Osteoporosis, Fractures and PPI usage

Proton pump inhibitors — Insoluble calcium, such as calcium carbonate, requires an acid environment for optimal absorption. As a result, drugs that reduce stomach acid secretion (proton pump inhibitors [PPIs] and H2 blockers) may reduce calcium absorption. Because calcium absorption decreases with aging, a further reduction in calcium absorption with the addition of such drugs may have an adverse impact on skeletal health, particularly in older individuals.

Some [51], but not all [52], studies with omeprazole showed that fractional absorption of calcium was reduced in postmenopausal women. A possible explanation for the different results among studies is a difference in study conditions, including selection of isotope-labelled calcium (calcium carbonate capsules versus calcium chloride solution), method of measurement (fasting serum isotope-labelled calcium levels versus dual isotope measurements with a meal), duration of omeprazole treatment (7 versus 30 days), and patient characteristics (mean age 76 versus 58 years). Dietary calcium (milk and cheese) absorption was not reduced in healthy individuals treated with omeprazole [53,54], suggesting that a meal induces a sufficient amount of acid secretion for calcium absorption despite PPI therapy.

The more important clinical question is whether PPIs affect fracture risk. In meta-analyses of case-control and cohort studies, the risk of hip, spine, and any-site fractures was modestly but significantly increased in patients taking PPIs (RRs 1.30, 1.56, and 1.16, respectively) [55-58]. In some studies [57,59], but not another [60], the risk was highest in long-term users of high dose PPI therapy. In one analysis, the risk was confined to patients with at least one other risk factor for hip fracture [61], and in another, to current or former smokers [57].

The largest prospective cohort study (the WHI Study) did not find an association between PPI use and hip fracture (HR 1.00, 95% CI 0.71-1.40) [62]. However, PPI use was associated with an increased risk of clinical vertebral (HR 1.47, 95% CI 1.18-1.82), wrist, and total fractures. There was a smaller number of hip fracture events compared with wrist, clinical spine, or total fractures. The lower number of events, combined with the fact that PPI users were more likely than nonusers to be taking hormone therapy, may have reduced the ability of the study to detect an increased risk of hip fracture in PPI users.

H2 blockers were associated with an increased risk of hip fracture in some reports (assumption of risk [AOR] 1.23, 95% CI 1.14-1.39) [59,61,63], but decreased [60], or unchanged [58,62] in others.

In a subsequent analysis of a national prescription database, concurrent use of PPIs and alendronate compared with alendronate alone was associated with loss of protection against hip fracture (fracture risk reduction with alendronate 39 versus 19 percent in non-PPI versus PPI users) [64]. Concurrent treatment with H2 blockers did not modify the treatment response to alendronate.

Although the association between PPIs and fracture is plausible, these observational studies do not prove causality. One possible mechanism by which PPIs and H2 blockers adversely affect bone is through impaired absorption of calcium carbonate due to achlorhydria, which increases bone loss and reduces

BMD. In a prospective cohort study, chronic PPI use was associated with lower baseline BMD at the femoral neck and total hip, but use over 10 years was not associated with accelerated BMD decline [65]. In addition, other studies have not found a decrease in BMD in PPI users compared with nonusers [66,67], albeit in one of these there was an increased risk of falls and fractures in PPI users [66]. Thus, factors independent of BMD (eg, frailty) may contribute to fracture risk, and PPI use may be a marker of frailty since PPI users are as a group sicker than controls [65]. Further studies investigating the relationship between PPIs and fracture are required.

In the interim, because omeprazole was shown to reduce the fractional absorption of calcium carbonate in fasting postmenopausal women [51], we recommend that postmenopausal women taking long-term PPI or H2 blocker therapy increase dietary calcium and, when necessary, use calcium supplements that do not require acid for absorption, such as calcium citrate. The treatment of postmenopausal women with or at risk for osteoporotic fracture is reviewed separately.

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