Chronic PPI Therapy and Calcium Metabolism

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Abstract

Proton pump inhibitors (PPIs) have been widely used since their introduction in the late 1980s because they are highly effective for acid-related conditions. However, some recent epidemiological studies have suggested a positive association between PPI therapy and the risk of osteoporotic fractures. The potential mechanisms underlying this association may be related to the physiologic effects of chronic acid suppression on calcium metabolism. First, chronic hypergastrinemia induced by PPI therapy may lead to parathyroid hyperplasia, resulting in increased loss of calcium from the bone. Second, profound gastric acid suppression may reduce the bioavailability of calcium for intestinal absorption. I will review the published evidence regarding these potential links and discuss their clinical implications.

Keywords

Proton pump inhibitors; hypergastrinemia; hyperparathyroidism; calcium absorption; osteoporosis; PPIs and calcium metabolism; PPI-induced hypergastrinemia; Parathyroid glands; Bone metabolism; Calcium balance

Introduction

Osteoporotic fractures represent an enormous public health issue worldwide. In the United States alone, an estimated 10 million Americans aged over 50 years have osteoporosis, while another 34 million have low bone mass. Each year, an estimated 1.5 million people in the United States suffer an osteoporosis-related fracture, an event that can lead to decreased quality of life and increased risk of death [1, 2].

PPIs are potent acid-suppressing medications that have proven efficacy against acid-related diseases. It is becoming increasingly common for patients to take these drugs on a chronic
basis to prevent recurrent GERD symptoms, avoid potential complications such as peptic stricture and Barrett’s esophagus, and prevent complications related to NSAIDs [3, 4]. Furthermore, because they are perceived to be safe, these agents are often prescribed inappropriately, and patients are maintained on treatment for extended periods of time. As a result, PPIs have become one of the most commonly prescribed classes of medication since their introduction in the late 1980s, with a high prevalence of chronic use [5]. With the recent availability of both over-the-counter and generic formulations, PPI use continues to escalate [6].

Since 2006, a number of epidemiologic studies have evaluated the association between PPI therapy and risk of osteoporotic fractures [7–16]. While some of these studies reported a positive association, others failed to demonstrate this effect. Since none of these studies was a randomized controlled trial, unmeasured confounding may be a potential source of bias. Furthermore, most of these studies did not account for nutritional status and use of vitamin/calcium supplements. Nevertheless, the US Food and Drug Administration issued a warning about this potential association and called for more research on this issue [17]. The primary potential mechanisms underlying this association may be related to the physiologic effects of chronic acid suppression on calcium metabolism. In this review, I will evaluate the published evidence regarding these mechanistic links.

**Potential mechanisms Linking PPIs and Calcium Metabolism**

The main physiologic change induced by PPI therapy is profound suppression of gastric acid secretion. Gastric acid suppression results in hypergastrinemia, and may cause malabsorption of calcium. Both hypergastrinemia and calcium malabsorption may negatively influence bone and mineral metabolism, at least in part through induction of hyperparathyroidism (Figure 1).

**PPI therapy and PTH levels**

Parathyroid hormone (PTH) is the principal calcium-regulating hormone and plays a pivotal role in calcium and bone metabolism. As the primary calcitropic hormone, PTH maintains serum calcium concentrations by stimulating bone resorption, increasing renal tubular calcium re-absorption, and stimulating renal calcitriol production, which leads to increased active transport of calcium in the upper intestine. PTH also plays a major role in bone remodeling, and recent evidence has shown that PTH has both catabolic and anabolic effects on the skeleton [18, 19]. PTH stimulates bone formation when given intermittently and stimulates bone resorption when administered continuously. In patients with hyperparathyroidism caused by hyperplasia or an adenoma, PTH secretion is inappropriately and persistently elevated in relation to the serum calcium concentration. In these settings, PTH induces excessive bone remodeling characterized by a rate of bone resorption that exceeds the rate of bone formation [20].

**PPI-induced Hypergastrinemia, the Parathyroid Glands, and Bone Metabolism**

Because PPIs are such potent inhibitors of acid secretion, they cause a significant increase in serum gastrin. By blocking gastric acid output and raising gastric pH, the PPIs inhibit somatostatin release from mucosal D cells located in the gastric antrum. Somatostatin
suppresses antral G cells, which release the hormone gastrin. Thus, PPIs indirectly cause hypergastrinemia by suppressing somatostatin release, which normally acts as a brake on gastrin release. Omeprazole, for example, causes a 2- to 6-fold increase in serum gastrin levels in 80–100% of the patients receiving long-term therapy [21–25]. About 20–30% of patients can have serum gastrin levels greater than 500 ng/L (>6× upper limit of normal) [23, 24, 26]. In most cases, the increase occurs during the first few months of PPI therapy and plateaus thereafter [22]. However, in two studies of GERD patients with a long follow-up period (up to 42 months), trends towards steadily increasing serum gastrin levels were observed [24, 27].

In addition to its well-known trophic effects on gastrointestinal tissues [28, 29], hypergastrinemia has been shown to have a stimulatory effect on the parathyroid glands. In rats, hypergastrinemia induced by antral exclusion led to hyperparathyroidism and increased parathyroid gland volume and weight, owing to hyperplasia of the parenchymal cells [30]. Furthermore, 5 weeks of omeprazole administration induced hypergastrinemia and resulted in hyperplasia and hypertrophy of the parathyroid glands and increased PTH gene expression in chickens [31, 32]. The omeprazole-evoked increase in the weight of the parathyroid glands and PTH gene expression was not affected by concurrent administration of ergocalciferol at a dose that increased serum calcium [32]. These changes were also coupled with reduced femur density in the chickens [32]. Furthermore, direct infusion of gastrin increased the weight of the parathyroid glands and reproduced the effect of omeprazole on PTH gene expression in the same animal model, suggesting that the trophic effect of omeprazole on the parathyroid glands was mediated through the induction of hypergastrinemia [32]. The same mechanism may also be responsible for the osteopenia observed in young rats that received long-term omeprazole treatment [33].

The only adult human study that has assessed the effect of PPI therapy on serum levels of PTH was conducted 18 years ago among a small group (7 males, 12 females; mean age 67, standard deviation 13 years) of Japanese patients with gastric ulcers [34]. The study showed that, after 8 weeks of omeprazole therapy, the mean PTH level increased by 28% compared to baseline among these patients. The increased PTH level was also accompanied by increases in several markers of bone turnover including serum osteocalcin, alkaline phosphatase, and tartrate-resistant acid phosphatase. However, urinary excretion of hydroxyproline and calcium decreased. Several factors made it difficult to definitively interpret these data. PTH was only measured at a single time-point, which may be misleading as it does not reflect the dynamic effect of PTH over a 24-h period. Second, the dose of omeprazole was only 20 mg po qd. The effect of such a relatively small dose of omeprazole on gastric acid secretion and gastrin level is uncertain. Gastrin levels were not measured. Furthermore, the patients were maintained on only 500–700 mg of calcium intake daily during the study, which could have affected PTH levels. Finally, the bone turnover markers used in this study, particularly urinary hydroxyproline excretion, had poor specificity, which might have contributed to the modest changes in bone remodeling observed. Despite these limitations, this study provided preliminary evidence supporting an effect of PPI therapy on PTH and bone turnover in humans.
PPI and Calcium Balance

Calcium is the major cation of bone mineral in human. The typical calcium content of the adult human body is 1 kg. Nearly all is found in the skeleton. After peaking at 35–40 years, bone mass decreases in both sexes. The decline occurs at an accelerated rate in women during the first 10 years after menopause. Thereafter, the rate of calcium decreases is comparable in both men and women.

Calcium balance in the elderly

A negative calcium balance in mid- to late adulthood has been postulated to be the main cause of osteoporosis. Calcium absorption is the most important determinant of calcium balance [35]. In fact, decreased calcium absorption has been shown to directly lead to increased risk of greater bone resorption and osteoporotic fractures, particularly vertebral and hip fractures, among elderly women [36, 37]. Elderly patients are also less able to increase calcium absorption efficiency to compensate for low calcium intake compared to younger individuals [35]. Furthermore, it is well reported that the dietary calcium intake among Americans is low. Using 1999–2000 NHANES data, Ervin et al. found median daily calcium intake from food sources for adults women aged ≥60 years to be 563 mg, well below the national adequate intake of 1,200 mg [38].

Calcium Supplementation

Given the low dietary intake of calcium, calcium supplementation is widely advocated to achieve the target calcium intake in the elderly population. Data from the 1999–2000 National Health and Nutrition Examination Survey indicated that nearly 20 % of Americans aged ≥60 years take calcium supplements [39]. The prevalence increased to 33.5 % when calcium-containing antacids were included. Calcium carbonate is the most commonly used form of calcium supplement. Calcium carbonate is the most commonly used and the least expensive form of calcium supplement, at approximately one-third the cost of the more expensive food source, which includes skim milk and calcium-fortified orange juice made from frozen concentrate. Cost is a consideration for many patients. Another reason for its popularity is that calcium carbonate supplements provide greater amounts of elemental calcium and consequently require fewer tablets than other forms of calcium.

Calcium Absorption

The absorption of ingested calcium takes place primarily in the small bowel and to a lesser extent in the colon. The absorption occurs via two mechanisms. Active transport of calcium occurs in the proximal duodenum. It is a transcellular process that requires metabolic energy and is dependent on vitamin D. Passive calcium transport of calcium involves paracellular diffusion down a chemical gradient. It occurs throughout the length of the small intestine.

If the calcium content of the chyme is relatively low, much of the calcium in solution is absorbed in the duodenum by active transport. Passive calcium transport accounts for most calcium absorption when calcium intake is adequate or high, largely in the more distal portions of the small intestine.
**Calcium Solubility and Gastric Acid**

In addition to factors such as intake, vitamin D status, and estrogen level, gastric acid-mediated solubilization of dietary calcium salts has been thought to be essential for the absorption of calcium [35, 40–42]. An acidic environment in the stomach facilitates the release of ionized calcium from insoluble calcium salts such as calcium carbonate [41]. Even if a calcium salt is precipitated in the small bowel, some calcium ions are still in solution. In rats, Chonan et al. have shown that gastrectomy or omeprazole therapy led to malabsorption of calcium phosphate and impaired BMD [43, 44]. Lowering gastrointestinal pH with dietary lactate reversed the calcium malabsorption in both cases [43, 44]. In human subjects with normal acid secretion, insoluble calcium salts (e.g., calcium carbonate), taken with or without food, are absorbed at similar rates as soluble calcium salts [41]. In contrast, in achlorhydric patients, the absorption of insoluble calcium salts such as calcium carbonate taken under fasting conditions virtually does not occur, while soluble calcium salts such as calcium citrate are still absorbed normally [42, 45]. Impaired calcium absorption has also been observed in post-gastrectomy patients [46, 47]. By contrast, in a study of young healthy subjects given an H2RA, the absorption rates of calcium carbonate co-ingested with a slightly acidic meal were comparable whether the gastric pH was titrated to 7.4 or 3.0 [48]. However, since the in vivo intragastric titration procedure was carried out by measuring the pH of small aliquots of gastric content obtained every few minutes, it is unclear if the pH of the entire gastric content could be maintained at a neutral level instantaneously throughout the experiment. Therefore, it is doubtful that this experiment could reproduce a pH milieu comparable to PA or PPI-induced profound acid suppression. Taken together, most of the existing data suggest gastric acid may be important for absorption of insoluble calcium salts such as calcium carbonate.

**Meal Effect and Calcium Absorption**

It has been reported that calcium carbonate absorption can be stimulated by coadministration with a meal [42, 49]. Therefore, it is routinely recommended that calcium carbonate supplements be taken with a meal. However, the meal used in the study of older PA patients contained juices and had a pH of 5.8, while the other study was conducted in young healthy subjects with presumably normal acid secretion [42, 49]. Furthermore, in a cross-over trial conducted in a group of apparently healthy post-menopausal females, Heller et al. found that the bioavailability of calcium carbonate given with a meal is still significantly lower than that of calcium citrate [50]. Compared with calcium carbonate, calcium citrate provided a 46 % greater peak-basal variation and 94 % higher change in AUC for serum calcium and a 41 % greater increment in urinary calcium. Moreover, the decrement in serum PTH concentration from baseline was significantly greater after calcium citrate. The authors postulated that one possible explanation for these findings may be that some of these apparently healthy post-menopausal women had impaired gastric acid secretion due to asymptomatic atrophic gastritis, which is prevalent in the elderly population. Regardless of whether the meal effect is true, it is often difficult for many individuals to take the supplement with meals.

*Curr Gastroenterol Rep*. Author manuscript; available in PMC 2015 August 05.
**PPI therapy and Calcium Absorption**

Six studies have directly examined the effect of PPI therapy upon calcium absorption (Table 1) [51–56]. Four of the studies suggested that omeprazole therapy may impair dietary calcium absorption [51–54]. Three of the studies relied on demonstrating decreased plasma total calcium concentration with omeprazole therapy as evidence of calcium malabsorption [51–53]. However, this method has been criticized for having a low signal-to-noise ratio [57]. This may be a relevant concern here because two of the studies were conducted among hemodialysis patients whose plasma calcium levels may have been influenced by other factors [52, 53]. The remaining three studies were specifically designed to examine the effect of PPI therapy on calcium absorption [54, 55]. Using a whole gut lavage method, Serfaty-Lacroixniere et al. reported that, among young healthy subjects, full-dose omeprazole therapy did not reduce the absorption of calcium contained in milk and cheese [55]. The null result may be related to the meal effect and the use of calcium contained in dairy products [35], which has very high bioavailability. In contrast, using a validated single oral radiotracer method, O’Connell et al. showed that among women ≥65 years of age, omeprazole at a dose of 20 mg QD taken for 7 days significantly reduced the absorption of calcium carbonate taken under fasting conditions [54]. It is unclear whether such malabsorption is reversible with co-ingestion of a meal. More recently, Hansen et al. evaluated changes in the absorption of calcium ingested with a meal among postmenopausal women related to omeprazole therapy [56]. They observed no reduction in fractional calcium absorption after 30 days of PPI therapy. However, the use of a soluble calcium salt (i.e., calcium chloride) and the inclusion of a glass of acidic orange juice with the meal made it difficult to interpret the findings. Future studies should determine whether the PPI therapy alters the fractional absorption of insoluble calcium coingested with a pH neutral meal.

**Conclusions**

A trophic effect of PPI therapy on parathyroid glands has been demonstrated in several animal models. However, its clinical relevance in human has yet to be properly investigated. It is obvious that calcium must be ionized and in solution to be absorbed. Therefore, profound acid suppression may theoretically interfere with calcium solubilization and absorption. However, the results of most of the studies on this issue are difficult to interpret or have limited clinical applicability because of methodological limitations. Using a valid approach, one study did demonstrate calcium carbonate malabsorption under fasting condition with high daily dose omeprazole. However, further studies are required to adequately evaluate the role of meal effect on the absorption of calcium carbonate in this setting.

What are the clinically implications of these data? Clearly, PPIs should only be prescribed when there is an appropriate clinical indication. Since clinical circumstances may change over time, it is also important to periodically review the clinical need for PPI therapy. Furthermore, the potential link between PPI therapy and parathyroid hyperplasia is mediated by chronic hypergastrinemia. Therefore, minimizing the duration and dose of PPI therapy should mitigate this effect. For example, on-demand PPI therapy may be a good option in GERD patients without moderate to severe erosive esophagitis. In addition, while it is quite
likely that PPI-induced hypochlorhydria can affect calcium solubility, it is clear that, when calcium intake is adequate, differences in solubility only play a minor role in the amount of calcium that is absorbed. Therefore, patients who require chronic PPI therapy should be instructed to ensure adequate daily calcium intake according to the daily recommended allowance corresponding to their age. Also, soluble calcium salts such as calcium citrate and calcium contained in milk and cheese have high bioavailability for absorption regardless of gastric pH. Therefore, if financially feasible, these can be the preferred sources of calcium for patient receiving chronic PPI therapy. If calcium carbonate must be used, the patient should be instructed to take it with a meal.

References


17. FDA. Drug safety communication: possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors. 2010


Figure 1.
Potential mechanistic links between PPI therapy and decreased bone strength
Table 1

Studies of the impact of omeprazole on calcium absorption

<table>
<thead>
<tr>
<th>Study</th>
<th>Study subjects</th>
<th>Type of calcium administered</th>
<th>Calcium absorption assay</th>
<th>Impaired calcium absorption?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graziani et al., 1995</td>
<td>Young healthy subjects</td>
<td>Meal containing calcium</td>
<td>Post-meal plasma calcium</td>
<td>Yes</td>
</tr>
<tr>
<td>Serfati-Lacrosniere et al., 1995</td>
<td>Young healthy subjects</td>
<td>Meal with calcium in dairy products</td>
<td>Whole gut lavage</td>
<td>No</td>
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<tr>
<td>Hardy et al., 1998</td>
<td>Hemodialysis patients</td>
<td>Calcium carbonate during and 5 min before meal</td>
<td>Monthly mean plasma calcium concentration</td>
<td>Yes</td>
</tr>
<tr>
<td>Graziani et al., 2002</td>
<td>Hemodialysis patients</td>
<td>Meal containing calcium</td>
<td>Post-meal plasma calcium</td>
<td>Yes</td>
</tr>
<tr>
<td>O'Connell et al., 2005</td>
<td>Healthy females &gt;65 years</td>
<td>Calcium carbonate given fasting</td>
<td>Single tracer method</td>
<td>Yes</td>
</tr>
<tr>
<td>Hansen et al., 2011</td>
<td>Healthy post-menopausal females</td>
<td>Calcium chloride given with a meal including acidic orange juice</td>
<td>Dual isotope method</td>
<td>No</td>
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</tbody>
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