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THE FINAL WORD ON PROTON PUMP INHIBITORS AND OSTEOPOROSIS?

Targownik LE, Leslie WD, Davison KS, et al; CaMos Research Group. The relationship between proton pump inhibitor use and longitudinal change in bone mineral density: a population-based from the Canadian Multicentre Osteoporosis Study (CaMos). *Am J Gastroenterol* 2012;107:1361–1369.

Osteoporosis is a common disease that is characterized by low bone mass and remains asymptomatic until patients develop a vertebral or other fracture (*J Bone Miner Res* 1994;9:1137–1141). The prevalence in adults over the age of 50 is approximately 20% for women and 7% for men. For adults who develop hip fractures, the estimated 1-year mortality rates range between 12% and 37% (*JAMA* 2009;302:1573–1579). Risk factors for osteoporosis include female gender, sedentary lifestyle, tobacco consumption, low body mass index, inflammatory bowel disease, hyperparathyroidism, and use of medications including corticosteroids, antiepileptics, thiazides, and antidepressants including selective serotonin reuptake inhibitor therapy.

Gastroesophageal reflux disease (GERD) is a common disorder affecting approximately 10% of Americans on a daily basis, and 40% of Americans monthly (*Clin Gastroenterol Hepatol* 2005;3:543–552; *Gut* 2005;54:710–717). In September 2012, the US Food and Drug Administration issued a warning regarding use of proton pump inhibitors (PPIs) and osteoporosis stating that “several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose PPI, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration

of PPI therapy appropriate to the condition being treated.”

In the current study by Targownik et al from the University of Manitoba (Canadian Multicentre Osteoporosis Study [CaMos]), the authors used a random population sample from 1995 to 1997 that included subjects over the age of 25. In-person, interviewer-administered questionnaires (IAQ) were administered to all subjects including medical history, intake of calcium and vitamin D, and bone mineral density (BMD) assessment using dual energy x-ray absorptiometry (DXA) on all enrolled subjects at L1–L4, the femoral neck, and total hip. Repeat questionnaire and BMD assessments occurred at years 5 and 10.

The authors subsequently analyzed the relationship between PPI use and change in BMD at each site between years 0–5, 0–10, and 5–10. They performed multivariate linear regression analysis to control for confounders including age, gender, body mass index, history of fracture, rheumatoid arthritis, inflammatory bowel disease, chronic liver, kidney thyroid disease, tobacco, alcohol, history of falls, and multiple predisposing medications including steroids, thiazides, β -blockers, nitrates, selective serotonin reuptake inhibitors, and tamoxifen. Data regarding adequate consumption of calcium and vitamin D (≥ 1200 mg calcium and/or ≥ 400 IU of vitamin D) was recorded.

There were a total of 9423 subjects enrolled in the study, of whom 8340 (88.5%) completed initial IAQ and BMD assessments. At 5 years, 6458 (77%) patients underwent repeat assessments of IAQ and BMD, and a total of 4512 (55%) completed the 10-year survey. Two hundred twenty-eight (3%) subjects used PPI at baseline, 8% at year 5, and 11.5% at year 10. Continuous PPI use was only reported by 0.9% of the cohort.

Compared with non-PPI users, PPI users had lower baseline BMD at the hip and femoral neck but not the lumbar spine. In general, PPI users tended to be older with higher body mass index ($P < .001$), greater intakes of

vitamin D and calcium, higher rates of prior nontrauma fractures ($P = .015$) and comorbidities, and users of multiple medications ($P < .001$ for use of steroids, thiazide diuretics, and selective serotonin reuptake inhibitors). After adjustment for confounding factors, regression models did not show association between use of PPI and rate of change of BMD at any measurements. In addition, use of bisphosphonates and hormone replacement therapy was associated with increases in BMD.

Comment. The presence of gastric acid and an acidic proximal duodenum are required to free ingested calcium from foodstuffs for absorption to occur in the small intestine. Lack of sufficient amounts of gastric acid can lead to secondary hyperparathyroidism, increased rates of osteoclastic bone resorption, and skeletal turnover, and subsequent reduction in bone mass.

Although short-term studies have suggested that PPI use can decrease calcium absorption, consequences of this effect have not been demonstrated in long-term outcomes analyses. Early published studies in small numbers of subjects where omeprazole 20 mg was administered to healthy subjects or patients undergoing dialysis, suggested that omeprazole resulted in decreased calcium absorption after short exposures to the drug ranging from 3 days to 20 months (Nephrol Dial Transplant 1995;10:1376–1380; Nephron 2002;91:474–479; Artif Organs 1998;22:569–573; Am J Med 2005;118:778). However, a randomized, controlled trial in healthy subjects measuring calcium absorption using gastrointestinal lavage after omeprazole 40 mg was administered for 17 days did not show any change in intestinal calcium absorption (J Am Coll Nutr 1995;14:364–368).

Subsequent case-control studies assessing potential associations between dose and duration of PPI therapy and hip fractures showed mixed results. The first study by Vestergard et al (Calcif Tissue Int 2006;79:76–83) performed in Denmark examined 124,655 cases with hip fracture compared with 373,962 controls matched for age and gender. The study found that the odds ratio for hip fracture in PPI users was 1.18 (95% confidence interval [CI], 1.12–1.43) for users <1 year ago and was 1.01 (95% CI, 0.96–1.06) for patients who used the drug >1 year ago. The odds ratio did not change depending on the PPI dosage. A subsequent study by Yang et al (JAMA 2006;296:2947–2953) compared 2722 cases of hip fractures in patients taking PPIs for >1 year and 10,834 hip fractures in patients not taking PPIs with 135,386 matched controls and found an odds ratio (OR) for PPIs of 1.44 (95% CI, 1.30–1.59) with the risk being 1.4 for ≤ 1.75 average daily doses and 2.65 when the average daily dose exceeded 1.75. The OR was 1.22 after 1 year of use and increased to 1.59 after 4 years. The third study by Targownik et al from Canada (CMAJ 2008;179:319–326) matched 15,792 cases with either vertebral, wrist, or hip fractures with 47,289 controls and reported ORs by PPI duration of use. Although at >1 year of PPI use the odds ratio was 0.99, it increased to 1.16 at 5 years of use, and to 1.92 after 7

years. A cause-and-effect relationship between PPI use and fractures was unable to be established based on a low magnitude of associations, probable bias based on the retrospective nature, and inconsistency between studies in demonstration of effect (Am J Gastroenterol 2009;104[Suppl 2]:S21–S26).

Subsequent studies assessed BMD based on DXA scans and again showed inconsistent results. A study by Yu et al in 2008 (Calcif Tissue Int 2008;83:251–259) did not show differences in rate of total hip BMD decline between PPI users and nonusers. Gray et al (Arch Intern Med 2010;170:765–771) showed that both users and nonusers had increases in BMD of the hip from baseline to year 3 of the study. However, increases in BMD were lower among PPI users than nonusers. Targownik et al (Gastroenterology 2010;138:896–904) subsequently were unable to demonstrate a relationship between BMD of the lumbar spine or hip and PPI exposure during the 5 years before BMD testing. In this study, use of PPIs was not associated with more rapid rates of BMD decline.

To add to the existing literature, a case-control study published in 2010 (Gastroenterology 2010;139:93–101) demonstrated that the excess hip fracture risk among PPI users was only present in persons with ≥ 1 other risk factor for fracture. In this study, patients with hip fractures were more likely than controls to have previously received >2-year supply of PPIs (OR, 1.30). Higher dosages were associated with increased risk (OR, 1.41 for dosages >1.5 pills per day).

Multiple meta-analyses assessing the risk of PPI use and fractures were published in 2011 (Eur J Gastroenterol Hepatol 2011;23:794–800; Am J Med 2011;124:519–526; Ann Fam Med 2011;9:257–267; Am J Gastroenterol 2011;106:1209–1218; Bone 2011;48:768–776). The majority of the studies concluded that the risk of hip fracture increased moderately among PPI users (relative risk, 1.2–1.30) in addition to spine fractures (relative risk, 1.6). However, the studies were limited by significantly heterogeneity, and when studies were adjusted for other risk factors for fracture, PPIs were no longer causal. H₂-receptor antagonists did not seem to be associated risk with fractures.

Based on these studies, it appears that low BMD may be a marker for other comorbid conditions that predispose subjects to use PPI and other medical therapy rather than a direct sequelae of PPI therapy. A study published in 2011 that calculated a “refractory GERD score” determined that higher use PPI was associated with female gender, higher comorbidity scores, and greater overall costs (Aliment Pharmacol Ther 2011;34:555–567).

Should every GERD patient in our gastroenterology practices be started on vitamin D and calcium therapy with their PPI prescriptions and referred for BMD testing? Based on the recent study from Targownik et al and the prior literature, I would make the argument that the typical GERD patient without significant comorbidities or risk for fractures not be referred to the bone density clinic for testing and treatment. However, gastroenterol-

ogists should discuss this issue with GERD patients who do have other risk factors for hip fracture so that testing can be performed if indicated. Certainly in GERD patients with established osteoporosis, PPI therapy should be continued if indicated because there is no evidence that it worsens this preexisting condition. In patients with milder heartburn symptoms, step-down therapy to H₂-receptor antagonists can be considered if patients have adequately controlled symptoms and are able to demonstrate healing of erosive esophagitis.

Certainly, in patients with GERD symptoms that are not relieved by PPI therapy, diagnostic testing should occur with ambulatory pH monitoring, esophageal manometry, and other testing as indicate to demonstrate that long-term PPI therapy is warranted.

LAUREN B. GERSON

Stanford University School of Medicine
Stanford, California

FIRST-LINE ERADICATION THERAPY FOR *HELICOBACTER PYLORI*: TIME FOR A CHANGE?

Liou J-M, Chen C-C, Chen M-J, et al. Sequential versus triple therapy for the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomised trial. *Lancet* 2013;381:205–213.

Helicobacter pylori is causally implicated in the pathogenesis of peptic ulcer disease and distal gastric adenocarcinoma (IARC Monogr Eval Carcinog Risk Hum 1994; 61:177–241; JAMA 1994;272:65–69). Triple therapy, consisting of a proton pump inhibitor (PPI) in combination with 2 antibiotics, which is currently used as a first-line treatment regimen for the eradication of *H pylori*, is not achieving acceptable eradication rates in some parts of the world (Nat Clin Pract Gastroenterol Hepatol 2008;5:321–331). This is driven, in part, by antimicrobial resistance to the antibiotics used, and has led some opinion leaders to call for a change in first-line eradication therapy. Sequential therapy consists of a PPI with amoxicillin for 5 days, followed by PPI with a 5-nitroimidazole and clarithromycin for a further 5 days. A meta-analysis of randomized controlled trials demonstrated superior eradication rates with sequential therapy compared with standard triple therapy (Ann Intern Med 2008;148:923–931), although many of these trials only compared sequential therapy with triple therapy for 7 days, whereas US guidelines recommend that triple therapy should be given for 14 days (Am J Gastroenterol 2007;102:1808–1825).

The authors conducted an open-label, randomized, controlled trial of sequential therapy for 10 days, sequential therapy for 14 days, or standard triple therapy for 14 days in *H pylori*-positive individuals recruited from 6 gastroenterology clinics in Taiwan. Patients were block randomized in a 1:1:1 ratio to receive the 3 eradication regimens, with treatment allocation concealed until after

the intervention was assigned. Patients were classified as *H pylori* positive if infection was confirmed using ≥ 2 of rapid urease testing, histology, culture, or serology. A subgroup of 201 patients was also enrolled based on a positive carbon-urea breath test (CUBT) only. Post-therapy *H pylori* status was confirmed ≥ 6 weeks after the end of treatment using a CUBT, using a previously validated threshold to confirm a positive test. Antibiotic resistance rates were examined using culture of *H pylori*, with assessment of minimum inhibitory concentrations for each antibiotic used. The primary outcome was *H pylori* eradication rate with each therapy, using an intention-to-treat analysis. Secondary endpoints included adverse event rates and compliance. Those individuals who failed first-line therapy were offered retreatment with a modified sequential therapy given for 14 days.

In total, 900 *H pylori*-positive patients were enrolled, 300 in each of the 3 treatment arms. Eradication rates were superior in the 14-day sequential therapy arm, compared with the 14-day triple therapy arm (90.7% vs 82.3%; $P = .003$), with a number needed to treat to prevent 1 patient failing therapy of 12. There were no differences in eradication rates between 14- and 10-day sequential therapy (90.7% vs 87.0%), or 10-day sequential therapy and 14-day triple therapy (87.0% vs 82.3%). There was no difference detected in adverse event rates or compliance between any of the 3 treatment arms.

Antibiotic susceptibility data were available for 552 (61.3%) of the 900 patients. Eradication rates in all 3 groups were affected by clarithromycin resistance, and metronidazole resistance impacted on eradication rates with both the 14- and 10-day sequential therapy eradication regimens. Where strains were susceptible to both clarithromycin and metronidazole, eradication rates were significantly higher with 14-day sequential therapy compared with 14-day triple therapy (99.0% vs 90.0%; $P = .006$). The authors used these susceptibility data to construct a decision model to assess the effect of resistance rates on efficacy of all 3 therapies. In this analysis, 14- or 10-day sequential therapy was superior to 14-day triple therapy in all regions, except those with high metronidazole and low clarithromycin resistance.

Comment. The authors concluded that their findings support the use of sequential therapy as first-line therapy for *H pylori* but that, ultimately, choice of first-line eradication regimen should be based on knowledge of local antibiotic resistance rates. Despite a declining prevalence of *H pylori* prevalence worldwide, even in regions with a high risk of gastric cancer such as China, it is estimated that the number of cases of gastric cancer will double between 2005 and 2050 owing to changing population demographics (Cancer Causes Control 2009;20:2021–2029). Studies suggest that primary prevention strategies, such as searching for and eradicating the bacterium in populations at high risk of gastric cancer, may reduce the future incidence (JAMA 2004;291:187–194; Ann Intern Med 2009;151:121–128) and also reduces costs of manag-