INTEGRIS

Great Plains Family Medicine

Does long term Proton Pump Inhibitor use lead to osteoporosis and an increase in fractures?

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Answer: Possibly

Level of Evidence: V

SUMMARY

Clinical Question: Does long term Proton Pump Inhibitor use lead to osteoporosis and an increase in fractures?

Answer: Possibly

Level of Evidence: V

INTRODUCTION

Since their introduction, proton pump inhibitors (PPIs) have become mainstays of treatment for a multitude of GI conditions including gastroesophageal reflux disease (GERD), H. pylori infections, peptic ulcer disease (PUD) and as co-therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) to assist with prevention of gastric ulcers.[1-3]It is estimated that PPIs account for 95% of acid suppressing drug prescriptions, with an estimated 14.9 million patients prescribed PPIs in the US in 2012.[4] Long-term therapy with PPIs has been associated with an increase in pathologic hip fractures secondary to osteoporosis, with significant mortality, morbidity and economic burden.[5] A large number of studies have sought to define relationship between long-term PPI use and fracture.

DISCUSSION

In a retrospective study in United States of 6774 men over 45 years old, stratified by age, exposure to omeprazole resulted in an elevated risk of hip fracture with as little as 2.5 months of exposure, and in a seemingly cumulative and dose-dependent fashion. However, this relationship was not seen with pantoprazole, and these were the only 2 PPIs studied.[6] In postmenopausal women, a retrospective study in Australia demonstrated a twofold increase in fracture in patients taking PPIs greater than 1 year or at 150% of standard daily dose.[7] Retrospective studies in Sweden showed a similar result.[8] Data mining of the FDA adverse reporting system found 169,562 entries of patients with PPI use, with a median age of fracture of 65.3 years and a sex ratio of female to male of 3.4. Most often reported fracture sites were thoracic cage and pelvic.[9] The data supporting correlation is advised, but there remains significant debate regarding causation.

In a cross-sectional longitudinal study published in 2010 using data from the Manitoba Bone Mineral Database, comparing patients with known osteoporosis by DEXA of hip (n=2193) to a control group without (n=5527), found no association between osteoporosis and fracture and PPI use.[10] This was despite a subclass of patient's using PPIs for over 5 years time. In 2016, the same group measured bone mineral density (BMD) using a 3D quantitative CT. They concluded that PPIs are not associated with changes in BMD. Additionally, they concluded that PPIs are also not associated with a change in bone structure or decrease bone strength that would increase the risk fracture.[11] The authors found the PPI use did not affect the rate of bone mineral loss regardless of dosing. Authors into similar studies came to the same conclusions in the absence of other risk factors. In total, this suggests that the association between PPIs and fracture may be due to confounders that we do not yet understand.[10]

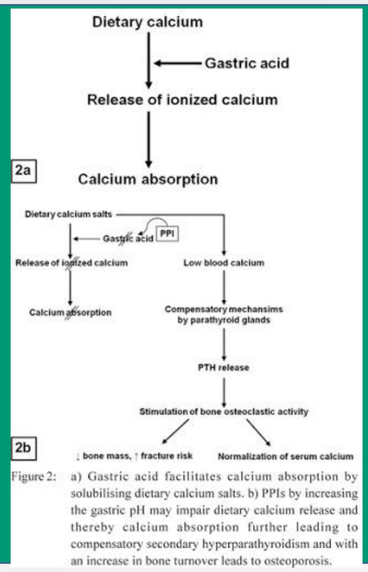

Figure 2: a) Gastric acid facilitates calcium absorption by solubilising dietary calcium salts. b) PPIs by increasing the gastric pH may impair dietary calcium release and thereby calcium absorption further leading to compensatory secondary hyperparathyroidism and with an increase in bone turnover leads to osteoporosis.

CONTINUED

Consensus on this issue will likely only be achieved through the recognition of a mechanism. Proposed mechanisms such as decreased calcium absorption due to low gastric acid have largely been disproven, and the effect of calcium on osteoporosis outcomes is now also in question. Additional mechanisms proposed to explain the association of PPIs with fractures are independent of bone mineral density. Once such mechanism is an impact osteoclasts bone specific proton pump function that is needed to promote localized bone reabsorption and downstream bone remodeling[12], but even this result is disputed.[11,13] Another study has reported that PPIs may increase function and lifespan of osteoblasts.[14] If accurate, in tandem, this mechanism could result in decreased bone turnover but may also lead to changes in bone modeling resulting in delayed healing of microfractures which in turn increase overall fracture risk.[15]

CONCLUSION

The association between chronic PPI use and risk of fracture continues to be clouded. Osteoporosis is an established risk factor for fractures, yet only approximately half of fractures occur in patients with diagnosed osteoporosis by DEXA screening.[16-18] Chronic PPI users are also more likely to have other comorbidities and frailty.[19-21]The only agreement that can be reached at this time is acknowledgment of correlation between chronic PPI users and fracture risk. Without an underlying mechanism we are unable to say definitively whether there is causation. Practitioners managing patients on PPIs should annually reevaluate patient's need for continuation or appropriateness for a trial of de-escalation. Patient's that remain on long-term PPIs should continue to undergo screening and intervention directed to decreasing the incidence of falls.

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References available on handout