oral daily dose was 500 mcg or above or receiving cyanocobalamin injection at least 1,000 mcg quarterly. Co-morbidity (such as diabetes, chronic obstructive pulmonary disease or COPD, and atrial fibrillation) was the documented event or existing condition prior to the study period. Patients with a prior stroke or neurologic conditions such as Parkinson’s disease or hemiplegia were recorded together as “prior stroke or neurologic deficits”.

Data Analysis

Mean with standard deviation (SD) and percentage were used to report continuous and discrete variables, respectively. To analyze the association between all fractures (i.e., hip fractures and non-hip fractures) and risk factors, we used binary logistic
regression models to estimate odds ratio (OR) and its 95% confidence interval (CI). Fractures of all types were further decomposed into non-hip and hip fractures and were analyzed by multinomial logistic regression models, which compared hip and non-hip fractures versus controls simultaneously. To evaluate the contributions of different types of risk factors, we grouped conceptually similar factors into blocks and entered them hierarchically (i.e., a new model retains all factors in the previous model): Model (M) 1 = serum calcium; M2 = serum albumin; M3 = serum creatinine and electrolytes (bicarbonate and potassium); M4 = current medication use (vitamin B12 supplements, proton-pump inhibitor [PPI], bisphosphonate, antipsychotic drugs, and diuretics); and M5 = demographics (age, gender), current smoking status, living setting (community vs. nursing home), and medical history (i.e., history of diabetes mellitus [DM] and prior stroke or neurologic deficits). We evaluated the model fit with pseudo-$R^2$ (or max-rescaled $R^2$) and the fit improvement with the log-likelihood ratio (LR) test and by the change in pseudo-$R^2$ ($\delta$-$R^2$). Statistical significance was set at a level of 0.05. Statistical software packages, PC SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used to perform the statistical analyses.

RESULTS

Characteristics of fracture cases and control patients

Fracture cases were significantly older (79.1±11.0 vs. 71.3±12.8 years), mainly female (81% vs. 60%), and the majority of fractured patients (98%) resided in the community. Fracture cases had a higher percentage of prior stroke(s) and/or neurologic deficits (19% vs. 12%), and had a lower percentage of diabetes (29% vs. 36%) and COPD (22% vs. 31%) compared to the controls (all $p$ values < 0.05; Table 1).

With regards to medication use, fracture cases had a lower percentage of using diuretics (35% vs. 43%) and steroid inhalers (7% vs. 12%), but had a higher percentage of using bisphosphonates (12% vs. 5%) and calcium supplements (21% vs. 16%) (all $p$ values < 0.05). As expected, the control group had

| Table 1: Characteristics of fracture cases’ and controls of hospitalized adults. |
|-------------------------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Variables                                      | All fractures    | Hip fracture     | Non-hip fracture | Controls         | P value          |
| Mean age (yr) (SD)                             | (N=335)          | (N=148)          | (N=187)          | (N=1036)         | (all fracture vs. control) |
| Mean age (yr) (SD)                             | 79.1 (11.0)      | 81.4 (9.7)       | 77.3 (11.7)      | 71.3 (12.8)      | $<0.001$         |
| Female                                         | 272 (81%)        | 113 (76%)        | 159 (85%)        | 626 (60%)        | $<0.001$         |
| Race: white                                    | 333 (99%)        | 140 (100%)       | 185 (99%)        | 101 (98%)        | 0.038            |
| Community-dwelling                             | 296 (88%)        | 125 (84%)        | 171 (91%)        | 769 (75%)        | $<0.001$         |
| Smoking status                                 |                    |                  |                  |                  |                  |
| Ever (current and past)                        | 135 (45%)        | 62 (47%)         | 73 (44%)         | 433 (50%)        | 0.177            |
| Current smoker                                 | 46 (14%)         | 17 (11%)         | 29 (16%)         | 153 (15%)        | 0.461            |
| Medical diagnosis                              |                    |                  |                  |                  |                  |
| Diabetes mellitus                              | 98 (29%)         | 35 (24%)         | 63 (34%)         | 378 (36%)        | 0.016            |
| Depression                                     | 80 (24%)         | 36 (24%)         | 44 (24%)         | 297 (29%)        | 0.088            |
| Prior stroke or neurologic deficits            | 63 (19%)         | 33 (22%)         | 30 (16%)         | 127 (12%)        | 0.003            |
| Atrial fibrillation                            | 50 (15%)         | 22 (15%)         | 28 (15%)         | 134 (13%)        | 0.353            |
| Medication use                                 |                    |                  |                  |                  |                  |
| PPI                                            | 114 (34%)        | 46 (31%)         | 68 (37%)         | 365 (35%)        | 0.714            |
| Diuretics (all types)                          | 118 (35%)        | 43 (29%)         | 75 (40%)         | 444 (43%)        | 0.015            |
| Vitamin B12 Supplement*                        | 39 (12%)         | 20 (14%)         | 19 (10%)         | 84 (8%)          | 0.049            |
| Calcium supplement                              | 71 (21%)         | 27 (18%)         | 44 (24%)         | 168 (16%)        | 0.035            |
| Anti-psychotics                                | 29 (9%)          | 12 (8%)          | 17 (9%)          | 88 (8%)          | 0.903            |
| Anti-depressants                               | 123 (37%)        | 41 (28%)         | 82 (44%)         | 360 (35%)        | 0.490            |
| Benzodiazepine/ anxiolytics                     | 64 (19%)         | 32 (22%)         | 32 (17%)         | 240 (23%)        | 0.116            |
| Narcotics                                      | 97 (29%)         | 35 (24%)         | 62 (33%)         | 308 (30%)        | 0.811            |
| Bisphosphonates                                | 41 (12%)         | 19 (13%)         | 22 (12%)         | 56 (5%)          | $<0.001$         |
| Steroid inhalers                               | 24 (7%)          | 6 (6%)           | 15 (8%)          | 120 (12%)        | 0.023            |
| Length of hospital stay (d)(SD)                 | 4.5(2.5)         | 5.1(2.4)         | 4.1 (2.5)        | 4.2 (2.7)        | 0.051            |
| Discharge diagnosis                            |                    |                  |                  |                  |                  |
| Pneumonia                                      | 15 (5%)          | 9 (6%)           | 6 (3%)           | 152 (15%)        | $<0.001$         |
| COPD acute exacerbation                        | 2 (1%)           | 0 (0%)           | 2 (1%)           | 121 (12%)        | $<0.001$         |
| Acute CHF                                      | 6 (2%)           | 5 (3%)           | 1 (1%)           | 114 (11%)        | $<0.001$         |
Central

Fractures of all types, before or after adjusting for serum albumin

Model fit (p < 0.01). Calcium level was negatively associated with hip fracture risk (adjusted OR=0.50, 95% CI=0.31-0.83), but was not significantly associated with non-hip fracture (adjusted OR=0.65, 95% CI=0.42-1.03) as shown in Model 5 logistic regression model data analysis (Table 3).

Risk factor profiles of hip and non-hip fractures

As shown in Table 3, risk factor profiles between hip and non-hip fracture were different. Diuretic use and history of prior stroke or neurologic deficit were significant risk factors for hip fracture, but not for non-hip fracture. On the other hand, concentration of serum creatinine, bicarbonate, and potassium and antipsychotic drug use were significantly associated with non-hip fracture (p<0.05), but not with hip fracture (p>0.1).

**DISCUSSION**

This retrospective case-control study demonstrated that lower serum calcium level was significantly associated with a higher risk for fractures of all types as well as for hip fractures independently of serum albumin levels after adjusting for other confounders among hospitalized adult patients. Our data revealed that one mg/dL higher serum calcium level was significantly associated with 42% lower risk for all-types fracture as well as 50% lower risk for hip fracture, and 35% lower risk for non-hip fracture (p<0.01, not statistically significant) after adjustment of confounders.

At least two studies have shown that patients with fractures have significantly lower mean serum calcium levels compared to controls [10,11]. LeBoff and colleagues reported that patients with an acute hip fracture who were hospitalized had significantly lower serum calcium and 25(OH)D levels as well as lower albumin levels compared to controls (patients having elective joint replacement with osteoporosis), and half of them had evidence of secondary hyperparathyroidism [10]. Their study excluded patients on medications that may affect bone health, patients living in nursing homes, and co-morbidities, which were all included in our data analysis. The study by Dhanwal and colleagues revealed similar findings when compared to the controls (patients’ relatives and visitors to the hospital) [11]. However, the study by Sakuma and colleagues did not reveal a difference in mean serum calcium levels between patients with hip fracture and controls while patients with hip fracture had lower serum albumin and 25(OH)D levels [12].

Our case-control study showed a similar mean serum calcium level between fracture cases and controls without the adjustment of confounders. However, with the adjustment of confounding factors, the association between serum calcium levels and the risk of fractures was strengthened. Further research is needed to confirm these findings and to identify other potential confounders that may influence the relationship between serum calcium levels and fracture risk.
### Table 2: Odds ratio (OR) with 95% confidence intervals (CI) for fractures of all types versus controls among hospitalized adults.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt; (OR with 95% CI)</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt; (OR with 95% CI)</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt; (OR with 95% CI)</th>
<th>Model 4&lt;sup&gt;d&lt;/sup&gt; (OR with 95% CI)</th>
<th>Model 5&lt;sup&gt;e&lt;/sup&gt; (OR with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium (mg/dL)</td>
<td>0.93 [0.71-1.21]</td>
<td>0.84 [0.61-1.13]</td>
<td>0.86 [0.63-1.18]</td>
<td>0.84 [0.61-1.16]</td>
<td>0.58 [0.40-0.85]&lt;sup&gt;**&lt;/sup&gt;</td>
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<tr>
<td>Albumin (g/dL)</td>
<td>1.24 [0.92-1.67]</td>
<td>1.19 [0.88-1.61]</td>
<td>1.22 [0.91-1.66]</td>
<td>1.36 [0.95-1.96]&lt;sup&gt;*&lt;/sup&gt;</td>
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<tr>
<td>Creatinine (mg/dL)</td>
<td>0.63 [0.45-0.86]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.66 [0.47-0.92]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.61 [0.41-0.9]&lt;sup&gt;**&lt;/sup&gt;</td>
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<tr>
<td>Bicarbonate (mmol/L)</td>
<td>0.95 [0.92-0.99]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.96 [0.92-1]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.96 [0.91-1.01]</td>
<td></td>
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<tr>
<td>Potassium (mmol/L)</td>
<td>1.16 [0.89-1.51]</td>
<td>1.13 [0.86-1.47]</td>
<td>1.21 [0.89-1.66]</td>
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<td>Vitamin B12 supplement</td>
<td></td>
<td></td>
<td></td>
<td>1.76 [1.11-2.74]&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.56 [0.92-2.64]&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>PPI use</td>
<td>0.88 [0.65-1.18]</td>
<td>1.02 [0.73-1.43]</td>
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<tr>
<td>Bisphosphonate use</td>
<td>2.11 [1.3-3.41]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1.54 [0.89-2.64]</td>
<td></td>
<td></td>
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<tr>
<td>Antipsychotic use</td>
<td>1.07 [0.65-1.73]</td>
<td>2.22 [1.24-3.94]&lt;sup&gt;**&lt;/sup&gt;</td>
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<tr>
<td>Diuretic use</td>
<td>0.82 [0.6-1.11]</td>
<td>0.66 [0.46-0.93]&lt;sup&gt;**&lt;/sup&gt;</td>
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<tr>
<td>Age</td>
<td></td>
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<td></td>
<td>1.09 [1.07-1.11]&lt;sup&gt;**&lt;/sup&gt;</td>
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<tr>
<td>Gender (female)</td>
<td></td>
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<td></td>
<td>3.18 [2.16-4.76]&lt;sup&gt;**&lt;/sup&gt;</td>
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<td>Current smoking status</td>
<td></td>
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<td></td>
<td>1.98 [1.23-3.18]&lt;sup&gt;**&lt;/sup&gt;</td>
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<tr>
<td>DM</td>
<td></td>
<td></td>
<td></td>
<td>1.11 [0.77-1.58]</td>
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<tr>
<td>Prior stroke or neurologic deficits</td>
<td>1.87 [1.19-2.92]&lt;sup&gt;**&lt;/sup&gt;</td>
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<tr>
<td>Living in the community (vs. nursing home)</td>
<td>7.08 [4.36-11.84]&lt;sup&gt;**&lt;/sup&gt;</td>
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</table>

Note: p< 0.10, p<0.05, p**<0.01, p***<0.001

<sup>a</sup> Model 1 was no adjustment.
<sup>b</sup> Model 2 was adjusted for serum albumin.
<sup>c</sup> Model 3 was adjusted for serum creatinine and electrolyte measurements (bicarbonate and potassium) in addition to the variables included in model 2.
<sup>d</sup> Model 4 was adjusted for current medication use (vitamin B12 supplements, proton-pump inhibitor (PPI), bisphosphonate, antipsychotic drugs, and diuretics) in addition to the variables included in Model 3.
<sup>e</sup> Model 5 was adjusted for demographics and medical history (age, gender, smoking status, history of diabetes mellitus (DM), history of prior stroke or neurologic deficits, and living arrangement [community vs. nursing home]) in addition to the variables included in the Model 4. The case numbers in fractures of all types and controls became 268 and 803, respectively, in the final model data analysis as we excluded subjects with missing values in any of the variables in the models. We evaluated model fit with pseudo-$R^2$ and the fit improvement with the log-likelihood ratio (LR) test and the change in pseudo-$R^2$ ($\delta R^2$).

**Abbreviations:** CI: Confidence Interval; DM: Diabetes Mellitus; OR: Odds Ratio; PPI: Proton-Pump Inhibitor

### Table 3: Odds ratio (OR) with 95% confidence intervals (CI) for non-hip and hip fractures versus controls in multi-nominal logistic regression models among hospitalized adults.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Model 3&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Model 4&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Model 5&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>1.01 [0.71-1.43]</td>
<td>0.84 [0.58-1.21]</td>
<td>0.91 [0.61-1.35]</td>
<td>0.92 [0.62-1.39]</td>
<td>0.96 [0.67-1.36]</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>1.25 [0.85-1.85]</td>
<td>1.22 [0.81-1.83]</td>
<td>1.2 [0.81-1.77]</td>
<td>1.18 [0.79-1.77]</td>
<td>1.23 [0.83-1.81]</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.51 [0.33-0.80]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.77 [0.51-1.17]</td>
<td>0.49 [0.31-0.79]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.89 [0.58-1.38]</td>
<td>0.47 [0.28-0.79]&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>0.94 [0.89-0.99]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.97 [0.92-1.03]</td>
<td>0.93 [0.88-0.98]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.99 [0.93-1.04]</td>
<td>0.94 [0.88-1.1]&lt;sup&gt;**&lt;/sup&gt;</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>1.40 [1.00-1.97]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.94 [0.65-1.34]</td>
<td>1.38 [0.98-1.94]&lt;sup&gt;**&lt;/sup&gt;</td>
<td>0.9 [0.62-1.13]</td>
<td>1.48 [1.01-2.16]&lt;sup&gt;**&lt;/sup&gt;</td>
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</table>

Note: p< 0.10, p<0.05, p**<0.01, p***<0.001

<sup>a</sup> Model 1 was no adjustment.
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<sup>e</sup> Model 5 was adjusted for demographics and medical history (age, gender, smoking status, history of diabetes mellitus (DM), history of prior stroke or neurologic deficits, and living arrangement [community vs. nursing home]) in addition to the variables included in the Model 4. The case numbers in fractures of all types and controls became 268 and 803, respectively, in the final model data analysis as we excluded subjects with missing values in any of the variables in the models. We evaluated model fit with pseudo-$R^2$ and the fit improvement with the log-likelihood ratio (LR) test and the change in pseudo-$R^2$ ($\delta R^2$).

**Abbreviations:** CI: Confidence Interval; DM: Diabetes Mellitus; OR: Odds Ratio; PPI: Proton-Pump Inhibitor
Vitamin B12 supplement & 1.59 [0.89-2.84] & 1.98 [1.11-3.53] & 1.51 [0.79-2.89] & 1.63 [0.85-3.12] \\
PPI use & 0.91 [0.62-1.34] & 0.84 [0.55-1.26] & 1.05 [0.69-1.58] & 0.99 [0.63-1.55] \\
Bisphosphonate Use & 2.02 [1.1-3.72] & 2.23 [1.21-4.11] & 1.49 [0.77-2.87] & 1.67 [0.85-3.26] \\
Antipsychotic Use & 1.1 [0.58-2.08] & 1.05 [0.55-2.03] & 2.48 [1.2-5.1] & 2.04 [0.96-4.34] \\
Diuretic use & 1.13 [0.77-1.66] & 0.56 [0.37-0.86] & 0.92 [0.6-1.41] & 0.43 [0.27-0.7] \\
Age & 1.08 [1.06-1.1] & 1.11 [1.08-1.13] & 1.001 & 0.004 & 0.024 & 0.054 & 0.296 \\
Smoking status & 1.24 [0.8-1.9] & 0.96 [0.59-1.56] & 1.39 [0.79-2.46] & 2.52 [1.47-4.5] \\
Pseudo-R\(^2\) & 0.001 & 0.004 & 0.024 & 0.054 & 0.296 \\
LR Test & NA & 1.99 & 17.01 & 25.75 & 231.85 \\
Df & NA & 2 & 6 & 10 & 12 \\
P & NA & 0.37 & 0.009 & 0.004 & <0.001 \\
Delta-R\(^2\) & NA & 0.003 & 0.020 & 0.030 & 0.242 \\

Note: \(p < 0.10, p' < 0.05, p'' < 0.01, p''' < 0.001\)

The above result remained significant and consistent for fractures of all types among those patients residing in the community (i.e., after excluding nursing home patients) in our study.

One may ask what are the main confounders (or suppressors) for the association between serum calcium levels and fracture risk in our study. We performed a series of separate multiple logistic regression model data analyses, and we had identified that with the inclusion of just five factors for the adjustment (i.e., age, gender, community residence status, current smoking, and serum albumin levels), the adjusted OR for the association was 0.60 (95% CI: 0.42-0.85; data not shown in table), almost as the same as the result of the Model 5 in Table 2. The above finding was also observed in the association between serum calcium levels and hip fracture with the adjustment of these five factors (adjusted OR=0.54, 95% CI: 0.33-0.87).

Because serum calcium levels in patients with acute fracture were measured after the fracture event, it is unclear what role the fracture event played on the dynamic changes of blood calcium levels in our study. Sato and colleagues examined the changes in bone and calcium metabolism following hip fracture in elderly patients [19]. Their study compared serum biochemical indices of bone and calcium metabolism in twenty elderly subjects shortly after suffering a hip fracture to the early recovery period with those measured in twenty healthy age-matched controls. The results demonstrated that increased bone resorption, and decreased bone formation, and hypercalcemia were present by 1 week following the hip fracture. Another small study of twelve older people with acute hip fracture reported no increased corrected mean serum calcium levels between admission and day 3 after admission [20]. If the above observations are correct
then the impact of fracture on serum calcium levels is minimal and unlikely to affect the results of our study.

Other risk factors for overall fracture reported here have also been reported by other studies [21,22], including previous stroke [22] and antipsychotic drug use [23]. The association between diuretic use and a lower risk of hip fracture as shown in Table 3 was interesting because our study included both thiazide and loop diuretics in the data analysis. Thiazide use has been reported associated with a reduction in risk of hip fracture [24-27] possibly by reducing age-related bone loss by decreasing urinary calcium excretion [24]. However, there was also a concern that initiation of diuretic therapy transiently increased the risk of hip fracture [28]. Regarding the association between serum creatinine and non-hip fracture (Table 3), we speculate that it may be explained by the mechanism of injuries that led to the fracture (e.g., compression fracture of spines vs. traumatic fall leading to hip fracture) as older adults with lower serum levels of calcium which is correlated with lower muscle mass [29,30] may be vulnerable to different types of fractures.

It has been suggested that the pathophysiology of osteoporotic hip fracture vs. non-hip fracture may proceed differently [31]. It has been reported that up to 60 percent of patients with hip fractures had one or more biomarkers indicating a negative calcium balance [10]. Furthermore, the Women's Health Initiative clinical trial demonstrated a trend of benefits of calcium and vitamin D supplementation toward the reduction in the incidence of hip fracture (and improvement on BMD of total hip), but no benefit at other skeletal sites [32]. On the other hand, a meta-analysis of three clinical trials of calcium monotherapy in women showed consistent adverse trends in hip fracture risk (with relative risk 1.50, 95% CI 1.06-2.12) [31]. Our study finding that lower serum calcium level was a significant risk factor for hip fracture but not for non-hip fracture also supports the possible different pathophysiology of hip vs. non-hip fractures.

As clinicians assess whether a patient having a low blood calcium concentration (or hypocalcaemia), it is a common practice to “correct” the measured total calcium level with individual’s serum albumin concentration [17]. Therefore, a patient with a low serum calcium level may become normocalcemic in the context of a proportionally low serum albumin level. As shown by several studies that serum albumin concentration is an important determinant for bone health [12-14,15], lower serum albumin levels may indicate a poor nutritional status or physical disability that may have placed these patients susceptible to adverse clinical outcomes [such as physical de-conditioning or subsequent fall]. Our study’s main finding that lower total blood calcium concentration was associated with higher fracture risk independently of serum albumin levels after adjustment for other confounders suggested that lower serum calcium concentration itself was a risk factor for fracture regardless of serum albumin status. It is quite possible that patients with lower serum calcium levels may have impaired functioning of nerves and muscles [17] that could lead to falls and subsequent fractures in addition to its contribution to osteoporosis.

Our study has several limitations that should be mentioned. First, the calcium level was measured only once at the time of admission, which may not represent the baseline status of each individual. Second, the controls used for this study were from hospitalized adults during a specified one-year period whereas fracture cases were obtained from duration of seven and a half consecutive years. Because of the difference in the study years, the case and control patients may have underlying unmeasured confounders (such as demographic shifts, practice changes or new treatment available for osteoporosis during the period) in our study. It has been suggested by one study that community controls may comprise a more appropriate control group in case-control studies of hip fracture in the elderly [33]. Third, our study did not have measurements of calcium metabolism profiles (such as concentrations of ionized calcium, 25(OH) vitamin D, and parathyroid hormone) in determining the underlying mechanism for low calcium levels. Additionally, our study also included the medications that may have affected serum calcium levels, including bisphosphonates. However, the effect of oral bisphosphonate therapy on serum calcium level was considered minimal despite a statistically significant decrease on the mean calcium level of patients receiving the bisphosphonate treatment as shown by a retrospective cohort study [34]. On the other hand, our study also included oral bisphosphonate therapy in the adjustment of data analysis. Fourth, our study did not have information in BMD among study patients, which was not possible to obtain due to the limitation of a case-control study. However, our study included serum creatinine level in the data analysis. Serum creatinine level has been shown to reflect muscle mass [29], and lower serum creatinine was shown independently associated with low BMD in subjects with normal kidney function [30]. Fifth, our study did include four patients who had serum calcium level above 10.5 mg/dL (but below 11 mg/dL). The underlying causes of these four patients were not determined; however, no diagnosis of hyperparathyroidism was made in these four patients. Sixth, potential confounders that are associated with fracture risks such as previous fracture history and physical activity were not available and, therefore, not included for the adjustment of data analysis. Lastly, the study patient population was mainly white and from one community, which may limit the overall generalizability of our findings.

CONCLUSION

This retrospective case-control study demonstrated that lower serum calcium level was significantly associated with a higher risk for fractures of all types as well as for hip fractures independently of serum albumin levels after adjusting for other confounders among hospitalized adult patients. Our study suggested that one mg/dL higher calcium level was associated with 42% lower risk for all-types fracture as well as 50% lower risk for hip fracture after adjustment of confounders. The profiles of risk factors for hip and non-hip fractures as shown by our study may suggest a different pathophysiology of hip and non-hip fracture.

AUTHORS’ CONTRIBUTIONS

JTG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: JTG, OP, TCK.
Acquisition of data: OP, JTG.
Analysis and interpretation of data: OP, JTG, MN, BC, TCK
Preparation of the manuscript: JTG, OP, MN, BC.
Statistical analysis: JTG, MN, TCK
All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

Drs. Gau, Perez, Nakazawa, Clark, and Kao reported no financial conflicts with this research topic and contents.

REFERENCES


