The relationship between long-term proton pump inhibitor therapy and skeletal frailty

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Abstract

Proton pump inhibitors (PPIs) are a commonly prescribed class of medications. Their use has been associated with an increased rate of fractures, most notably hip fractures. However, there does not seem to be a clear association between PPI use and bone mineral density measurements, assessed by dual X-ray absorptiometry. The mechanism by which PPI use increases the risk of fractures remains unclear. This review will summarize the current evidence on this topic.

Keywords

Proton-pump inhibitors; Fractures; Osteoporosis; Fragility

Introduction

Proton pump inhibitors (PPIs) are one of the most commonly prescribed classes of medications worldwide. They are commonly used in the treatment of gastric esophageal reflux disease (GERD) and peptic ulcer disease, and serves as an effective prophylactic agent in patients treated concurrently with a non-steroidal anti-inflammatory drug (NSAID). PPIs act through irreversibly inhibiting the activity of Na⁺/K⁺/H⁺ pumps located on parietal cells of the gastric lumen, thus preventing the secretion of hydrogen ions into the gastric lumen [1]. As such, PPIs are able to raise the pH level of the gastric lumen, and prevent associated complications seen with such an acidic environment. Many patients are prescribed a PPI on a chronic basis, since GERD, the most common reason for requiring a PPI, is a chronic condition, and long-term continued therapy with a PPI is required to suppress the symptoms. PPIs, as a class, are generally regarded as a safe medication and are well tolerated by patients. The rate of drug discontinuation due to an adverse event from PPI use ranges from 1 to 2 % [2].

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Increasing evidence has revealed a number of complications associated with prolonged PPI use. These complications include an increased risk of community-acquired pneumonia [3, 4], *Clostridium difficile* infection [5, 6], vitamin B12 deficiency [7], and acute interstitial nephritis. In addition, PPIs have been associated with a negative effect on bone mineral metabolism, with a subsequent decline in bone mineral density (BMD) and an associated increase risk of fractures. This article will review the current evidence assessing the effect that PPI therapy has on BMD and fracture risk in addition to proposed mechanisms by which PPI use may have a negative impact on bone mineral metabolism.

Potential mechanisms

The exact mechanism by which PPI use results in a decline in BMD and resultant increase in fracture risk is still unclear. There are a number of proposed mechanisms by which PPIs may increase risk of fractures. It has been hypothesized that an acidic environment in the gastric lumen is necessary for effective absorption of calcium. Dietary calcium is often found in an insoluble form at a neutral pH, as it is often found bound to food proteins. However, in the setting of an acidic pH, ionized calcium becomes released from these proteins, and becomes soluble, a form that can be readily absorbed [8]. Therefore, an acidic pH environment in the gastric lumen is necessary for effective calcium absorption [9]. It has been hypothesized that the lack of acidic environment in the setting of PPI use can lead to a decrease in serum calcium, with resultant secondary hyperparathyroidism and an increase in bone resorption.

Another hypothesis is the role of increased gastrin levels on fracture risk. Long-term PPI therapy has been associated with increased levels of gastrin, which subsequently leads to hyperplasia of the enterochromaffin-like cells (ECL cells) in the gastric lumen. ECL cells can be stimulated to produce histamine. Histamine is an agent that can bind to receptors on mature and precursor osteoclasts. Binding of histamine to its receptor on osteoclasts promotes osteoclastogenesis, and thus, this may be the underlying mechanism accounting for the increase in fracture risk. Furthermore, an observational study suggested the blockade of type 1 histamine receptors on osteoclasts with an H1 receptor antagonist may have beneficial effects in reducing the rate of hip fractures (adjusted OR 0.86, 95 % CI 0.79–0.93), regardless of PPI use. This suggests that type-1 histamine may contribute to the underlying mechanism by which PPIs increase fracture risk. How great the relative impact type-1 histamine has on the overall fracture risk remains unclear.

Effect of PPI on risk of falls

Another proposed explanation for the increase in fracture risk with chronic PPI use is due to an increase in rate of falls rather than an effect that PPIs have on bone metabolism and its structural integrity. Fractures, including hip fractures, can occur in women with a normal BMD, and thus, an increase rate of falls is often attributed as the reason for fracturing in these individuals [10]. Aside from a low BMD, reduced motor function is an independent risk factor for sustaining a fracture after minimal trauma [11].

There are a number of proposed mechanisms by which PPI use may increase risk of falls, ultimately leading to an increase in fractures. Long-term PPI use has been associated with

vitamin B12 deficiency due to malabsorption, which can increase risk of falls [12]. One prospective cohort study found patients treated with PPIs were more likely to have low serum vitamin B12 levels compared to those not treated with a PPI [13]. Furthermore, this study also found patients treated with a PPI were more likely to have self-reported numbness of the feet, which can be seen in vitamin B12 deficiency, and can certainly contribute to an increased risk of falling [13]. In addition, long-term PPI use has also been associated with visual disturbances, which subsequently increases risk of falls [14].

A large case-control study of 64,399 elderly Swedish patients admitted to hospital for a fall found that use of drugs to treat peptic ulcer disease or GERD resulted in an increase risk of falling (OR 2.05, 95 % CI 1.94–2.17 in males, and OR 1.74, 95 % CI 1.67–1.81) [15]. In addition, a large prospective cohort of postmenopausal elderly women found that long-term PPI use (continuous therapy for 1 year or more) was associated with an increased risk of falls and fracture-related hospitalizations (adjusted odds ratio [AOR] = 2.17, 95 % CI 1.25–3.77 and 1.95, 95 % CI 1.20–3.16, respectively). This study also found that patients treated with long-term PPIs had an increased risk of self-reported falling (AOR = 1.51, 95 % CI 1.00–2.27) [13]. In addition, the timed up and go test, an inexpensive and easy to perform test, has been validated to predict risk of falling. Having a slow timed up and go test (>10.2 s) has been shown to be an independent risk factor for both non-vertebral and hip fractures (Hazard ratio [HR] of 1.84 and 2.48, respectively) [16]. A prospective cohort study of elderly postmenopausal women found those treated with long-term PPI therapy had a significantly slower timed up and go test performance [13]. The Romberg test, a screening clinical test for assessing falls risk, was also found to be abnormal in a higher percentage of elderly women treated with a PPI compared to those not with the medication [13].

Overall, there has been sufficient evidence linking PPI use with an increase risk of falls. The mechanism by which PPIs increase this falls risk is still uncertain.

Effect of PPIs on bone mineral density

Most of the current evidence suggests that chronic PPI use does not have a significant negative correlation with BMD changes assessed by dual-energy X-ray absorptiometry (DXA). The risk of sustaining a fracture after minimal trauma can be attributed to an increased risk of falls, but also from low BMD values (which signifies low bone quantity), and poor structural bone quality. Analysis from the prospective cohort, the Women's Health Initiative, assessed the effect of PPI use on BMD values in 161,806 postmenopausal women between the ages of 50 and 79 years. The baseline BMD values at various sites did not differ significantly between PPI users and non-users [17]. In addition, there was only a marginal decline in BMD for the total hip at the 3-year follow-up assessment seen in PPI users. There was no difference in the BMD changes at other sites between the PPI users and non-users [17].

Furthermore, the cross-sectional analysis of the Manitoba BMD database aimed to determine if long-term PPI use was associated with osteoporosis and accelerated BMD declines. This study found that PPI use was not associated with osteoporosis at baseline, determined by BMD measurements at the total hip or lumbar spine (OR 0.84; 95 % CI 0.55–

1.34 and OR 0.79; 95 % CI 0.59–1.06, respectively) [18]. In addition, longitudinal DXA measurements revealed no significant decrease in BMD seen in the long-term PPI users compared to the non-users [18].

The assessment of the Western Australia Data Linkage Service (WADLS) database also found no difference in the total hip and total body BMD seen in elderly women treated with long-term continuous PPI therapy compared to non-users [13]. Finally, a recent survey of the Study of Women's Health Across the Nation (SWAN) found no change in BMD at the lumbar spine, femoral neck, or total hip between users of PPIs, H2 receptor antagonists, or non-users [19].

Overall, the literature generally suggests that PPI use does not have a negative association on BMD values measured at multiple sites.

Effect of PPIs on fracture rates

Even though it is debatable if PPI use has a negative impact on bone structure, there is consistent evidence linking long-term PPI use to fractures. Fractures can have a significant impact on patient morbidity, and quality of life. In addition, vertebral and hip fractures also have an impact on mortality rates [20]. The association between PPI use and fractures was first reported by Yang and colleagues [21]. This was a nested case–control study conducted using the General Practice Research Database from the United Kingdom. The rate of hip fractures in PPI users was compared to those not on an acid suppression agent and to those on H2 receptor antagonists (H2RA). From 13,556 hip fractures and 135,386 controls, the adjusted odds ratio (AOR) for hip fracture associated with PPI therapy for greater than 1-year duration was 1.44 (95 % CI 1.30–1.59). There was a dose response seen, as those treated with high-dose long-term PPI had a greater risk of hip fracture (AOR = 2.65, 95 % CI 1.80–3.90).

Since this publication, a number of groups have published similar findings, associating long-term PPI use with hip fractures. A large case–control study utilizing the National Hospital Discharge Register of Denmark found 124,655 patients who sustained a fracture from January 1, 2000 to December 31, 2000 [22]. This study found patients exposed to PPI therapy had a modestly increased risk of all fractures (AOR = 1.08, 95 % CI 1.05–1.11) and a similarly increased risk for hip fractures (AOR = 1.13, 95 % CI 1.05–1.21). However, patients treated with an H1-receptor antagonist (H1RA) also had a slight increased risk of all fractures (AOR = 1.03, 95 % CI 1.01–1.06) but interestingly they had a lower risk of hip fractures (AOR = 0.86, 95 % CI 0.79–0.93). In fact, patients exposed to both PPIs and H1RAs had an overall lower rate of fractures (AOR = 0.92, 95 % CI 0.87–0.98). This observational study confirms the previously reported increase in fracture rate in patients treated with a PPI, but H1RA treatment may be a confounder on the association between PPI use and fracture risk. This finding may hint that the underlying pathogenesis by which PPI therapy is associated with an increase in fracture risk may be related to an elevated histamine level; thus, H1RA may blunt the negative histamine effects.

Further supporting the notion that there is a dose response in the relationship between PPI therapy and fracture risk [21], there is also evidence that patient adherence to PPI therapy also has an effect on fracture risk. One study assessing data from Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) program found the overall incidence of fractures was higher in PPI users than in non-users (8.7 vs 5.0 per 100 person-years, respectively) [23]. Patient adherence to PPI therapy was assessed by the proportion of days covered (PDC), ranging from 1.0 in patients with full adherence to 0.0 in patients with complete non-adherence. In patients with high adherence rates (PDC ≥ 0.80), the adjusted HR for fractures at any site relative to non-PPI users was 1.46 ($p < 0.0001$). Patients with intermediate (PDC = 0.40–0.79) and with low (PDC < 0.40) of drug adherence had an adjusted HR of 1.30 ($p = 0.02$) and 0.95 ($p = 0.75$) relative to non-users. This study demonstrated a gradient response for PPI adherence rates and risk of fractures, where patients with high compliance rates also had the highest risk of fractures, while the group with the lowest adherence rates had no statistically significant increase for fractures relative to non-users.

Finally, the Women's Health in the Lund Area (WHILA) study found that utilizing logistic regression analysis, PPIs are an independent risk factor for fractures (OR 2.53, 95 % CI 1.28–4.99) [24].

Interaction between PPIs and osteoporotic therapy

A case–control study conducted using the Korean Health Interview Review and Assessment Service database found that the adjusted odds ratio of sustaining a hip fracture was 1.71 (95 % CI 1.31–2.23) in PPI users treated concurrently with a bisphosphonate. However, the adjusted odds ratio of sustaining a hip fracture in PPI users who were not taking a bisphosphonate was 1.30 (95 % CI 1.19–1.42) [25]. In addition, among patients treated with bisphosphonate, concurrent PPI use increased the risk of sustaining an incident fracture at any site, with an OR of 1.30 (95 % CI 1.18–1.43) [26]. These results suggest that there may be an interaction between PPIs and bis-phosphonates. However, the exact mechanism of this is unclear. There have been no studies to date assessing the fracture risk in patients taking a PPI with concurrent denosumab or teriparatide therapy.

Conclusions

PPIs are a very commonly prescribed medication. Increasing risk of fractures is one adverse effect of PPIs that are often overlooked. PPI use is also often not considered when evaluating a patient's 10-year fracture risk [27]. Multiple observational studies have shown PPIs do indeed increase the risk of fractures, particularly hip fractures compared to non-users of PPIs. The reported HRs for increased risk of any fractures are typically quite modest, ranging from 1.15 to 1.43 [28, 29]. Additionally, the increase risk for hip fractures associated with PPI use was also quite modest (RR 1.30, 95 % CI 1.19–1.43) based on a meta-analysis [30]. However, given the high prevalence of patients treated with a PPI, this modest increase risk of fractures still poses a significant impact on fracture risk on a population level. In addition, there is growing evidence that PPI therapy may increase the risk of falling. Furthermore, we must not forget that falls, particularly in the elderly

population, may lead to other consequences, such as a decline in functional status, and requiring institutionalization [31].

Future research is required to further understand the underlying mechanism by which PPI use leads to a subsequent increase risk for fractures, as this area is still poorly understood and controversial. Furthermore, future efforts need focus on increasing the awareness of health-care practitioners and patients about the risk that PPIs pose to fracture risk, especially in patients in other risk factors for fractures. Effective knowledge translational strategies are required to close this care gap, which is essential given the large number of patients being prescribed a PPI for various medical conditions.

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