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Proton Pump Inhibitor Use and Increased Risk for Bone Fracture:

A Literature Review

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Title: Proton Pump Inhibitor Use and Increased Risk for Bone Fracture: A Literature Review

Department: Nursing

Degree: Master of Science

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Abstract

Proton pump inhibitors (PPIs) are the most commonly prescribed class of medication for gastric acid-related conditions. They are generally well-tolerated, have a seemingly high safety profile, and have superior acid-suppressing capabilities compared to other agents, but new evidence suggests the long-term use of PPI therapy may not come without consequence (Strand, Kim, & Peura, 2017). Recently, research discovered a potential association between PPI use and a variety of medical complications such as enteric infection, pneumonia, malabsorption of vitamins and minerals, renal disease, and bone fracture. This review investigates the association between PPI use and an individual's risk for bone fracture and includes a case presentation, which illustrates a situation in which PPI therapy is considered for the treatment of gastroesophageal reflux disease (GERD). Furthermore, an analysis of recently-published academic literature regarding PPI use and bone health is presented.

Background

Proton pump inhibitors were first introduced by a Swedish pharmaceutical company in 1979 and are now one of the most commonly prescribed classes of medications worldwide (Connelly, 2016). They are well-tolerated and highly effective – qualities which have made them the hallmark of treatment for gastric acid-related disorders (Strand et al., 2017). Proton pump inhibitor therapy is indicated for the treatment of numerous gastrointestinal conditions including dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), Barrett's esophagus, eosinophilic esophagitis, stress gastritis, and Zollinger-Ellison syndrome (ZES) (Strand et al., 2017). Proton pump inhibitors are also used to prevent nonsteroidal anti-inflammatory drug (NSAID) associated ulcer formation and play a role in *Helicobacter pylori* infection eradication (Strand et al., 2017). Currently, six PPIs are approved for use in the United States of America – omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole (Strand et al., 2017).

Proton pump inhibitors were initially thought to have a high safety profile, but recent literature suggests otherwise. Several research studies found PPI use may be associated with several medical complications including an increased risk of bone fracture; however, the results among studies are controversial and a causal relationship between PPI use and bone fracture has yet to be identified.

This review was created to further examine PPI use and its effect on bone health. The next section describes a case report of a 52-year-old woman with a cough. The patient's assessment and examination findings correlated with two possible diagnoses, one of which may have required PPI therapy. Following the case report, 10 research articles pertaining to PPIs and bone health were analyzed in a literature review.

Case Report

A 52-year-old Caucasian female presented to the clinic with complaints of a dry, non-productive cough that started three months prior. She described the cough as bothersome and stated, “I feel like I have a constant tickle in my throat.” It was present upon waking, persisted throughout the day, and was more prominent at night or after she consumed a large meal. She tried over-the-counter (OTC) cough suppressants and cough drops, but they did not provide much relief. To the best of her knowledge, she had not been around anyone that was ill. She was concerned she contracted a form of influenza, but a system review, history assessment, and physical examination revealed findings inconsistent with an influenza infection.

She did not feel unwell and denied fever, chills, headache, fatigue, weakness, and tiredness. She had not experienced changes in her vision, hearing, or taste and had no complaints of ear pain, tinnitus, nasal congestion, nasal drainage, sinus pressure, sinus tenderness, or sore throat. She denied chest pain, nor did she feel short of breath. Occasionally, she would get heartburn, but OTC antacids effectively relieved the discomfort. She denied abdominal pain, nausea, vomiting, diarrhea, constipation, hematochezia, and changes in urination including urgency, frequency, dysuria, and hematuria. She had no complaints of myalgias, arthralgias, or changes in her skin and denied feelings of anxiety or depression.

The patient’s personal and familial medical history was relatively insignificant. She was an only child and her mother and father were, at the time, alive and healthy. Her past surgical history was unremarkable and her only medical problem included hypertension, for which she was prescribed lisinopril six months earlier. She never used tobacco or illicit drugs; she would drink wine on occasion. Her dietary habits were concerning – she was a heavy coffee drinker (3-5 cups daily) and she often consumed large, “fulfilling” meals. She was married, worked at a

local university, and had two children who lived at home. There were no pets in the household. She received all her childhood vaccinations and had been vaccinated for the current influenza season.

The patient's physical examination was unremarkable. Her vital signs were normal. She was alert, oriented, and did not appear in distress. No abnormalities were noted upon assessment of her head, eyes, ears, nose, and oral cavity. Inspection and assessment of her neck found no adenopathy, thyromegaly, or tracheal deviation. Her lung sounds were clear in all fields upon auscultation, although, a dry cough was noted. Active bowel sounds were present in all four abdominal quadrants, and her abdomen was soft and non-tender to palpation. A genitourinary assessment was deferred. The patient's skin was pink, warm, dry, and intact. Her behavior was appropriate, and she did not appear anxious.

The patient's assessment and examination findings correlated with four differential diagnoses. The first differential diagnosis was GERD. The patient's cough was more prominent at night and after she ate a large meal. Additionally, she was an avid coffee drinker and would occasionally experience heartburn. The second differential diagnosis was a lisinopril-induced cough. Lisinopril is an angiotensin-converting-enzyme (ACE) inhibitor, a class of medication known to cause a dry, hacking, bothersome cough. The onset of a cough caused by ACE inhibitors ranges from hours to months; she began treatment with lisinopril six months beforehand. The third and fourth differential diagnoses included post-nasal drip and upper respiratory infection.

The medical profile of each diagnosis was carefully analyzed. The patient's chief complaint, related findings, and lifestyle habits correlated most GERD, but a lisinopril-induced cough could not be confidently ruled out. It was decided to involve the patient in the plan of care.

Each potential diagnosis was discussed in detail and the patient's questions and concerns were addressed. She was given two options – she could continue taking the lisinopril and begin short-term PPI therapy or she could forgo PPI therapy and switch her antihypertensive medication. The patient chose to change the lisinopril to hydrochlorothiazide. She was supposed to schedule an appointment two weeks later for symptom re-evaluation. If her symptoms remained, short-term PPI therapy would then be recommended.

Literature Review

The above case report illustrates how easy it could be to over-prescribe PPIs or to prescribe them for inappropriate conditions. Many patients use PPIs to control symptoms of chronic conditions, meaning they are often used for extended periods of time. Proton pump inhibitor use has increased dramatically in recent years, especially among geriatric populations, but they are also being prescribed to children and young adults for non-specific symptoms (Freedberg et al., 2015). Proton pump inhibitors are available over-the-counter or by prescription; therefore, it is impossible to estimate how many individuals use these agents, but pharmacological data approximates 113 million prescriptions are filled each year worldwide (University of California Berkeley School of Public Health, 2017). This widespread use of PPIs has generated concern about their long-term safety profile, including their effect on the skeletal system. If PPI use is found to negatively impact skeletal health, it will be important for clinicians to become more cognizant of their prescribing habits. To further investigate the relationship between PPIs and their effect on bone health, a literature review was performed.

Literature Search

A search for literary material was conducted using two research databases, the Cumulative Index to Nursing and Allied Health (CINAHL) and PubMed. Between the two

databases, 32 articles were chosen for more in-depth evaluation, and 10 were deemed useful for this review. Due to differences among database filters, the search limitations were not identical, but similar. With CINAHL, each search was limited to text in the English language that was published in an academic journal between 2013 and 2018. With PubMed, article types were limited to case reports, clinical studies, clinical trials, comparative studies, controlled clinical trials, practice guidelines, meta-analyses, observational studies, randomized controlled trials, and systematic reviews. The results were further limited to those that involved only human subjects, were published between 2013 and 2018, and were in the English language. Five search phrases were used with each database: *long-term use of proton pump inhibitors*, *proton pump inhibitors and osteoporosis*, *side effects of proton pump inhibitors*, *proton pump inhibitors and calcium absorption*, and *proton pump inhibitors and fracture*. The first search phrase, *long-term use of proton pump inhibitors*, yielded 38 results within CINAHL. Due to the high yield, the results were sorted by “most relevant,” and the first 20 texts listed were evaluated; four were chosen for further review. The remaining four phrases yielded 13, 15, 8, and 15 results, respectively, all of which were screened for relevancy. Of these, 11 were further reviewed. With PubMed, each search phrase, other than *proton pump inhibitors and calcium absorption* (18 results), yielded a tremendously high number of results. The phrases *long-term use of proton pump inhibitors*, *proton pump inhibitors and osteoporosis*, and *proton pump inhibitors and fracture* yielded 335, 43, and 80 results, respectively. The phrase *side effects of proton pump inhibitors* yielded 1,343 results, many of which were duplicates of prior searches. All results were sorted by “best match,” and the first 20 texts listed were screened for relevancy. Seventeen articles were further examined.

Many of the 32 articles contained information and statistics on both PPIs and bone health, but over half-were deemed irrelevant or were reviews of primary studies already chosen for use. Four articles concentrated on PPI use and its effect on gastrointestinal absorption of vitamins and minerals; the information provided was determined to be insignificant to the overall objective of this review, so they were discarded. One article from CINAHL utilized rats as research subjects and was excluded. The remaining omitted articles contained generalized information about PPIs, only referenced research studies to emphasize a point, or focused on PPI use in conjunction with other medications and medical conditions.

Ten articles were selected and consisted of 5 literature reviews, 2 cohort studies, 2 case-control studies, and one cross-sectional study. All the articles investigated the effect of PPI use on the skeletal system – four specifically focused on PPI use and an increased risk for bone fracture, while the other 6 examined the association between PPI use and changes in bone mineral density (BMD), the development of osteoporosis, and the incidence of osteoporotic fracture.

Proton Pump Inhibitors and Bone Fracture

Bone fractures occur in individuals of all ages and are either traumatic or pathologic in nature. Pathological fractures occur when an underlying cause weakens the bone structure, making it more susceptible to break. Recently, it has been suggested that PPI use may negatively affect bone metabolism and increase an individual's risk of fracture. Abramowitz et al. (2016) conducted a systematic review and determined PPI users were more likely to experience an “any-site”, spinal, or hip fracture compared to non-PPI users. Spinal fractures among PPI users had the highest odds ratio (OR) of 1.50 followed by hip fractures, which had an OR of 1.30; the OR range for “any-site” fractures varied from 1.44-2.65, but the information was collected from low

quality research (Abramowitz et al., 2016). Comparably, Zhou, Huang, Li, Sun, and Liu (2016) found a moderate increase in spine (95% CI 1.38-1.82) and hip (95% CI 1.16-1.36) fracture risk among PPI users. The authors considered the presence of heterogeneity among the studies that investigated hip fracture risk and performed a stratified analysis that limited the review to cohort studies – a moderate increase in fracture risk was still found (95% CI 1.06-1.45) (Zhou et al., 2016).

Most of the literature on PPI use and increased risk of bone fracture focus on menopausal women or the elderly. To further strengthen the association between PPI use and increased risk of bone fracture, Adams et al. (2014) and Freedberg et al. (2015) conducted studies using men, children, and young adults as participants. The study by Adams et al. (2014) examined men aged 45 years or older; the case subjects had sustained a hip fracture during the study period, whereas the control subjects had not. Freedberg et al.'s (2015) study included male and female individuals between 4 and 29 years age. Like Adams et al. (2014), Freedberg et al.'s (2015) case selection included individuals who sustained any fracture; those in the control group had no history or diagnosis of fracture. The exposure of interest in both studies was PPI use and both studies further evaluated whether dosage and duration of PPI therapy affected the results. Both studies found an association between PPI use and an increased risk of bone fracture; however, Freedberg et al. (2015) only found an association among young adults (18-29 years old), not among children (4-18 years old). Adams et al.'s (2014) study found men who took omeprazole (for an average of 150 days) and were compliant with treatment had an increased risk of hip fracture (OR 1.31) versus non-PPI users. Freedberg et al. (2015) discovered young adults who had been exposed to at least 180 cumulative doses of PPI therapy had a significantly increased risk of hand and foot fractures (OR 1.39).

Proton Pump Inhibitors and Changes in Bone Mineral Density

Bone mineral density measurements reflect an individual's overall bone health. Low BMD values are associated with osteoporosis and increased fracture risk and are often a result of aging, genetics, disease, or medication use. Osteoporosis has become a major medical concern – it is estimated that 1 in 3 women and 1 in 5 men over 50 years old will experience an osteoporotic fracture in their lifetime (Byreddy, Bouchonville, & Lewiecki, 2015).

Proton pump inhibitors have been implicated as increasing a person's bone fracture risk. Recent research has focused on BMD changes among PPI users, but the findings are inconsistent. Arj et al. (2016) and Solomon et al. (2015) evaluated femur and lumbar *T*-scores in PPI users and non-PPI users; a *T*-score < -2.5 was indicative of osteoporosis and a *T*-score between -2.5 and -1 indicated osteopenia. Arj et al. (2016) conducted a cross-sectional study that included males and females between 20 and 45 years of age and found a significant decrease of mean femoral and lumbar *T*-scores (-0.44 ± 1.11 , -0.94 ± 0.92) in subjects who had been on PPI therapy for at least two years compared to non-PPI users (0.19 ± 0.95 , -0.53 ± 1.24). On the contrary, Solomon et al.'s (2015) findings failed to correlate PPI use with decreased BMD – the mean femoral and lumbar *T*-scores of PPI users (0.83 ± 0.13 , 1.07 ± 0.16) were comparable to those of non-users (0.78 ± 0.12 , 1.16 ± 0.24).

Fraser et al. (2013) decided to take a unique route by prospectively examining the association of PPI use and incident of fragility fracture while using BMD as a controlled confounding variable. The results indicated PPI use was associated with incident fragility fracture, even after adjusting for baseline femoral *T*-scores. Byreddy et al. (2015) and Andersen, Johansen, and Abrahamsen (2016) searched the literature for evidence to substantiate the association of PPI use and the development of osteoporosis and increased risk of bone fracture.

The authors found numerous studies which further support the association of PPI use and changes in bone health, but they also identified widespread diversity among the research; therefore, they propose further inquiry on the topic is needed.

Special Considerations

The most common finding among the studies was that fracture risk was dependent on PPI formulation, dosage, and duration of therapy – longer, more intense PPI therapy as well as certain PPI formularies (omeprazole and esomeprazole) were significantly associated with an increased risk of bone fracture and changes in BMD. Additionally, even though an association has been found between PPI use and increased risk of bone fracture, the mechanism of action remains unknown. Mulcahy (2015) set out to find a causal relationship between PPI use and development of osteoporosis and increased risk of bone fracture. She reviewed eight studies that found fracture risk is increased in women who use PPIs, but none were able to explain why, leaving her to conclude that although an association exists between PPI and fracture risk, the causation has yet to be discovered (Mulcahy, 2015).

There is no doubt that more information and further investigation is needed on this topic. It will be interesting to watch the body of evidence grow; however, some researchers have voiced concern over the ethical aspects and feasibility of randomized control trials. Until more data can be gathered, “we must rely on observational studies” (Fraser et al., 2013, p. 1164).

Learning Points

Current evidence regarding long-term PPI use and increased risk for bone fracture is inconsistent and controversial, but if an association between the two is proven to exist, treatment guidelines and recommendations for gastric acid-related disorders will need to be revised. It is

important for clinicians to carefully evaluate individuals before prescribing PPI therapy.

Furthermore, it is apparent that additional research on the long-term effects of PPI use is needed.

In conclusion, this report adds to the growing body of evidence that PPI use may be associated with an increased risk of bone fracture and offers the following clinical considerations for health care providers:

- Proton pump inhibitors were once thought to be relatively safe, but new evidence suggests they may be associated with several medical complications including an increased risk for bone fracture.
- Proton pump inhibitors are over-prescribed or prescribed inappropriately, making them one of the world's most commonly prescribed class of medications. Careful evaluation of individuals with gastric acid-related disorders is essential before initiating PPI therapy.
- If PPI therapy must be initiated, clinicians should consider the patient's age and comorbid burden. The lowest recommended dose for the shortest duration of time should be prescribed and alternative treatments should be used in high-risk individuals.
- Further research regarding PPI therapy and bone fracture is needed. This may be difficult because prospective, randomized, controlled studies may be considered unethical or unfeasible; however, research into the underlying mechanism by which PPI use increases the risk for fracture may be beneficial.

References

- Abramowitz, J., Thakkar, P., Isa, A., Truong, A., Park, C., & Rosenfeld, R. M. (2016). Adverse event reporting for proton pump inhibitor therapy: An overview of systematic reviews. *Otolaryngology - Head & Neck Surgery*, 155(4), 547-554. Retrieved from <http://ezproxylr.med.und.edu:2056/10.1177/0194599816648298>
- Adams, A. L., Black, M. H., Zhang, J. L., Shi, J. M., & Jacobsen, S. J. (2014). Proton-pump inhibitor use and hip fractures in men: A population-based case-control study. *Annals of Epidemiology*, 24(4), 286-290. Retrieved from <https://doi.org/10.1016/j.annepidem.2014.01.004>
- Andersen, B. N., Johansen, P. B., & Abrahamsen, B. (2016). Proton pump inhibitors and osteoporosis. *Current Opinion in Rheumatology*, 28(4), 420-425. Retrieved from <http://ezproxylr.med.und.edu:2056/10.1097/BOR.0000000000000291>
- Arj, A., Razavi Zade, M., Yavari, M., Akbari, H., Zamani, B., & Asemi, Z. (2016). Proton pump inhibitors use and change in bone mineral density. *International Journal of Rheumatic Diseases*, 19(9), 864-868. doi:10.1111/1756-185X.12866
- Byreddy, D. V., Bouchonville, M. F., II, & Lewiecki, E. M. (2015). Drug-induced osteoporosis: From Fuller Albright to aromatase inhibitors. *Climacteric*, 18(2), 39-46. doi:10.3109/13697137.2015.1103615
- Connelly, D. (2016). The development and safety of proton pump inhibitors. *The Pharmaceutical Journal*, 296(7890), 348-349. doi:10.1211/PJ.2016.20201343
- Fraser, L. A., Leslie, W. D., Targownik, L. E., Papaioannou, A., Adachi, J. D., & CaMos Research Group. (2013). The effect of proton pump inhibitors on fracture risk: Report

- from the Canadian Multicenter Osteoporosis Study. *Osteoporosis International*, 24(4), 1161-1168. doi:10.1007/s00198-012-2112-9
- Freedberg, D. E., Haynes, K., Denburg, M. R., Zemel, B. S., Leonard, M. B., Abrams, J. A., & Yang, Y.-X. (2015). Use of proton pump inhibitors is associated with fractures in young adults: A population-based study. *Osteoporosis International*, 26(10), 2501-2507. doi:10.1007/s00198-015-3168-0
- Mulcahy, E. A. (2015). The state of the science of proton pump inhibitors causing osteoporotic changes in postmenopausal women. *Gastroenterology Nursing*, 38(2), 129-133. Retrieved from <http://ezproxylr.med.und.edu:2056/10.1097/SGA.0000000000000102>
- Solomon, D. H., Diem, S. J., Ruppert, K., Lian, Y. J., Liu, C. C., Wohlfart, A., . . . Finkelstein, J. S. (2015). Bone mineral density changes among women initiating proton pump inhibitors or H2 receptor antagonists: A SWAN cohort study. *Journal of Bone and Mineral Research*, 30(2), 232-239. doi:10.1002/jbmr.2344
- Strand, D. S., Kim, D., & Peura, D. A. (2017). 25 years of proton pump inhibitors: A comprehensive review. *Gut and Liver*, 11(1), 27-37. doi:10.5009/gnl15502
- University of California Berkeley School of Public Health (2017). Proton pump inhibitors: How safe are they? Retrieved from https://www.healthandwellnessalerts.berkeley.edu/alerts/digestive_health/How-Safe-AreProton-Pump-Inhibitors_7793-1.html
- Zhou, B., Huang, Y., Li, H., Sun, W., & Liu, J. (2016). Proton-pump inhibitors and risk of fractures: An update meta-analysis. *Osteoporosis International*, 27(1), 339-347. doi:10.1007/s00198-015-3365-x