Proton pump-inhibiting drugs, calcium homeostasis, and bone health

Matthew J Wright, Deborah D Proctor, Karl L Insogna, and Jane E Kerstetter

Proton pump inhibitors (PPIs) are commonly used drugs, several of which are available without a prescription. Two recent studies have demonstrated increased hip fracture rates associated with PPI use. Theoretically, PPIs could impair intestinal calcium absorption resulting in increased rates of bone loss and a greater risk of fragility fracture.

© 2008 International Life Sciences Institute

INTRODUCTION

Proton pump inhibitors (PPIs) are the most potent acid-suppressing drugs available and millions of individuals are currently using these medications.¹ Common diseases of the gastrointestinal (GI) tract such as gastroesophageal reflux disease (GERD), and gastric and duodenal ulcers are treated with PPIs.¹² PPIs specifically target the H⁺, K⁺ ATPase pump of the parietal cell, and thus, inhibit the final step in the release of protons into the stomach. Other drugs that suppress acid production, such as histamine H₂ receptor antagonists (H₂RA), block only selective pathways involved in the activation of the parietal cell, resulting in less effective suppression of acid production. PPIs are protonatable weak bases, which concentrate in acidic spaces with a pH less than 4. Apart from the resorption lacunae of osteoclasts, the secretory canaliculus of a stimulated parietal cell is the only known compartment in the body with a pH this low; therefore, PPIs accumulate in the canaliculus and are converted to the active inhibiting compound tetracyclic sulfenamide. Sulfenamide is a permanent cation that binds to cysteines on the surface of the acid pump and reduces membrane permeability to prevent exchange of hydrogen and potassium ions.² These medications are available by prescription and have also been available over the counter since late 2002.³ The long-term effects of PPI use on calcium and bone homeostasis have not been extensively studied. However, this is a potentially significant question because those who are prescribed PPIs are older and consume them chronically, oftentimes for years and decades. While this review focuses solely on the effects of PPIs on calcium absorption, impaired gastric acid production may also decrease the intestinal absorption of other cations such as iron, vitamins such as B₁₂, and even macronutrients such as protein as summarized in a recent review.⁴ Changes in intestinal flora, intestinal motility and, as discussed below, pH-dependent changes in nutrient bioavailability may all play a role in altered nutrient absorption in the absence of adequate gastric acid production.

An emerging concern about chronic PPI therapy is the effect it may have on calcium absorption. In particular, it is suggested that stomach acid and the slightly acidic milieu of the proximal duodenum are both required to free ingested calcium from the food matrix making it available for absorption. Consistent with this idea, Recker et al.⁵ demonstrated more than 20 years ago that absorption of calcium (from calcium carbonate) was impaired in fasting achlorhydric patients. If normal gastric acid production is required for calcium ionization and subsequent absorption, then the millions of individuals using PPIs may be at increased risk for calcium malabsorption, negative calcium balance and potentially bone loss.

PPI, H₂RA, AND BONE FRACTURES

Long-term PPI use and the risk of hip fracture was recently examined in a large retrospective, case-control
study by Yang et al.\textsuperscript{1} Individual cases and controls were selected from the United Kingdom’s General Practice Research Database (GPRD), which contains medical records from 98% of the population. Subjects were excluded if 1) at the time of enrollment, there were less than 365 days of follow up available for analysis, 2) the patient was younger than 50 years, 3) the patient had sustained a hip fracture before the start or within the first year of follow up, or 4) took \(\text{H}_2\text{RA}\) or PPI therapy during non-database follow up time. Cases included all individuals with hip fractures at least one year after initial database entry. The analysis included up to 10 non-fracture controls for each study subject with a hip fracture. The 192,028 subjects receiving PPI therapy and the 187,686 patients who received \(\text{H}_3\text{RAs}\) as well as 1.4 million patients not taking acid-suppressing medications were included in the primary analysis while only those patients taking \(\text{H}_3\text{RAs}\) and the non-users were included in a secondary analysis. Among the non-drug users there were 10,834 incident hip fractures. Among the PPI users there were 2,722 incident hip fractures.

Conditional logistic regression was used to determine all unadjusted and adjusted odds ratios (OR), and confidence intervals (CI) were used to interpret them.\textsuperscript{1} Potential confounders such as BMI, medication use, health, age, and sex were considered in calculating adjusted odds ratios (AOR). These investigators found that PPI treatment for greater than 1 year resulted in an increase in hip fracture risk with an OR of 1.82 (95\% CI 1.67–2.00) as compared to acid suppressor nonusers; when adjusted for confounding variables the AOR was 1.44 (95\% CI 1.30–1.59). The PPI group considered in these analyses also contained \(\text{H}_2\text{RA}\) users. When only long-term PPI users were compared to acid suppression nonusers the AOR for hip fracture was 1.62 (95\% CI 1.41–1.89). There was a significant increase in the risk of hip fracture with long-term \(\text{H}_2\text{RA}\) use as well, with an AOR of 1.34 (95\% CI, 1.14–1.38). Additionally, there was a strong dose-dependent increase in hip fracture risk observed with both acid-suppressing medication such that long-term, high-dose PPI use was associated with the highest risk of hip fracture (AOR, 2.65; 95\% CI, 1.80–3.90). Importantly, Yang et al.\textsuperscript{1} controlled for the diagnosis of GERD in the multivariate analysis, thereby mitigating the confounding effect of the disease state itself.

Similar findings were reported by Vestergaard et al.\textsuperscript{6} from a long-term, case-controlled study that found PPI use was associated with an increased risk of fracture. Subjects were sampled from a relatively homogeneous, Caucasian Danish population. Participant data were obtained from the National Board of Health, the Danish Medicines Agency, and the National Bureau of Statistics. Together, these three large databases contained information on all hospital and mental hospital inpatient and outpatient visits, as well as outpatient clinics and emergency room visits. Data were gathered on all drugs sold at pharmacies throughout the country from 1996 to 2000. Eligible cases consisted of all individuals who suffered a fracture in the calendar year 2000 (\(n = 124,655\)). For comparison, three control subjects per case were selected using incidence density sampling and matched by age and sex. Among cases and controls, the use of acid-suppressing medication (both PPIs and \(\text{H}_2\text{RAs}\)) was the major variable of interest.

Conditional logistic regression was used to analyze the association between fracture risk and acid-suppressing medication.\textsuperscript{6} Potential confounding variables such as comorbidity, medications interfering with bone metabolism, socioeconomic status, and prior fracture were controlled for in calculating AORs. Vestergaard et al.\textsuperscript{6} found that PPI use was associated with an increased risk of any fracture, as well as increased risk of hip and spine fracture compared to PPI nonuse. However, \(\text{H}_2\text{RA}\) use (when compared to \(\text{H}_2\text{RA}\) nonuse) was associated with a surprising reduction in the overall risk of hip and spine fracture.

It is possible that the different conclusions regarding \(\text{H}_2\text{RA}\) use and fracture reported by Yang et al.\textsuperscript{1} and Vestergaard et al.\textsuperscript{6} lie in the duration of observation. The study by Yang et al.\textsuperscript{1} included data spanning 13 years as compared to only five years in the Vestergaard et al.\textsuperscript{6} study. Perhaps more prolonged exposure is necessary to see effects on fracture risk with less potent acid inhibitors such as \(\text{H}_2\text{RAs}\) which, on average, only block 70\% of gastric acid production while PPI use suppresses acid production by up to 97\%.\textsuperscript{7,8} However, an earlier case-controlled study, Grisso et al.\textsuperscript{9} demonstrated that \(\text{H}_2\text{RA}\) use for only three years was associated with an increased risk of hip fracture in men. Despite the conflicting conclusions about the risk of fracture with \(\text{H}_2\text{RA}\) use, these two very large, long-term, case-controlled studies\textsuperscript{1,6} both report a strong association of PPI use with fracture risk.

**GASTRIC ACID SUPPRESSION, CALCIUM ABSORPTION, AND BONE HEALTH**

One mechanism by which PPIs may affect fracture incidence is by impairing intestinal calcium absorption.\textsuperscript{1} Without an acidic environment in the stomach and upper small bowel, calcium may be retained in its food matrix preventing absorption.\textsuperscript{5} Impaired calcium absorption leads to compensatory physiologic responses including secondary hyperparathyroidism. Secondary hyperparathyroidism refers to the increase in circulating levels of parathyroid hormone (PTH) when serum levels of ionized calcium fall (as would occur with reduced
efficiency in intestinal calcium absorption). In an attempt to rectify the deficit in calcium absorption, PTH activates a variety of compensatory mechanisms, one of which is to increase the rate of osteoclastic bone resorption. Over time, this would lead to an increase in the rate of skeletal turnover as well as a reduction in bone mass, both of which increase the risk of fracture. Unfortunately, there are no data available on the effect of long- or short-term PPI use on serum PTH levels in healthy adults.

Similarly, there are no long-term studies on the effects of PPIs on calcium absorption. Table 1 summarizes the short-term studies examining the effect of gastric acid suppression on calcium absorption\textsuperscript{10–15} and bone turnover.\textsuperscript{16,17} Graziani et al.\textsuperscript{10} studied calcium absorption in patients with end-stage renal disease. Dialysis patients receiving 4–5 hours of standard bicarbonate hemodialysis three times per week were studied on and off omeprazole (20 mg every 8 h) in a crossover fashion. The increment in blood calcium following a test meal was used as an index of calcium absorption. The investigators found that the post-meal increment in plasma calcium, measured as area under the curve, was significantly reduced with PPI treatment compared to PPI nonuse, but no direct measure of intestinal calcium absorption was made.

Hardy et al.\textsuperscript{12} performed a similar study in hemodialysis patients and also concluded that gastric acid played an important role in calcium absorption. Sixteen patients on hemodialysis were studied in a crossover design. Subjects ingested calcium carbonate before and with meals for two months, and repeated the intervention again while also taking omeprazole. These investigators found significantly lower corrected plasma calcium levels during the PPI therapy. However, as with the Graziani\textsuperscript{10} study, Hardy et al.\textsuperscript{12} did not directly measure intestinal calcium absorption. The well-recognized disturbances in the PTH-1-alpha hydroxylase axis as well as in skeletal metabolism that occur with end-stage renal disease make it difficult to interpret these data as unequivocal evidence that PPIs directly affect calcium absorption. Nonetheless, each study showed a decrease in plasma calcium when the only experimental procedure that changed was the addition of PPI use; an observation consistent with a fall in intestinal calcium absorption.\textsuperscript{10,12}

In a study of eight healthy men, Graziani et al.\textsuperscript{11} also examined the effects of omeprazole on indices of calcium absorption using a crossover study design. Subjects were placed on a low calcium diet for seven days to stimulate calcium absorption. Following a test meal containing 1 g of calcium, post-prandial plasma calcium rose significantly in subjects taking placebo but did not change when the same subjects ingested omeprazole. The integrated increment in postprandial serum calcium and total urinary calcium excretion were significantly higher when the study subjects consumed placebo compared to omeprazole. The investigators attributed these differences to reduced calcium absorption when the subjects took omeprazole.\textsuperscript{11}

O’Connell et al.\textsuperscript{13} recently reported the effects of omeprazole on fractional calcium absorption in 18 women over the age of 65 years using \textsuperscript{45}Ca tracer methodology and a randomized crossover study design. Fractional calcium absorption was directly determined from 1 g of \textsuperscript{45}Ca-labeled calcium carbonate given without food. The average absolute difference in fractional calcium absorption within study subjects between placebo and omeprazole treatments was –5.5%, representing an average percent decline in absorption efficiency of 41%.\textsuperscript{13} While this is the first study to directly measure the effect of a PPI on fractional calcium absorption using isotopes in normal subjects, it is limited by the fact that the subjects were fasting. Further, the administered calcium was calcium carbonate, which may be less effectively absorbed in the fasting state.\textsuperscript{5}

In contrast to these data, Serfaty-Lacrosniere et al.\textsuperscript{14} could find no effect of omeprazole on calcium absorption using whole gut lavage methodology. This method of measuring intestinal absorption involves initial cleansing of the GI tract by lavage. Following a 4-hour rest period, a test meal is provided. Twelve hours later, a second GI lavage is undertaken and all unabsorbed minerals from the test meal are collected. Thirteen healthy subjects were studied using this approach and assigned to receive either 40 mg/d of omeprazole (n = 5) or to act as controls and receive no drug (n = 8). Subjects in both the control and omeprazole groups underwent two experimental studies, one in which hydrochloric acid (HCL) was exogenously provided through a nasogastric tube and one without exogenous HCL. Fractional calcium absorption during omeprazole therapy (with and without HCL) was not significantly different from that observed in the control group.\textsuperscript{14} In this study, the placebo-treated subjects had a median age of 59 years, while the omeprazole subjects had a median age of 39 years.\textsuperscript{14} The recognized age-dependent decline in calcium absorption might be one reason a difference in fractional absorption was not found between the two groups.

The effects of H\textsubscript{2}RA on intestinal calcium absorption have not been studied extensively. However, Bo-Linn et al.\textsuperscript{15} examined the effects of cimetidine on calcium absorption using the intestinal lavage technique in normal volunteers and a crossover study design. They found no effect of cimetidine on calcium absorption.

Few studies have been conducted that directly determine the effect of PPIs on skeletal metabolism. In one study, Mizunashi et al.\textsuperscript{16} sought to determine if PPIs could suppress bone resorption in vivo by inhibiting the osteo-
Table 1  Summary of short-term studies examining the effect of acid-suppressing medications on intestinal calcium absorption, rates of skeletal turnover and bone mass.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Duration of exposure to study drug</th>
<th>No. of subjects</th>
<th>Subject characteristics</th>
<th>Medication used to block acid</th>
<th>Outcome measured</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium absorption studies</td>
<td>Graziani et al.⁹</td>
<td>Crossover</td>
<td>3 days</td>
<td>30</td>
<td>Dialysis; men and women, 34–65 y</td>
<td>Omeprazole, 20 mg Q 8 h</td>
<td>Increment in serum Ca</td>
</tr>
<tr>
<td></td>
<td>Graziani et al.¹⁰</td>
<td>Crossover, placebo-controlled</td>
<td>3 days</td>
<td>8</td>
<td>Healthy men, 36–52 y</td>
<td>Omeprazole, 20 mg Q 8 h</td>
<td>Increment in serum Ca</td>
</tr>
<tr>
<td></td>
<td>Hardy et al.¹¹</td>
<td>Crossover</td>
<td>2 months</td>
<td>16</td>
<td>Dialysis, men and women, mean age 61.4 ± 12.1 y</td>
<td>Omeprazole, 20 mg QD</td>
<td>Increment in serum Ca</td>
</tr>
<tr>
<td></td>
<td>O’Connell et al.¹²</td>
<td>Randomized, placebo-controlled</td>
<td>7 days</td>
<td>18</td>
<td>Healthy women, 65–89 y</td>
<td>Omeprazole, 20 mg QD</td>
<td>Fractional intestinal Ca absorption using Ca isotopic tracers</td>
</tr>
<tr>
<td></td>
<td>Serfaty-Lacrosniere et al.¹³</td>
<td>Randomized, placebo-controlled</td>
<td>17 days</td>
<td>13</td>
<td>Healthy men and women, 30–71 y</td>
<td>Omeprazole, 40 mg QD</td>
<td>Calcium absorption using gastrointestinal lavage</td>
</tr>
<tr>
<td></td>
<td>Bo-Linn et al.¹⁴</td>
<td>Crossover</td>
<td>1 day</td>
<td>6</td>
<td>Healthy men and women 21–36 y</td>
<td>Cimetidine, 600 mg on experimental day</td>
<td>Calcium absorption using gastrointestinal lavage</td>
</tr>
<tr>
<td>Skeletal turnover and BMD studies</td>
<td>Mizunashi et al.¹⁵</td>
<td>Randomized</td>
<td>8 weeks</td>
<td>32</td>
<td>History of gastric ulcer</td>
<td>Omeprazole, 20 mg QD</td>
<td>Serum Ca, PTH, TRAP, AP, osteocalcin; urinary Ca, hydroxyproline</td>
</tr>
<tr>
<td></td>
<td>Kocsis et al.¹⁶</td>
<td>Pre versus post omeprazole treatment</td>
<td>2 weeks</td>
<td>34</td>
<td>Pediatric patients with GERD or H. pylori infection</td>
<td>Omeprazole, 20 mg QD</td>
<td>Serum Ca, C telopeptide, osteocalcin, AP; urinary Ca</td>
</tr>
<tr>
<td></td>
<td>Adachi et al.¹⁷</td>
<td>Case-controlled</td>
<td>&gt;2 years</td>
<td>33</td>
<td>History of gastric and duodenal ulcers</td>
<td>Cimetidine, ranitidine, or famotidine</td>
<td>Bone density by DXA</td>
</tr>
</tbody>
</table>

Abbreviations: AP, alkaline phosphatase; DXA, dual energy x-ray absorptiometry; GERD, gastroesophageal reflux disease; PTH, parathyroid hormone; TRAP, tartrate-resistant acid phosphatase.
clast proton pump. Thirty-two patients with a history of gastric ulcers on a maintenance dose of H$_2$RAs, were all switched to omeprazole or no treatment. Urinary hydroxyproline (a marker of bone resorption) and urinary calcium decreased after omeprazole treatment as compared to those subjects who discontinued all acid-suppressing medication. Paradoxically, serum tartrate-resistant acid phosphatase, serum alkaline phosphatase, and osteocalcin all increased with omeprazole treatment. A rise in these three serum markers would generally be taken to reflect an increase in bone turnover. It is difficult to reconcile these apparently conflicting changes in serum and urine markers of bone turnover in response to the PPI.

Kocsis et al. found no effect of omeprazole use on bone turnover in 45 children with GERD or dyspepsia treated with 20 mg/day of omeprazole for 2 weeks. Compared to pretreatment values, there were no significant changes in any marker of bone turnover or urinary calcium pre- versus post-omeprazole treatment. However, the high rate of bone turnover normally observed in childhood may have masked any effect of PPIs on the skeleton.

In the only study to determine the impact of acid suppression on bone density, Adachi et al. compared bone mineral density (BMD) in chronic H$_2$RA users and healthy controls and there were no significant differences in BMD between the two groups.

**CONCLUSION**

In general, the studies summarized above are limited by several factors including disease states that could influence mineral metabolism in and of themselves (such as renal failure or achlorhydria) or the use of indirect or invasive methods of assessing calcium absorption. One approach would be to conduct a randomized, double-blind, placebo-controlled study using a paired study design in normal women aged 40–70 years old (the population at greatest risk for fracture). The study should use normal food as the source of calcium and isotopic tracer technology to measure both calcium absorption and skeletal kinetics in the same subject while taking a PPI or placebo. This would at least allow researchers to determine if PPIs affect physiologic calcium absorption in normal individuals, although it would not address this issue in disease states or with chronic PPI use.

It is clear that well designed intervention trials are needed to address this important question particularly given the widespread use of chronic PPI therapy among the elderly and the increasing prevalence of osteoporosis and hip fracture in this same population.

**Acknowledgment**

KLI and JEK contributed equally to this work.

**Funding.** This publication was made possible in part of by grant number SUL 1RR024139 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research.

Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at http://www.ncrr.nih.gov/. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp. This work was also supported by a grant from the United States Department of Agriculture (USDA 2006-35200-16568).

**Conflict of interest.** The authors have no potential conflicts of interest.

**REFERENCES**


