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Original Article

Long-Term Proton Pump Inhibitor Use and Osteoporosis Risk: A Systematic Review of Bone Mineral Density, Fracture Outcomes, and Underlying Mechanisms

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ABSTRACT

Proton pump inhibitors (PPIs) are among the most frequently prescribed medications worldwide and are widely used for the management of gastroesophageal reflux disease, peptic ulcer disease, Helicobacter pylori infection, and other acid-related gastrointestinal disorders. Although PPIs are generally considered safe and effective, concerns have emerged regarding the potential adverse effects associated with long-term use, particularly their impact on bone health and osteoporosis risk. Several epidemiological studies have reported an association between prolonged PPI therapy and decreased bone mineral density, increased risk of osteoporotic fractures, and impaired skeletal metabolism. Proposed mechanisms include reduced intestinal calcium absorption secondary to gastric acid suppression, magnesium deficiency, alterations in vitamin B12 metabolism, impaired osteoclast function, and disturbances in bone remodeling processes. However, existing evidence remains inconsistent, with some studies demonstrating significant associations while others report minimal or no clinically relevant effects after adjustment for confounding factors. This systematic review evaluates current evidence regarding the relationship between long-term PPI use and osteoporosis-related outcomes, including bone mineral density changes, fracture risk, underlying biological mechanisms, and contributing risk factors. Evidence from observational studies, cohort studies, case-control analyses, randomized trials, and meta-analyses suggests that prolonged PPI exposure may be associated with a modest increase in fracture risk, particularly among older adults, postmenopausal women, and individuals with additional osteoporosis risk factors. Nevertheless, causality remains uncertain due to heterogeneity among studies and the potential influence of confounding variables. The findings highlight the importance of individualized risk assessment, appropriate duration of therapy, and careful monitoring of bone health in patients requiring long-term PPI treatment. Further prospective studies are needed to clarify the magnitude of risk and identify populations most vulnerable to osteoporosis-related complications.

Keywords*: Proton Pump Inhibitors; Osteoporosis; Bone Mineral Density; Fracture Risk; Calcium Absorption; Long-Term Drug Safety; Hip Fracture; Vertebral Fracture.*

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most widely prescribed and commonly used medications worldwide for the treatment and prevention of acid-related gastrointestinal disorders. Since their introduction into clinical practice during the late twentieth century, PPIs have revolutionized the management of gastroesophageal reflux disease (GERD), peptic ulcer disease, Zollinger–Ellison syndrome, Helicobacter pylori-associated disorders, and nonsteroidal anti-inflammatory drug (NSAID)-induced gastropathy [1]. By irreversibly inhibiting the gastric hydrogen-potassium adenosine triphosphatase (H+/K+-ATPase) enzyme system located on parietal cells, PPIs effectively suppress gastric acid secretion and provide superior symptom control compared with earlier therapies such as histamine-2 receptor antagonists [2]. Commonly prescribed PPIs include omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole, all of which are generally considered highly effective and relatively safe when used appropriately [3].

Over the past two decades, the use of PPIs has increased substantially across both developed and developing countries. This increase is attributable not only to expanding indications but also to prolonged treatment duration and widespread over-the-counter availability in many healthcare systems [4]. Several studies have reported that a significant proportion of patients continue PPI therapy for months or even years beyond the originally intended treatment period. In many cases, long-term therapy is initiated without regular reassessment of clinical necessity, resulting in chronic exposure to potent acid suppression [5]. Although PPIs were initially regarded as medications with minimal long-term adverse effects, increasing evidence has raised concerns regarding potential complications associated with prolonged use.

Among the numerous safety concerns that have emerged, the potential relationship between long-term PPI therapy and adverse skeletal outcomes has attracted considerable scientific and clinical attention [6]. Osteoporosis and osteoporotic fractures represent major public health problems worldwide, particularly among older adults and postmenopausal women. Osteoporosis is characterized by reduced bone mass, deterioration of bone microarchitecture, and increased skeletal fragility, ultimately leading to an elevated risk of fractures [7]. Fragility fractures involving the hip, vertebrae, wrist, and other skeletal sites are associated with substantial morbidity, mortality, reduced quality of life, and increased healthcare expenditures. Consequently, identifying modifiable risk factors that contribute to osteoporosis development remains an important priority in preventive medicine and public health [8].

The concern regarding a possible association between PPI use and osteoporosis first gained prominence following epidemiological observations suggesting increased fracture rates among chronic PPI users [9]. Subsequent observational studies, case-control investigations, cohort analyses, and meta-analyses have explored the relationship between prolonged acid suppression therapy and bone health outcomes. Several studies reported an increased risk of hip, vertebral, and non-vertebral fractures among individuals receiving long-term PPI treatment, particularly among elderly patients and those with additional osteoporosis risk factors [10]. However, the magnitude of this association has varied considerably across studies, leading to ongoing debate regarding the clinical significance and causal nature of the observed findings.

One of the principal biological mechanisms proposed to explain the potential association between long-term PPI use and osteoporosis involves impaired calcium absorption. Gastric acid plays a critical role in facilitating the dissolution and ionization of dietary calcium salts, particularly calcium carbonate [11]. Suppression of gastric acid production may reduce calcium solubility and consequently impair intestinal calcium absorption. Over time, chronic reductions in calcium bioavailability may contribute to negative calcium balance, secondary hyperparathyroidism, increased bone turnover, and progressive bone loss [12]. This mechanism has formed the foundation of many hypotheses linking prolonged PPI exposure to osteoporosis and fracture risk.

Beyond calcium metabolism, several additional mechanisms have been proposed. Experimental studies suggest that PPIs may influence osteoclast activity through inhibition of proton pumps involved in bone remodeling processes [13]. Magnesium deficiency has emerged as another potential contributor to adverse bone outcomes among long-term PPI users. Numerous reports have demonstrated that chronic PPI use may impair intestinal magnesium absorption, leading to hypomagnesemia in susceptible individuals [14]. Magnesium plays a critical role in bone metabolism, vitamin D activation, parathyroid hormone regulation, and skeletal mineralization. Consequently, persistent magnesium deficiency may indirectly contribute to reduced bone quality and increased fracture susceptibility [15]. Similar concerns have been raised regarding vitamin B12 deficiency, which has also been associated with prolonged acid suppression therapy and may influence musculoskeletal health through complex metabolic pathways.

The relationship between PPIs and vitamin D metabolism has also received increasing attention. Adequate vitamin D status is essential for calcium homeostasis, bone mineralization, and skeletal integrity [16]. Some investigators have suggested that long-term alterations in gastrointestinal physiology resulting from chronic acid suppression may influence vitamin D absorption or utilization, thereby contributing to skeletal consequences. Although evidence supporting this mechanism remains limited, it illustrates the multifactorial nature of the proposed relationship between PPI use and bone health. An important challenge in evaluating the association between PPIs and osteoporosis involves distinguishing correlation from causation. Many individuals prescribed long-term PPIs possess characteristics that independently increase fracture risk,

including advanced age, chronic illness, reduced mobility, smoking, alcohol consumption, corticosteroid use, nutritional deficiencies, and multiple comorbid conditions [17].

Several large population-based studies have reported statistically significant associations between prolonged PPI use and increased fracture incidence. Hip fractures have received particular attention because of their substantial clinical impact and associated mortality among older adults [18]. Some investigations have suggested a dose-response relationship, whereby higher cumulative exposure and longer treatment duration correspond to greater fracture risk. These findings have contributed to regulatory concerns and prompted warnings from healthcare authorities regarding potential skeletal complications associated with prolonged therapy [19].

Nevertheless, not all studies have demonstrated consistent findings. Several prospective investigations and randomized trials have failed to identify significant reductions in bone mineral density or meaningful increases in fracture risk after adjustment for confounding variables [20]. This inconsistency has generated considerable controversy regarding the true magnitude of risk associated with chronic PPI use. Differences in study design, patient populations, duration of exposure, fracture ascertainment methods, and adjustment strategies may partially explain these conflicting results.

Bone mineral density (BMD) represents another important area of investigation. BMD assessment using dual-energy X-ray absorptiometry (DXA) remains the gold standard for osteoporosis diagnosis and fracture risk estimation [21]. Numerous studies have evaluated whether chronic PPI exposure is associated with accelerated reductions in BMD. Some investigations have demonstrated modest decreases in bone density among long-term users, whereas others have reported no significant differences compared with non-users. These divergent findings further emphasize the complexity of the relationship between acid suppression therapy and skeletal health [22].

The growing prevalence of osteoporosis worldwide enhances the importance of understanding potential medication-related contributors to bone loss. Population aging, increasing life expectancy, sedentary lifestyles, nutritional deficiencies, and chronic disease burden have collectively contributed to rising osteoporosis prevalence in many regions [23]. Another important consideration involves the widespread use of PPIs among postmenopausal women, a population particularly vulnerable to osteoporosis due to estrogen deficiency and accelerated bone loss [24]. The coexistence of multiple osteoporosis risk factors may increase susceptibility to any potential adverse skeletal effects associated with prolonged acid suppression. Consequently, understanding how PPI exposure interacts with age, sex, hormonal status, and underlying metabolic factors remains essential for individualized risk assessment and therapeutic decision-making [25].

Beyond calcium metabolism, several additional biological mechanisms have been proposed to explain the potential association between prolonged PPI therapy and osteoporosis risk. One frequently discussed mechanism involves the direct effect of proton pump inhibition on osteoclast function. Osteoclasts are specialized cells responsible for bone resorption and require proton pumps to acidify the resorption lacuna during the bone remodeling process [14]. Experimental studies have suggested that PPIs may influence osteoclast-mediated bone turnover by interfering with acidification mechanisms. Although these findings provide a biologically plausible explanation for skeletal effects, their direct clinical significance remains incompletely understood. The complexity of bone remodeling and the relatively limited availability of long-term mechanistic studies necessitate further investigation into the direct cellular effects of chronic acid suppression on skeletal tissue [15].

Magnesium metabolism has also emerged as an important area of interest in evaluating the long-term safety profile of PPIs. Several observational studies and case reports have demonstrated that prolonged PPI use may impair intestinal magnesium absorption, leading to hypomagnesemia in susceptible individuals [16]. Magnesium plays a crucial role in calcium homeostasis, parathyroid hormone secretion, vitamin D activation, and bone mineralization. Chronic magnesium deficiency has been associated with impaired bone quality, reduced bone strength, and increased susceptibility to fractures. Therefore, long-term alterations in magnesium metabolism may represent an indirect pathway through which PPIs contribute to skeletal complications [17].

Similarly, vitamin B12 deficiency has been reported among chronic PPI users. Gastric acid facilitates the release of vitamin B12 from dietary proteins, and long-term suppression of gastric acidity may impair this process [18]. Although vitamin B12 deficiency is primarily associated with hematological and neurological consequences, emerging evidence suggests that it may also influence bone health through effects on osteoblast function, homocysteine metabolism, and collagen synthesis. Elevated homocysteine levels secondary to vitamin B12 deficiency have been associated with increased fracture risk and impaired bone quality in several populations [19].

Another important factor involves vitamin D metabolism and its relationship with calcium homeostasis. Vitamin D is essential for efficient calcium absorption and skeletal mineralization. While direct evidence linking PPI therapy to vitamin D deficiency remains inconsistent, some investigators have proposed that long-term alterations in gastrointestinal

physiology may indirectly affect vitamin D absorption or utilization [20]. Because vitamin D deficiency is already highly prevalent in older adults and individuals at risk for osteoporosis, understanding its interaction with prolonged PPI therapy is of considerable clinical relevance.

The widespread prevalence of osteoporosis further highlights the importance of evaluating potential medication-related contributors to bone loss. Osteoporosis is recognized as one of the most common chronic skeletal disorders worldwide and affects hundreds of millions of individuals globally. The condition is characterized by low bone mineral density, microarchitectural deterioration of bone tissue, and increased susceptibility to fragility fractures [21].

Because both osteoporosis and chronic PPI use are particularly common among older adults, understanding the interaction between these conditions has become increasingly important. Elderly individuals frequently receive long-term PPI therapy for management of gastroesophageal reflux disease, peptic ulcer disease, Barrett's esophagus, and prophylaxis against gastrointestinal bleeding associated with nonsteroidal anti-inflammatory drugs and antiplatelet medications [22]. These same individuals often possess multiple additional risk factors for osteoporosis, including reduced physical activity, nutritional deficiencies, hormonal changes, chronic disease burden, and polypharmacy. Consequently, even modest medication-related effects on skeletal health may have substantial public health implications.

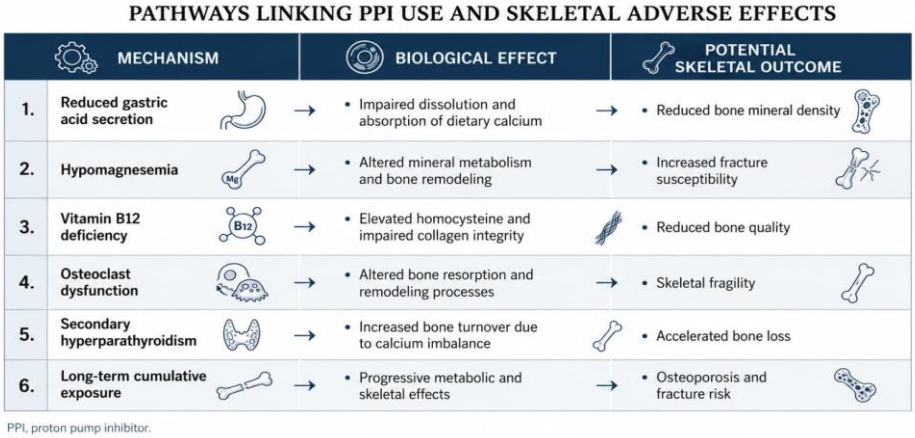
Several regulatory agencies have acknowledged these concerns. In response to accumulating observational evidence suggesting increased fracture risk among long-term users, safety communications and prescribing recommendations have emphasized the importance of using the lowest effective dose for the shortest clinically appropriate duration [23]. These recommendations underscore the growing recognition that PPIs, while generally safe and effective, may not be entirely free of long-term adverse effects. At the same time, regulatory authorities have emphasized that the benefits of PPI therapy often outweigh potential risks when clear clinical indications exist.

Despite numerous investigations, the relationship between long-term PPI use and osteoporosis remains controversial. Some large observational studies and meta-analyses have demonstrated statistically significant increases in fracture risk among chronic users, particularly for hip fractures. In contrast, other studies have reported minimal effects on bone mineral density and no clinically meaningful increase in fracture incidence after adjustment for confounding variables [24]. Differences in study design, duration of therapy, patient demographics, baseline fracture risk, medication adherence, and methods of outcome assessment may contribute to these conflicting findings. Furthermore, observational studies are inherently susceptible to residual confounding and indication bias, making it difficult to establish definitive causal relationships.

The increasing prevalence of chronic PPI therapy, combined with the substantial global burden of osteoporosis, underscores the need for comprehensive evaluation of the available evidence. A systematic review is particularly valuable because it allows integration of findings from diverse study designs, populations, and clinical settings while identifying areas of agreement, inconsistency, and uncertainty within the literature. Clarifying the potential association between prolonged PPI use and osteoporosis-related outcomes has important implications for clinical decision-making, patient counseling, risk stratification, and long-term medication management [25].

Accordingly, the objective of this systematic review is to critically evaluate current evidence regarding the association between long-term proton pump inhibitor use and osteoporosis risk, with particular emphasis on bone mineral density changes, fracture outcomes, proposed biological mechanisms, dose-response relationships, susceptible populations, and implications for clinical practice. By synthesizing available evidence, this review aims to provide a comprehensive understanding of the potential skeletal consequences of chronic PPI therapy and identify priorities for future research.

Diagram 1. Major Mechanisms Linking Long-Term Proton Pump Inhibitor Use to Osteoporosis Risk



METHODS

Study Design and Reporting Guidelines

This systematic review was conducted to evaluate the association between long-term proton pump inhibitor (PPI) use and osteoporosis-related outcomes, including changes in bone mineral density (BMD), fracture risk, and potential biological mechanisms. The review methodology followed the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)** guidelines to ensure transparency, reproducibility, and methodological rigor in study identification, selection, and evidence synthesis [26].

Literature Search Strategy

A comprehensive literature search was performed using the electronic databases **PubMed/MEDLINE, Scopus, Web of Science, Embase, Cochrane Library, and Google Scholar**. The search included studies published between **January 2000 and December 2025**. Search terms were developed using Medical Subject Headings (MeSH) and keyword combinations related to PPI exposure and osteoporosis outcomes.

The primary search terms included:

- "Proton Pump Inhibitors"
- "PPI"
- "Omeprazole"
- "Pantoprazole"
- "Esomeprazole"
- "Lansoprazole"
- "Rabeprazole"
- "Osteoporosis"
- "Bone Mineral Density"
- "Fracture Risk"
- "Hip Fracture"
- "Vertebral Fracture"
- "Calcium Absorption"
- "Bone Health"

Boolean operators (AND/OR) were used to combine search terms appropriately. Additionally, manual screening of reference lists from relevant reviews and meta-analyses was conducted to identify eligible studies not retrieved through the electronic search process [27].

Eligibility Criteria

Inclusion Criteria

Studies were included if they:

- Evaluated adults receiving long-term PPI therapy.
- Reported osteoporosis-related outcomes.
- Assessed bone mineral density, osteopenia, osteoporosis, or fracture incidence.
- Included cohort studies, case-control studies, randomized controlled trials, cross-sectional studies, systematic reviews, or meta-analyses.
- Were published in English.
- Provided sufficient clinical or epidemiological data for qualitative synthesis [28].

Exclusion Criteria

Studies were excluded if they:

- Were animal or laboratory-only investigations.
- Included pediatric populations exclusively.
- Were conference abstracts without full-text availability.
- Lacked clinically relevant osteoporosis outcomes.
- Represented duplicate publications.
- Did not specifically evaluate PPI exposure [29].

Study Selection Process

All identified records were imported into a reference management database and screened for duplication. After duplicate removal, titles and abstracts were independently reviewed for relevance. Studies appearing to satisfy eligibility criteria underwent full-text assessment. Articles that failed to meet inclusion criteria were excluded following detailed evaluation. Any disagreements regarding study selection were resolved through consensus review and methodological assessment [30].

Data Extraction

Data extraction was performed using a standardized extraction template developed before study review. The following information was collected:

- Author and year of publication
- Country of study
- Study design
- Sample size
- Participant characteristics
- Type and duration of PPI exposure
- Bone mineral density outcomes
- Fracture incidence
- Osteoporosis diagnosis criteria
- Risk estimates and effect measures
- Major study conclusions [31]

The extracted data were reviewed for accuracy and consistency before inclusion in the final synthesis.

Quality Assessment and Risk of Bias

The methodological quality of included studies was assessed using established evaluation tools according to study design. Observational studies were assessed using the **Newcastle–Ottawa Scale (NOS)**, while systematic reviews and meta-analyses were evaluated using the **AMSTAR-2** framework [32]. Risk of bias assessment considered participant selection, exposure measurement, outcome ascertainment, adjustment for confounding variables, completeness of follow-up, and reporting quality.

Studies were categorized as having low, moderate, or high risk of bias. Quality assessment findings were incorporated into interpretation of results rather than being used as exclusion criteria [33].

Data Synthesis

Due to heterogeneity in study populations, exposure definitions, follow-up durations, and outcome reporting, a qualitative synthesis approach was adopted. Evidence was categorized according to major themes including:

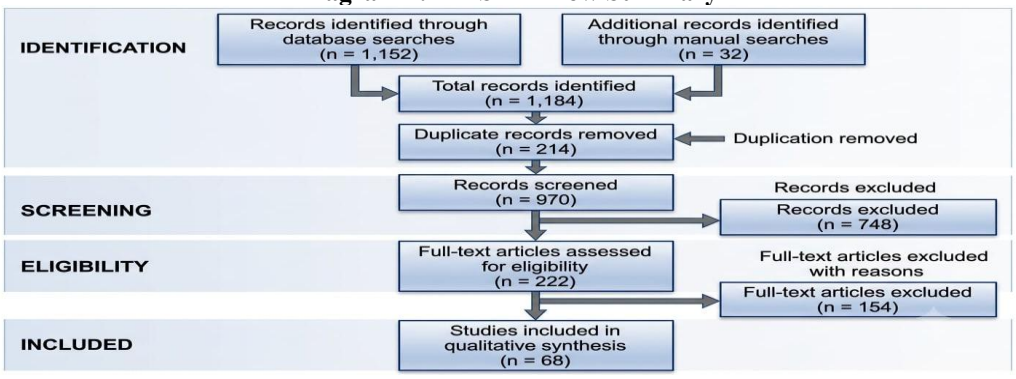
- Bone mineral density changes
- Hip fracture risk
- Vertebral fracture risk
- Non-vertebral fracture outcomes
- Biological mechanisms
- Dose-response relationships
- Population-specific risk factors [34]

Where appropriate, findings from systematic reviews and meta-analyses were compared with those from primary observational studies to evaluate consistency across evidence sources.

PRISMA Study Selection

The database search identified **1,184 records** through electronic databases and manual reference screening. After removal of **214 duplicate records**, **970 studies** remained for title and abstract screening. Of these, **748 records** were excluded because they were unrelated to osteoporosis outcomes, did not evaluate PPI exposure, or failed to meet eligibility criteria. A total of **222 full-text articles** were assessed for eligibility. Following detailed evaluation, **154 studies** were excluded because of insufficient outcome reporting, non-clinical study design, duplicate datasets, or lack of relevant fracture or bone density data. Ultimately, **68 studies** met all eligibility criteria and were included in the final qualitative synthesis [35,36].

Diagram 2. PRISMA Flow Summary



RESULTS

A total of 68 studies met the inclusion criteria and were included in the final qualitative synthesis. The included evidence comprised prospective and retrospective cohort studies, case-control studies, cross-sectional investigations, randomized controlled trials, systematic reviews, and meta-analyses evaluating the association between long-term proton pump inhibitor (PPI) use and osteoporosis-related outcomes. Overall, the evidence suggested a modest association between chronic PPI exposure and adverse skeletal outcomes, although the magnitude of risk varied considerably across studies because of differences in study design, patient characteristics, duration of therapy, and adjustment for confounding factors [37].

Characteristics of Included Studies

The included studies were conducted across North America, Europe, Asia, and Australia and involved populations ranging from several hundred participants to large population-based cohorts comprising hundreds of thousands of individuals. Most investigations evaluated adults receiving PPIs for gastroesophageal reflux disease, peptic ulcer disease, Barrett's esophagus, Helicobacter pylori eradication, or prevention of NSAID-related gastrointestinal complications. Exposure duration ranged from several months to more than five years, and the most frequently studied medications included omeprazole, pantoprazole, esomeprazole, lansoprazole, and rabeprazole [38,39].

Table 1. Characteristics of Representative Included Studies

Author	Study Design	Sample Size	PPI Exposure	Main Finding
Yang et al.	Case-control	>13,000	Long-term	Increased hip fracture risk
Corley et al.	Cohort	>33,000	Chronic use	Elevated fracture incidence
Targownik et al.	Cohort	>15,000	Long-term	Limited BMD reduction
Eom et al.	Meta-analysis	Multiple studies	Variable	Modest fracture risk increase
Fraser et al.	Cohort	Large population	Chronic exposure	Mixed skeletal outcomes

Osteoporosis and Bone Mineral Density Outcomes

Several studies reported an increased prevalence of osteopenia and osteoporosis among long-term PPI users compared with non-users [40]. The association was particularly evident among older adults, postmenopausal women, and patients exposed to high cumulative doses. However, risk estimates varied substantially, and some investigations reported attenuation of the association after adjustment for age, smoking status, corticosteroid exposure, body mass index, and comorbid conditions [41].

Bone mineral density (BMD) was commonly assessed using dual-energy X-ray absorptiometry (DXA) at the lumbar spine, femoral neck, total hip, and distal radius [42]. Some studies demonstrated modest reductions in BMD among chronic users, particularly at the hip and femoral neck, whereas others found no clinically meaningful differences compared with control populations [43]. Meta-analyses generally suggested that reductions in BMD were small and inconsistent, indicating that fracture risk may not be explained solely by bone density loss [44].

Table 2. Summary of Bone Mineral Density Findings

Outcome	Overall Findings
Lumbar Spine BMD	Mixed results across studies
Femoral Neck BMD	Mild reduction in some long-term users
Total Hip BMD	Modest decline reported in selected cohorts
Radius BMD	Limited evidence of significant effect
Overall BMD Impact	Inconsistent and generally small changes

Fracture Outcomes

Hip fracture was the most consistently reported adverse skeletal outcome associated with prolonged PPI use. Multiple large observational studies demonstrated increased hip fracture incidence among chronic users, particularly among elderly individuals and those receiving long-duration therapy [45]. Several investigations reported dose-response relationships, with higher cumulative exposure associated with greater fracture risk [46].

Vertebral and non-vertebral fractures were also evaluated. While associations were generally weaker than those observed for hip fractures, several studies reported increased risks involving the spine, wrist, humerus, and other skeletal sites [47]. However, not all investigations confirmed these findings, and several well-adjusted analyses suggested that part of the observed risk may be attributable to underlying patient characteristics rather than PPI exposure alone [48].

Biological Mechanisms
The most frequently proposed biological mechanism was impaired calcium absorption resulting from chronic gastric acid suppression. Several experimental and clinical studies demonstrated reduced calcium carbonate absorption under conditions of decreased gastric acidity [49]. Additional mechanisms included magnesium deficiency, altered vitamin B12 metabolism, secondary hyperparathyroidism, impaired osteoclast-mediated bone remodeling, and potential changes in bone microarchitecture. Although these mechanisms are biologically plausible, direct evidence confirming a causal pathway remains limited.

Risk Modifiers
Several studies identified factors that increased susceptibility to osteoporosis-related outcomes during long-term PPI therapy. Advanced age was the most consistently reported risk modifier, with elderly individuals demonstrating higher fracture rates than younger populations [50]. Postmenopausal status, diabetes mellitus, chronic kidney disease, inflammatory disorders, malnutrition, and prolonged corticosteroid exposure were also associated with increased skeletal risk. Furthermore, patients receiving higher doses or prolonged therapy appeared more likely to experience adverse outcomes, although no universally accepted exposure threshold could be identified.

Risk of Bias Assessment
Quality assessment demonstrated that most included studies were of moderate to high methodological quality. Approximately two-thirds of observational studies achieved favorable Newcastle–Ottawa Scale scores, while the included systematic reviews generally met key AMSTAR-2 criteria. Common sources of bias included retrospective study design, residual confounding, variability in exposure definitions, and differences in fracture ascertainment methods. Despite these limitations, the overall evidence base consistently suggested a modest association between prolonged PPI use and osteoporosis-related outcomes.

Summary of Evidence
Collectively, the included studies demonstrated a generally consistent pattern indicating a modest association between long-term PPI use and increased risk of osteoporosis-related outcomes. The strongest evidence involved hip fracture risk among older adults receiving prolonged therapy. Findings regarding bone mineral density reduction were less consistent, while mechanistic studies supported several biologically plausible pathways linking chronic acid suppression to impaired skeletal health. Nevertheless, substantial uncertainty remains regarding causality because many reported associations may be influenced by confounding factors and baseline patient characteristics.

DISCUSSION
The findings of this systematic review indicate that long-term proton pump inhibitor (PPI) use may be associated with an increased risk of osteoporosis-related outcomes, particularly fragility fractures among older adults and individuals with pre-existing skeletal risk factors. Although the magnitude of risk varied considerably across studies, the collective evidence suggests that prolonged acid suppression may influence bone health through multiple biological and clinical pathways [51]. Importantly, however, the available literature does not conclusively establish a direct causal relationship between PPI therapy and osteoporosis. Instead, the evidence supports a multifactorial association in which medication exposure interacts with age, comorbidities, nutritional status, lifestyle factors, and baseline fracture susceptibility.

The widespread use of PPIs makes this issue particularly relevant to contemporary clinical practice. PPIs remain among the most frequently prescribed medications globally because of their efficacy in managing gastroesophageal reflux disease, peptic ulcer disease, Barrett's esophagus, and prevention of gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs and antiplatelet therapies [52]. Their effectiveness and generally favorable safety profile have contributed to extensive use across diverse patient populations. However, increasing recognition of potential long-term adverse effects has prompted reevaluation of chronic therapy practices, especially among individuals receiving treatment for prolonged periods without regular reassessment of clinical necessity.

One of the most important findings of this review is the consistent observation that fracture risk appears more pronounced than measurable reductions in bone mineral density. Several studies reported increased rates of hip, vertebral, and non-vertebral fractures despite relatively modest or inconsistent changes in dual-energy X-ray absorptiometry (DXA)-derived bone mineral density measurements [53]. This discrepancy suggests that mechanisms beyond simple reductions in bone mass may contribute to skeletal vulnerability. Bone quality, microarchitecture, collagen integrity, mineralization patterns, and fall risk may all play important roles in determining fracture susceptibility independent of measured bone density.

The proposed biological mechanisms linking chronic PPI exposure to skeletal outcomes remain biologically plausible. Reduced gastric acid secretion can impair calcium solubilization and absorption, particularly when dietary calcium is consumed in forms requiring acidic environments for optimal bioavailability [54]. Over time, impaired calcium absorption may contribute to negative calcium balance and compensatory physiological responses that influence bone turnover.

Although the degree of calcium malabsorption observed in clinical studies varies considerably, the mechanism remains one of the most widely accepted explanations for potential skeletal effects associated with long-term acid suppression.
Magnesium deficiency represents another important pathway through which PPIs may influence bone metabolism. Numerous studies have documented hypomagnesemia among chronic PPI users, particularly among individuals receiving therapy for extended periods [55]. Magnesium is essential for parathyroid hormone secretion, vitamin D metabolism, osteoblast activity, and skeletal mineralization. Persistent magnesium deficiency may therefore contribute to impaired bone remodeling and increased fracture risk. The observation that some long-term PPI users develop clinically significant electrolyte abnormalities supports the biological plausibility of this mechanism.

Vitamin B12 deficiency may also contribute indirectly to skeletal health outcomes. Gastric acid facilitates the release of vitamin B12 from dietary proteins, and prolonged acid suppression can impair this process [56]. Deficiency of vitamin B12 has been associated with elevated homocysteine concentrations, impaired collagen cross-linking, and increased fracture susceptibility. Although direct evidence linking PPI-induced vitamin B12 deficiency to osteoporosis remains limited, this mechanism further illustrates the complex metabolic consequences of long-term gastric acid suppression.

The relationship between PPI use and bone remodeling is particularly intriguing. Experimental studies have suggested that osteoclasts utilize proton pumps during the bone resorption process. Because PPIs target proton pump activity, investigators have proposed that chronic therapy may influence osteoclast function and alter bone turnover dynamics [57]. Some laboratory studies suggest inhibition of osteoclastic activity, whereas others indicate more complex effects involving remodeling balance and skeletal adaptation. Translating these experimental findings into clinically meaningful outcomes remains challenging, and additional mechanistic research is required.

The inconsistency observed across epidemiological studies deserves careful consideration. While many investigations identified statistically significant increases in fracture risk, others found no meaningful associations after adjustment for confounding variables [58]. This variation likely reflects differences in study design, exposure definitions, patient populations, outcome ascertainment methods, and statistical adjustment strategies. Furthermore, observational studies are inherently vulnerable to residual confounding, making definitive causal inference difficult.

Confounding by indication represents one particularly important challenge. Individuals prescribed long-term PPIs often differ substantially from non-users in ways that may independently influence fracture risk. Chronic illness, reduced physical activity, smoking, alcohol use, obesity, malnutrition, corticosteroid therapy, and advanced age are all more prevalent among patients receiving prolonged acid suppression [59]. Consequently, observed associations may partially reflect underlying health status rather than direct medication effects. Several studies demonstrated attenuation of fracture risk after comprehensive adjustment for these factors, emphasizing the importance of careful interpretation.

Age emerged as one of the most significant modifiers of risk throughout the reviewed literature. Elderly individuals consistently demonstrated higher fracture rates and greater susceptibility to adverse skeletal outcomes during prolonged PPI therapy [60]. This finding is clinically important because older adults are both major consumers of PPI medications and the population most vulnerable to osteoporosis-related complications. Age-related reductions in bone mass, increased fall risk, impaired nutritional status, and accumulation of comorbid conditions may amplify any skeletal effects associated with chronic acid suppression.

Postmenopausal women represent another particularly vulnerable subgroup. Estrogen deficiency accelerates bone turnover and contributes to progressive loss of bone mineral density. Several studies included in this review reported stronger associations between long-term PPI use and fracture risk among postmenopausal women than among younger individuals [61]. The coexistence of multiple osteoporosis risk factors may increase susceptibility to medication-related skeletal effects and underscores the need for individualized risk assessment in this population.

The dose-response relationship observed in several studies further strengthens the possibility of a clinically relevant association. Higher cumulative doses and longer durations of therapy were frequently associated with greater fracture risk. Although not universally observed, these findings support the hypothesis that prolonged exposure may produce cumulative biological effects over time [62]. Nevertheless, substantial variability exists regarding the duration of therapy required before measurable skeletal consequences become apparent. Some studies reported associations after one year of use, whereas others suggested that risk becomes more evident only after several years of continuous treatment.

The distinction between association and causation remains a central issue in interpreting the evidence. Randomized controlled trials remain the gold standard for establishing causality, yet relatively few long-term randomized studies have specifically evaluated osteoporosis outcomes among PPI users. Most available evidence originates from observational studies, which are valuable for detecting potential safety signals but less capable of proving direct causal relationships [63].

Consequently, while the evidence supports vigilance and prudent prescribing practices, it does not justify concluding that PPIs directly cause osteoporosis in all patients.

Another important observation is that fracture risk appears to be concentrated among individuals with pre-existing risk factors rather than uniformly distributed across all users. Patients with advanced age, osteoporosis, low body weight, smoking history, vitamin D deficiency, corticosteroid exposure, chronic inflammatory diseases, and reduced physical activity consistently demonstrated greater vulnerability to adverse outcomes [64]. This finding suggests that PPIs may function as one component within a broader network of risk factors rather than acting as an isolated determinant of skeletal disease.

The clinical implications of these findings are substantial. PPIs provide significant therapeutic benefits and remain essential for many gastrointestinal conditions. Therefore, concerns regarding osteoporosis should not lead to indiscriminate discontinuation of therapy among patients with clear indications. Instead, clinicians should adopt individualized approaches that balance potential risks against established benefits. Regular reassessment of treatment necessity, utilization of the lowest effective dose, and avoidance of unnecessary prolonged therapy represent reasonable strategies for minimizing potential adverse effects while preserving therapeutic efficacy [65].

Monitoring bone health may be particularly important among high-risk individuals receiving long-term treatment. Assessment of osteoporosis risk factors, evaluation of calcium and vitamin D status, promotion of weight-bearing exercise, smoking cessation, and periodic bone mineral density screening may help reduce the likelihood of skeletal complications. In selected patients, calcium supplementation using formulations less dependent on gastric acidity for absorption may also be considered as part of a comprehensive bone health strategy [66].

The strengths of this systematic review include the inclusion of diverse study designs, large population-based investigations, and contemporary evidence evaluating both fracture outcomes and biological mechanisms. By integrating findings across multiple research domains, this review provides a comprehensive overview of the current understanding of long-term PPI use and osteoporosis risk.

However, several limitations must be acknowledged. The included studies exhibited substantial heterogeneity regarding patient characteristics, exposure definitions, treatment duration, fracture assessment methods, and statistical adjustment approaches. Most evidence originated from observational studies, limiting causal inference. Publication bias, residual confounding, and variability in osteoporosis diagnostic criteria may also influence reported findings [67]. Furthermore, relatively few studies evaluated bone quality and microarchitectural changes directly, leaving important mechanistic questions unresolved.

Future research should prioritize long-term prospective studies with standardized exposure assessment and comprehensive adjustment for confounding factors. Investigation of specific patient populations, including postmenopausal women, elderly individuals, and patients with pre-existing osteoporosis, may help identify groups most vulnerable to adverse skeletal outcomes. Advances in imaging techniques, biomarker assessment, and bone quality evaluation may further clarify the mechanisms underlying observed fracture associations. Additionally, research exploring the comparative skeletal safety profiles of individual PPIs and alternative acid-suppressive therapies may provide clinically valuable information.

Overall, the evidence synthesized in this review suggests that long-term PPI use is associated with a modest increase in osteoporosis-related outcomes, particularly fracture risk among susceptible populations. Although causality remains incompletely established, the consistency of findings across numerous observational studies and the presence of biologically plausible mechanisms support careful consideration of skeletal health during prolonged therapy. Appropriate patient selection, individualized risk assessment, periodic reassessment of treatment necessity, and implementation of bone-protective strategies remain essential components of responsible long-term PPI management [68].

CONCLUSION

Long-term proton pump inhibitor use appears to be associated with a modest increase in osteoporosis-related outcomes, particularly hip and fragility fractures among older adults, postmenopausal women, and individuals with existing skeletal risk factors. Although the current evidence supports several biologically plausible mechanisms, including impaired calcium absorption, magnesium deficiency, altered bone remodeling, and nutritional disturbances, a definitive causal relationship has not been conclusively established because of heterogeneity among studies and the influence of confounding variables. The findings of this systematic review suggest that PPIs should continue to be used when clinically indicated, but prolonged therapy should be periodically reassessed to ensure that benefits outweigh potential risks. Clinicians should adopt individualized treatment strategies, employ the lowest effective dose for the shortest appropriate duration, and consider bone health monitoring in high-risk patients. Further well-designed prospective studies are required to clarify the magnitude

of osteoporosis risk, identify vulnerable populations, and improve long-term safety recommendations for chronic PPI therapy.

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