Curr Gastroenterol Rep (2010) 12:448–457
DOI 10.1007/s11894-010-0141-0

Association of Long-Term Proton Pump Inhibitor Therapy with Bone Fractures and Effects on Absorption of Calcium, Vitamin B_{12}, Iron, and Magnesium

Tetsuhide Ito · Robert T. Jensen

Published online: 30 September 2010

Abstract Proton pump inhibitors (PPI) are one of the most widely used classes of drugs. PPIs have a very favorable safety profile, and it is unusual for a patient to stop them because of side effects. However, with increasing numbers of patients chronically taking PPIs for gastroesophageal reflux disease and other common, persistent conditions, the long-term potential adverse effects are receiving increasing attention. An insufficiently studied area receiving much attention is the long-term effect of chronic acid suppression on the absorption of vitamins and nutrients. This increased attention results from the reported potential adverse effect of chronic PPI treatment leading to an increased occurrence of bone fractures. Interest in this area has led to examination of the effects of PPIs on calcium absorption/metabolism and numerous cohort, case-control, and prospective studies of their ability to affect bone density and cause bone fractures. In this article, these studies are systematically examined, as are studies of the effects of chronic PPI use on absorption of VB_{12}, iron, and magnesium. Studies in each area have led to differing conclusions, but when examined systematically, consistent results of several studies support the conclusion that long-term adverse effects on these processes can have important clinical implications.

Keywords Proton pump inhibitor · PPI · Acid suppression · H^+K^+ATPase inhibitor · Omeprazole · Lansoprazole · Rabeprazole · Pantoprazole · Esomeprazole · Hip fractures · Vitamin B_{12} · Cobalamin · Iron deficiency anemia · Hypomagnesemia · Hypocalcemia · Osteoporosis · Zollinger-Ellison syndrome

Introduction

Several animal and human studies support the conclusion that gastric acid secretion can affect the absorption of several nutrients, vitamins, and drugs [1–3]. The effect on absorption of vitamin B_{12}, iron, calcium, and magnesium has received particular attention recently because of the widespread maintenance use of proton pump inhibitors (PPIs) and H^+K^+ATPase inhibitors (omeprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole), which are potent acid suppressants [4•, 5–8]. These drugs generate more than $13.5 billion in sales (third largest selling drug class), and in 2009 more than 119 million PPI prescriptions were written in the United States; therefore, PPIs are widely used, and many patients take them for extended periods [9]. This situation is particularly true in patients with gastroesophageal reflux disease (GERD), which occurs monthly in up to 40% of American adults; in the proportion of patients with moderate to severe GERD, long-term maintenance treatment with PPIs is needed to control symptoms [2]. Many studies show the risk of minor adverse effects from PPIs is low, with rates of withdrawal in various studies of less than 1% to 2% [8]. Furthermore, the risk of long-term adverse events in most large reports is low;

T. Ito
Department of Medicine and Bioregulatory Science,
Graduate School of Medical Science,
Kyushu University,
Fukuoka, Japan
e-mail: itopapa@intmed3.med.kyushu-u.ac.jp

R. T. Jensen (✉)
Digestive Diseases Branch, National Institutes of Diabetes and Digestive and Kidney Diseases,
National Institutes of Health,
Building 10, Room 9C-103,
Bethesda, MD 20892, USA
e-mail: robertj@bdg10.niddk.nih.gov

however, because large numbers of patients take these drugs on a long-term basis, and because of their known effects on nutrient absorption, the possible long-term effects in this area are receiving increasing attention. These studies report conflicting results, particularly the possibility that long-term PPI use increases the occurrence of bone fractures (possibly by decreasing calcium absorption) [6–8, 10–15]; can result in vitamin B_{12} deficiency [2, 3, 7, 8, 13, 16–18]; and can lead to iron deficiency [2, 3, 7, 8, 19–21]. The recent results in each of these controversial areas are briefly reviewed in this article, concentrating on articles published within the past few years.

Long-Term Use of PPIs: Effects on Vitamin B_{12} Absorption

It is well established that gastric acid secretion is needed for dietary vitamin B_{12} (VB_{12}) absorption from foods [2, 3, 22] (Table 1). VB_{12} is an essential nutrient that must be acquired from the diet and is present in foods bound to protein. The presence of gastric acid is needed for the pancreatic proteases to cleave the VB_{12} from the protein, allowing its reassociation with intrinsic factor and eventual absorption in the terminal ileum [2, 3, 18, 22]. In short-term studies, various acid suppressants (histamine-2 receptor antagonists [H2RAs], PPIs) were reported to decrease the absorption of VB_{12} from foods, but not to decrease the absorption of crystalline VB_{12}, which is not protein bound [2, 18, 23–25].

The most recent study examined 36 long-term care patients, aged 60 to 80 years (17 taking long-term PPIs, 19 not taking PPIs), and the effect of a VB_{12} nasal spray for 8 weeks on VB_{12} status (Table 1) [26•]. At baseline, the chronic PPI users had lower serum VB_{12} levels and higher methylmalonic acid levels (MMA), and a greater percentage were VB_{12}-deficient (75 vs 11%, P=0.006). After 8 weeks of VB_{12} nasal spray (500 μg, once weekly), serum VB_{12} levels were significantly increased in comparison to pretreatment in the chronic PPI users, and the frequency of VB_{12} deficiency was significantly decreased from pretreatment in the chronic PPI users (75% to 24%, P=0.012) [26•]. These authors concluded that older individuals who are long-term PPI users are at increased risk of VB_{12} deficiency, and should be more systematically screened for VB_{12} deficiency than currently performed in most institutions of chronic care. Limitations of this study include the open study design, no placebo control, and relatively small number of subjects.

In 2008, three studies evaluated the effects of PPIs on VB_{12} status and reached different conclusions (Table 1) [16, 27, 28]. Two were cross-sectional studies of elderly patients [16, 27] and one was a longitudinal study in patients with Zollinger-Ellison syndrome (ZES) [28]. In the first cross-sectional study, the effects of chronic use (> 6 years) of H2RAs (150 patients), PPIs (141 patients), or neither (251 patients) were examined in elderly patients in nursing homes or at community ambulatory care facilities [27]. Low/marginally low VB_{12} status was found in 20% of the nursing home patients and 29% of the community care patients, consistent with other studies reporting 25% in such patients, with a range of 3% to 40% [17, 27]. VB_{12} deficiency can cause neurologic disorders, including neuropathy, spinal cord degeneration, gait disorders (leading to falls), depression, and dementia, which are reversible if diagnosed in time. These results demonstrate VB_{12} deficiency is a problem in older persons, and thus the importance of identifying any contributing factor. In the first cross-sectional study, PPI use, but not H2RA use, was associated with lower VB_{12} levels, the percentage decrease in VB_{12} levels correlated with the time of PPI use, and concomitant use of oral VB_{12} delayed, but did not prevent, this decrease (Table 1) [27]. In the second cross-sectional study, serum VB_{12} levels, homocysteine (HCY) levels, and mean corpuscular volume (MCV) were compared in 125 older (> 65 years), long-term PPI users and their partners not taking PPIs (Table 1) [16]. No differences in serum VB_{12}, serum HCY, or MCV were detected. These two studies differed in populations studied, with older patients in the first study (81 vs 73 years) [27]. Other differences were the percentage of female patients (63% vs 50%) and possibly ethnicity. Whether these factors contributed to the differences in results is unclear.

The third 2008 study was a longitudinal study of patients with ZES (Table 1) [16]. Surgery offers a long-term cure in only 40% of patients with ZES [29], thus they require lifelong acid antisecretory treatment, for which PPIs are now the drugs of choice [30, 31]. In this study of 61 acid hypersecretors (46 with ZES) receiving long-term treatment (up to 12 years) with PPIs, 10% had low VB_{12} levels and 31% had normal levels with VB_{12} deficiency (increased HCY/MMA with normal folate) [16]. No decrease was seen in serum VB_{12} levels with duration of PPI treatment. This study's potential deficiencies were lack of clarity regarding whether all patients had all studies yearly, lack of a control group not taking PPIs, and no correction for possible multivitamin use. This study's results differ from a previous prospective study [18] involving 130 patients with ZES followed for a mean of 4.5 years, in which patients treated with PPIs developed lower levels of VB_{12}, but not lower levels of folate; the lower levels of VB_{12} correlated with the presence of PPI-induced hyposecretion, and the duration of PPI treatment correlated inversely with VB_{12} levels (P= 0.013). A limitation of the latter study was that serial HCY/MMA levels were not measured, so the true level of VB_{12} deficiency may have been higher.

Table 1 Long-term studies of effects of proton pump inhibitors on vitamin B_{12}

Study, year	Number of patients	Type of patient	Type of study	Study design	Results
Rozgony et al. [26•], 2010	17 (long-term PPI)/19 (no PPI)	Age 60–80 y; long-term care	Prospective	Baseline VB12 and MMA levels, and after 8-wk treatment with VB12 nasal spray in PPI users	1. At baseline, long-term PPI users had lower VB12, increased MMA, and increased % VB12 deficiency (75% vs 11%, P=0.006) 2. Nasal VB12 spray increased VB12, decreased VB12 deficiency
Dharmarajan et al. [27], 2008	659 (141 PPIs, 150 H2RA, 271 neither), over 72-mo period (average=18 mo)	Age 60–102 y; long-term care and community	Cross-sectional sample	Serum VB12, demographics, VB12 history, multivitamin use	1. H2RA use did not influence VB12 levels, but PPIs users had lower levels (P<0.00005) 2. Oral VB12 slowed, but did not prevent, decrease in VB12 levels 3. VB12 status low/marginal in 20% of nursing home and 29% of community elderly patients
den Elzen et al. [16], 2008	125 long-term (> 3 y) PPI users, 125 partners (non-PPI users)	Age ≥65 y	Cross-sectional sample	Serum VB12, HCY levels, MCV	1. No difference in VB12 levels for PPI users, nonusers 2. Low VB12 levels in 3% of users and 2% of nonusers 3. No difference in HCY levels or mean MCV
Hirschowitz et al. [28], 2008	61 acid hypersecretors (46 Zollinger-Ellison syndrome, 15 other) taking PPIs	Acid hypersecretors (basal acid output >15 mEq/h)	Longitudinal study	Yearly VB12 levels (in 41 patients for whom HCY and MMA levels were determined)	1. 10% had low VB12 levels without signs of VB12 deficiency 2. 31% had normal VB12 levels but increased MMA/HCY with normal folate levels 3. Concluded that acid decrease does not explain VB12 deficiency
Valuck and Ruscin [17], 2004	53 VB12-deficient patients compared to 212 controls for H2RA/PPI use	Age ≥65 y	Case-control study	Control for age, gender, multivitamin use, *Helicobacter pylori* infection rate, compare chronic current use of H2RA/PPIs	1. Chronic current use of PPIs/H2RAs associated with increased VB12 deficiency (OR, 4.45) 2. No association found with short-term or past H2RA/PPI use 3. Suggest chronic use of H2RA/PPI associated with higher VB12 deficiency.
Force et al. [32], 2003	125 patients requiring VB12 supplementation compared to 500 controls	Statewide Medicaid population (109,444 patients)	Case-control study	Controls matched for age, gender	1. 18% of VB12-supplemented patients exposed to chronic acid suppression (> 12 mo PPI/H2RA compared to 11% of control group (P=0.025) 2. Concluded that initiation of VB12 treatment is associated with chronic gastric acid-suppressive therapy

HCY homocysteine, *H2RA* histamine-2 receptor antagonist, *MCV* mean corpuscular volume, *MMA* methylmalonic acid, *PPI* proton pump inhibitor, *VB12* vitamin B_{12}

Two older case-control studies dealing with this subject are included in Table 1 [17, 32]. In a case-control study from 2004 among a geriatric population (≥ 65 years), the use of H2RA/PPIs and several other variables were compared in 53 patients with vitamin B_{12} deficiency to 212 controls (matched for age, gender, multivitamin use, and frequency of *Helicobacter pylori* infection) [17]. The current chronic use of H2RA/PPIs was associated with a significant increase in risk of VB_{12} deficiency (OR, 4.45), and no association was found with past or short-term H2RA/PPI use. The authors concluded their results support an association between chronic use of H2RA/PPIs by older adults and the development of VB_{12} deficiency. In a second case-control study from 2003, involving 10,844 statewide Medicaid patients, 125 patients who had parenteral VB_{12} supplementation started were identified, and the frequency of

chronic H2RA/PPI use and other variables were compared to 500 age- and gender-matched controls (Table 1) [32]. For the patients requiring VB_{12} supplementation, 18% had been exposed to chronic suppressive acid therapy (> 12 months of H2RA/PPI) compared to 11% of the control group, which was a significant difference (OR, 1.82; CI 1.08–3.09; P= 0.025). These study investigators concluded that an association exists between the need for parenteral VB_{12} supplementation and chronic suppressive gastric acid therapy.

Many of the studies summarized in Table 1 suggest an association among the prolonged, chronic use of gastric acid-suppressant drugs (particularly PPIs), the development of lower VB_{12} levels, and an increased frequency of VB_{12} deficiency, especially in the older population. However, this finding is neither firmly established nor widely acted on, and thus remains controversial. Although needed, randomized trials would be costly and adequate control groups would be difficult to define; thus it is unlikely they will be forthcoming. Based on the available information, it would seem appropriate to evaluate VB_{12} status at appropriate intervals in long-term users of PPIs, especially in the older population, who may have poorer nutrition and lower body stores initially, and in unique groups of patients requiring lifelong PPI treatments (eg, those with ZES or other gastric acid hypersecretory states).

Long-Term Use of PPIs: Effects on Calcium Absorption/Metabolism and Bone Fractures

The effect of PPIs on calcium absorption/metabolism has received much attention recently and is even more controversial than its possible effect on VB_{12} status. In a 2006 nested case-control study using the General Practice Research database from the United Kingdom, Yang et al. [6] reported that long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fractures (Table 2). The study cohort consisted of PPI users and non-users of acid suppression drugs who were aged older than 50 years, and included all patients with an incident hip fracture between 1987 and 2003 (Table 2) [6]. PPIs (OR 1.44; 95% CI, 1.3–1.59) and H2RAs (OR 1.23; 95% CI, 1.09–1.40) taken for longer than 1 year were associated with an increased risk of hip fractures, and the risk was significantly greater with PPI use than with H2RAs (adjusted OR [AOR] for >1 year of use 1.34; 95% CI, 1.14–1.38). The adjusted rate of hip fractures was significantly higher in patients who were prescribed long-term, high-dose (> 1.75-fold average daily dose) PPIs (AOR, 2.65), and the risk progressively increased with the duration of PPI treatment [6]. The positive association with hip fractures and PPI therapy was stronger in men (OR 1.78; 95% CI, 1.42–2.22) than in women. These results were consistent with a 2006 case-control study by Vestergaard et al. [33] in a Danish population, which showed that PPI use was associated with an increased risk of hip fractures (OR, 1.45; 95% CI, 1.28–1.165) (Table 2). In contrast to the study by Yang et al. [6], the study by Vestergaard et al. [33] observed neither a dose-response effect nor a duration-response effect of PPI use with hip fractures. This finding may be related to the difference in follow-up in the two studies, with a follow-up of 15 years in the study by Yang et al. [6] and only 5 years in the study by Vestergaard et al. [33]. Several subsequent studies showed differing results, which are discussed in this section (Table 2).

Limited animal and human studies show that gastric acid secretion can facilitate calcium absorption and that acid suppressants (eg, PPIs) can decrease calcium absorption and decrease bone density [4•, 6, 13, 34–38]. An acidic environment in the stomach facilitates the release of ionized calcium from insoluble calcium salts, and calcium solubilization is thought to be important for calcium absorption [4•, 6, 13, 34–38]. Several conditions that cause hypochlorhydria or achlorhydria in humans (eg, gastrectomy, pernicious anemia, and atrophic gastritis) are associated with an increased occurrence of osteoporosis and bone fracture; it is assumed that these conditions are secondary to the effect of low gastric acid levels on calcium absorption [4•, 6, 13, 34–36, 39]. Limited experimental evidence indicates that PPIs also may potentially influence bone resorption by inhibiting the osteoclastic proton transport system, thus ameliorating the negative effect of PPIs increasing the occurrence of osteoporosis by decreasing calcium absorption [6, 39–41].

The large, case-control studies by Yang et al. [6] and Vestergaard et al. [33] led to considerable interest in the possibility that chronic PPI use could lead to an increase in bone fractures, and resulted in speculation about the possible mechanisms [5, 9, 10, 13, 42–46]. These studies and others reviewed below aroused sufficient attention that in May 2010, the US Food and Drug Administration (FDA) issued a warning of the "possible increased risk of fractures of the hip, wrist, and spine with high doses or long-term use of a class of medications called proton pump inhibitors. The product labeling will be changed to describe this possible increased risk" (US FDA News Release, May 25, 2010).

Since 2006, five studies [14••, 33, 37, 43, 47] reported that long-term use of PPIs is associated with an increased occurrence of bone fractures, whereas two studies [12, 15] reported no association. Only Roux et al. [48••] prospectively studied the effect of PPIs on bone fractures, whereas the others were either nested control studies, cross-sectional studies, or cohort studies (Table 2). The investigation by Roux et al. [48••] was confined to 1211 postmenopausal females who were studied at baseline and at the end of a 6-year period for vertebral fractures assessed by radiographs

Table 2 Long-term studies of effects of proton pump inhibitors on calcium absorption/metabolism and/or bone fractures

Study, year	Number of patients	Type of patient	Type of study	Study design	Results
Wright et al. [38], 2010	12 healthy volunteers	Healthy volunteers	Placebo-controlled, double-blind, crossover study	Purpose: to evaluate the acute effect of omeprazole on intestinal calcium absorption	Neither calcium absorption nor urinary calcium levels differed between PPI use (3 days) and placebo group, despite marked difference in gastric acid suppression
Gray et al. [14••], 2010	N	Age 50–79 y	Prospective	Follow-up 7.8 y: compare drug information with main outcomes of self-reported fractures, and for subsample, 3-y change in BMD	1. Multivariate adjusted HRs for current PPI use were 1.00 (95% CI, 1.18–1.82) for hip fractures; 1.47 (CI 1.05–1.51) for spine; 1.26 (CI, 1.15–1.36) for total fractures 2. PPI use associated with marginal effect on 3-y BMD change at hip (P=0.05), but not other sites
Targownik et al. [12], 2010	**1.** 2193 patients (hip) (3956 spine) with decreased BMD compared to 5527 (hip) (10,257 spine) controls without **2.** 2193 longitudinal BMD study	Patients from MBMDD	Cross-sectional and longitudinal study	1. Patients in MBMDD with hip/lumbar decreased BMD (t score≤-2.5) compared to 3 controls 2. Compare all patients who had 2 BMD measurements between 2001 and 2006 (n=2549).	1. PPI use >1500 doses over 5 y not associated with having osteoporosis at the hip (OR, 0.84; 95% CI, 0.55–1.34) or lumbar spine (OR, 0.79; CI, 0.59–1.06) 2. In the longitudinal study, PPIs did not cause significant decrease in BMD at either the hip or lumbar spine
Corley [47], 2009	33,592 patients with hip fracture matched to 130,741 controls (Kaiser database)	All patients with hip fracture matched to control (age, gender, ethnicity	Nested control study	Identified all cases of hip fracture in Kaiser database and then matched to 4 controls with similar age, gender, and ethnicity; analyzed PPI/H2RA use	1. Patients using PPI ≥2 y had 30% increased risk of hip fracture (OR, 1.3; 95% CI, 1.21–1.39) and patients using H2RA had 18% increased risk 2. Higher doses for longer time had greater risk (PPI dosage >1.5 pills for 8–10 y, OR, 39; CI 1.4–4.08) 3. Greatest risk for patients age 50–59 y (OR, 2.31; CI, 1.67–3.19) 4. Risk of hip fracture increased with time/dose of PPI
Roux et al. [48••], 2009	1211 postmenopausal women	Postmenopausal women in osteoporosis and ultrasound study	Prospective study	At baseline and end of 6-y follow-up, vertebral fractures assessed by radiographs and correlated with PPI use	1. At baseline, 5% were using omeprazole 2. Age-adjusted rates for vertebral fractures were 1.89 (omeprazole users) and 0.60 per 100 person-years for nonusers (RR, 3.41; P=0.009) 3. Multivariate analysis risk factors include omeprazole use (RR, 3.10; P=0.0271), age >65 y (RR, 2.34; P=0.44), low lumbar spine BMD (RR, 2.38; P=0.04)
Kirkpantur et al. [11], 2009	68 maintenance hemodialysis patients (group 1, 36 PPI users, group 2, 32 PPI nonusers)	Maintenance hemodialysis patients	Cohort study	Radius, hip, and spine BMD assessed and correlated with PPI use and other variables	1. Mean duration of PPI use: 27±5 mo 2. PPI users had lower BMD at all sites (P=0.019–0.04) 3. Serum calcium, PTH, and phosphate were similar in both groups 4. Multivariable analysis for PPI use >18 mo: 1.31 for low BMD in radius, 0.98 in femoral neck, 0.94 in trochanter, 1.19 in lumbar spine

Table 2 (continued)

Study, year	Number of patients	Type of patient	Type of study	Study design	Results
Kaye and Jick [15], 2008	1. Phase 1: 4414 patients each matched to up to 10 controls 2. Phase 2: 1098 cases vs 10,923 controls	Ages 50–79 from GPRD (UK)	Two-phase, matched, nested control study	Phase 1: Match cases with hip fracture between 1995 and 2005 to controls Phase 2: Match cases and controls without major risk factors for hip fracture	1. Phase 1: PPI use did not increase risk of hip fracture (OR, 0.9; 95% CI, 07–1.1) 2. No evidence for association of hip fracture with increased PPI dose or with a specific PPI
Targownik et al. [49], 2008	15,792 cases of osteoporosis-related fracture matched with 47,289 controls for age, gender, and comorbidities	In Population Health Research Data Repository (Manitoba), identified all with hip, vertebra, wrist fracture from 1996–2004	Retrospective, matched cohort study	Compared PPI use and other variables in those with or without fractures	1. PPI use≤6 y not associated with increased fractures 2. PPI use >6 y associated with increased risk of fractures (AOR, 1.92; 95% CI, 1.16–3.18, P=0.011). 3. PPI use ≥5 y associated with increased risk of hip fracture (AOR, 1.62; CI, .02–2.58, P=0.04); and even higher risk after ≥7 y (AOR, 4.55; CI, 1.68–12.39, P=0.002)
Yu et al. [37], 2008	5755 men and 5339 women >65 y from the MrOS and SOF studies	Age >65 y with SOF women recruited 1986–1988, men recruited 2000–2002 (community dwelling)	Cohort study and prospective	Compared PPI use and other variables to BMD and BMD change with time	1. On multivariate analysis, men, but not women, using either PPIs or H2RA had lower BMD (hip, femur) (P<0.01) 2. PPIs in women increased the rate of nonspinal fracture (RH, 1.34; CI, 1.10–1.64) 3. PPIs in men not taking calcium supplements increased the rate of nonspinal fracture (RH, 1.49; CI, 1.04–2.14) 4. No increased rate of bone loss with time in PPI/H2RA users (P=0.09)
Yang et al. [6], 2006	13,556 hip fracture cases and 135,386 controls from GPRD (UK) database	Age >50 y	Nested case-control study	Compared characteristics including PPI/H2RA use in patients with/without hip fractures	1. Overall adjusted OR for hip fracture for patients on PPIs >1 y was increased at 1.44 (95% CI, 1.30–1.59) 2. Risk of hip fracture increased in both H2RA (OR, 1.23) and PPI users >1 y (OR, 1.44) 3. Risk increased with duration of PPI use and was higher with high PPI dose (> 1.75 average) (AOR, 2.65).
Vestergaard et al. [33], 2006	124,655 with fracture and 373,962 controls from Danish population for the year 2000	All cases with any fracture and controls (age/gender matched)	Case-control study	Compared characteristics with primary endpoint; use of PPI, H2RA, antacids	1. PPIs associated with increased risk of fracture (OR, 1.18; 95% CI, 1.12–1.43): OR, 1.45, CI 1.28–1.65 for hip; OR, 1.60, CI 1.25–2.04 for spine 2. H2RA associated with a decreased risk if used within past year 3. Antacids did not change overall risk, but increased risk for hip and spine fractures 4. No dose-response was seen with PPIs

AOR adjusted odds ratio, *BMD* bone mineral density measured by densitometry, *GPRD (UK)* General Practice Research Database (United Kingdom), *HCY* homocysteine, *H2RA* histamine-2 receptor antagonist, *MBMDD* Manitoba Bone Mineral Density Database, *MCV* mean corpuscular volume, *MMA* methylmalonic acid, *MrOS* Osteoporotic Fractures of Men Study, *PPI* proton pump inhibitor, *PTH* parathyroid hormone, *RH* relative hazard, *SOF* Study of Osteoporotic fractures, *WHI* Women's Health Initiative Observation Study and Clinical Trials

and correlated with PPI use (Table 2). The age-adjusted rate for vertebral fractures was 3.1-fold higher in chronic PPI users compared to nonusers (1.89 vs 0.60 per 100 person-years). This increase is larger than the 18% risk for any fracture, 45% increase for hip fracture, and 60% increase for spine fracture with chronic PPI use reported by Vestergaard et al. [33]; the 23% increase reported for hip fractures by Yang et al. [6]; the 34% increase reported for women in nonspinal fractures by Yu et al. [9]; the 92% increase reported by Targownik et al. [43]; the 30% increase reported by Corley et al. [47]; and the 47% increase reported for spine and 26% increase for total fractures reported by Gray et al. [14••] (Table 2).

The study by Yang et al. [6] presented evidence of both an increasing effect of higher doses of PPIs on hip fractures and an increasing effect with longer durations of chronic PPI use (Table 2). Similar results were reported by Corley et al. [47]. In the 2008 study by Targownik et al. [49], a time-dependent effect was seen: PPI use for 6 years or less was not associated with an increased occurrence of all fractures; however, PPI use longer than 6 years was associated with a 92% increase in all fractures, and PPI use longer than 5 years was associated with a 62% increase in hip fractures (Table 2). In contrast, no dose effect was seen in the study by Vestergaard et al. [33]. These results raise the possibility that a factor contributing to the variability in the different studies (other than different study methods, populations, and methods of assessing fracture rate) is the failure to clearly define the daily amount of PPI and the duration of its use in the patients studied. This issue is a particular problem now that PPIs are available over the counter, and can be missed as a patient medication even with careful questioning.

Although most of the above studies support the conclusion that chronic PPI use is associated with an increased occurrence of bone fractures, the likely mechanism of this effect is not clear [5, 12, 13, 37, 38, 42, 45, 48••]. The most widely assumed mechanism is that long-term PPI use leads to decreased intestinal absorption of calcium, resulting in negative calcium balance, increased osteoporosis, development of secondary hyperparathyroidism, increased bone loss, and increased fractures [5, 12, 13, 37–39, 42, 45, 48••]. Each of these findings is controversial, even the effect of PPIs on calcium absorption. Calcium is thought to be absorbed in ionized form primarily in the upper small intestine, and the ionization is facilitated by an acidic medium to release calcium from its salt form or food complex [4•, 6, 13, 34–38]. Animal studies show that PPIs, H2RAs, and achlorhydria can reduce calcium absorption and/or acid increased calcium absorption [34, 42]. Short-term studies in humans have provided conflicting results. In some studies, PPIs, H2RAs, or achlorhydria were shown to decrease calcium absorption [35, 39, 50, 51], with omeprazole causing a 41% decrease in one study [35], whereas in other studies they have not decreased calcium absorption (Table 2) [38, 39, 52–55]. The 2010 study by Wright et al. [38] is particularly well done: dual, stable-isotope, state-of-the-art methods were used to assess changes in serum and urinary calcium in a placebo-controlled, double-blind, cross-over study in 12 healthy volunteers, with or without treatment for 3 days with omeprazole (20 mg, twice daily) (Table 2). In this study, neither calcium absorption nor urinary calcium levels differed between PPI treatment periods and placebo treatment, despite a marked inhibition of acid secretion in the PPI-treated group [38]. The factors contributing to these markedly different results are unclear, although one important variable in these studies may be whether they are done fasting or in a fed state [38]. Furthermore, the effects of PPIs on skeletal metabolism have not been well studied, and the available studies give differing results. In some investigations, markers of bone turnover have been altered by PPI treatment in humans, suggesting that PPIs alter bone resorption, whereas in other studies, no effect on bone turnover was seen [39, 40, 56].

The ability of PPIs to alter bone mass and/or cause osteoporosis is also unclear. In animal studies, the PPI omeprazole reduced bone density [57]. In contrast, some human studies report no effect of PPIs to cause alterations in bone turnover and/or bone density, as well as no effect in causing osteoporosis. Four studies reviewed in Table 2 also investigated effects of PPIs on bone mineral density, with differing results [11, 12, 14••, 37]. In the 2010 study by Gray et al. [14••], the use of PPIs for more than 3 years was associated with a marginal decrease in hip bone mineral density (BMD), but not at other sites. In a study of patients with chronic renal disease who were on dialysis, those who chronically used PPIs had lower BMDs at all sites (P= 0.01–0.04). In the study by Yu et al. [37], women, but not men, chronically using PPIs had lower hip and femur BMD (P<0.01), and no increased rate of bone loss was seen in PPI/H2RA users (P=0.09). In the 2010 study by Targownik et al. [12], chronic PPI use was not associated with having osteoporosis of the hip or lumbar spine, and in the longitudinal part of the study, PPIs did not cause a significant change in BMD in either the hip or spine. These investigators concluded that the association between PPI use and hip fracture was probably related to factors independent of osteoporosis [12].

Other possible explanations for an effect of PPI on bone fractures and bone metabolism include PPI-induced hypergastrinemia resulting in parathyroid hyperplasia/hypertrophy and increased parathyroid hormone secretion [42, 56]; the ability of PPIs to alter the osteoclastic-based vacuolar proton pump may contribute to alterations in bone turnover and thus to fracture risk [33, 58]; an increased occurrence

of comorbidities (eg, thiazide use, different body mass index, different alcohol intake) that contribute to the development of bone fractures, in PPI users in some studies [12, 48••]; low VB_{12} levels, which have been associated with a lower BMD, may be caused by the PPIs [48••, 59, 60]; PPI users may have a different diet because of intolerances secondary to gastritis [33]; or the bone alterations may be related to PPI aggravation of gastric disease, particularly from *H. pylori* [33].

Long-Term Use of PPIs: Effects on Iron Absorption

Relatively few studies have assessed directly the long-term effect of chronic PPI use on iron absorption. The results of the available studies are controversial.

Numerous animal and human studies support the conclusion that the absorption of iron is affected by gastric acidity [2, 24, 61]. Dietary iron is present in food as either non-heme (66%) or heme iron (32%); absorption of non-heme iron is markedly improved by gastric acid. Gastric acid helps the food sources containing non-heme iron to dissociate and to solubilize the iron salts, allowing their reduction to the ferrous state, which allows the formation of complexes with ascorbate, sugars, and amines, in turn facilitating absorption [2, 24, 61]. Numerous clinical conditions associated with achlorhydria/hypochlorhydria (atrophic gastritis, pernicious anemia, gastric resections, vagotomy) have been shown to be associated with decreased iron absorption and/or iron-deficiency anemia [2, 24, 61]. In rats, PPI treatment decreased iron absorption in animals taking a low-iron diet [61]. In some studies of patients with long-term PPI use, evidence was found for decreased iron absorption, which was attributed to the PPI (decreased ferritin, iron levels, iron deficiency anemia) [20]; however, no effect was seen in other studies [21, 62]. The former study [20] was a case report of two anemic patients who failed to respond to oral iron treatment while taking a PPI, but whose iron status improved when the PPI was withdrawn. One patient tested on the PPI demonstrated decreased iron absorption, leading the authors to attribute the failure to respond to oral iron replacement to malabsorption secondary to PPI use [20]. In contrast, in a study involving 109 patients with ZES who require lifelong PPI treatment (and who had continuous PPI treatment for at least 6 years), over a 4-year period, no evidence was found of iron deficiency, decreased absorption, or decreased iron stores, although decreased levels of VB_{12} were found in many of these patients [18]. Patients with hereditary hemochromatosis are treated with frequent phlebotomies, which increase intestinal iron absorption [63•]. In a study of seven such patients [63•], PPI administration for 7 days decreased non-heme iron absorption from a meal, and long-term PPI use resulted in a significant reduction ($P<0.01$) in the yearly volume of blood that needed to be removed to keep body iron stores at the appropriate level [63•].

Long-Term Use of PPIs: Effects on Magnesium Absorption

Hypomagnesemia has been reported with PPI use in fewer than 25 cases [64–67, 68•, 69–71]. In a recent review of 10 cases [68•], the patients had been taking PPIs a mean of 8.3 years; they presented with severe symptomatic hypomagnesemia ($\leq$ 0.54 mmol/L); and morbidity was significant (fatigue, unsteadiness, paresthesia, tetany, seizures, cardiac arrhythmias, hospitalizations). The hypomagnesemia resolved when PPI therapy was stopped and recurred if PPI therapy was re-introduced [64, 65, 68•]. In some cases, hypomagnesemia was accompanied by hypokalemia and/or hypercalcemia [66, 68•, 69].

At present, the mechanism of PPI-induced hypomagnesemia is not clear. One study tested the hypothesis that it occurs in poor metabolizers of PPIs, but that was not the case [69]. The study investigators concluded that hypomagnesemia is not specific to a given PPI, but is a generic problem with the PPI class of drugs, because it recurs even when PPIs are changed from one to the other [69]. It was proposed that PPI-induced hypomagnesemia is likely caused by gastrointestinal magnesium loss, although this is unproven at present [65, 68•, 69].

Conclusions

The data reviewed here support the importance of long-term investigations of the possible effects of chronic PPI treatment on absorption of important nutrients, including calcium, vitamin B_{12}, iron, and magnesium. In general, the studies in each area have led to differing conclusions, but when examined systematically, several studies show consistent results supporting the conclusion that long-term adverse effects on these processes can have important clinical implications. In addition to studies of bone fractures, more prospective studies are urgently needed for each of these nutrients. Furthermore, whereas the clinical implications in many cases are much better defined, in almost all cases, the mechanisms of the observed clinical effects are unclear. Therefore, detailed, careful studies of the long-term effects of PPIs on the absorption of these nutrients (vitamins, minerals) and studies of PPI mechanism(s) for inducing clinical problems potentially related to these processes (fractures, anemia, VB_{12} deficiency manifestations, hypomagnesemia) are critically needed.

Acknowledgments This work was partially supported by intramural funds of the National Institutes of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Disclosure No potential conflict of interest relevant to this article was reported.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lahner E, Annibale B, Delle Fave G: **Systematic review: impaired drug absorption related to the co-administration of antisecretory therapy**. *Aliment Pharmacol Ther* 2009, **29:**1219–1229.
2. Jensen RT: **Consequences of long-term proton pump blockade: Highlighting insights from studies of patients with gastrinomas**. *Basic Clin Pharmacol Toxicol* 2006, **98:**4–19.
3. McColl KE: **Effect of proton pump inhibitors on vitamins and iron**. *Am J Gastroenterol* 2009, **104(Suppl 2):**S5–S9.
4. • Lodato F, Azzaroli F, Turco L, et al.: **Adverse effects of proton pump inhibitors**. *Best Pract Res Clin Gastroenterol* 2010, **24:**193–201. *This article is a recent general review of all adverse effects of PPIs, including the absorption of vitamins and nutrients and possible effects on bone fractures*.
5. Moayyedi P, Cranney A: **Hip fracture and proton pump inhibitor therapy: balancing the evidence for benefit and harm**. *Am J Gastroenterol* 2008, **103:**2428–2431.
6. Yang YX, Lewis JD, Epstein S, Metz DC: **Long-term proton pump inhibitor therapy and risk of hip fracture**. *JAMA* 2006, **296:**2947–2953.
7. Ali T, Roberts DN, Tierney WM: **Long-term safety concerns with proton pump inhibitors**. *Am J Med* 2009, **122:**896–903.
8. Thomson AB, Sauve MD, Kassam N, Kamitakahara H: **Safety of the long-term use of proton pump inhibitors**. *World J Gastroenterol* 2010, **16:**2323–2330.
9. Studies link PPIs to increased risk of bacterial infection, bone fracture. Today in Medicine May 21, 2010:1–4.
10. Targownik LE: **Another bad break for proton-pump inhibitors?** *Nat Rev Rheumatol* 2009, **5:**478–480.
11. Kirkpantur A, Altun B, Arici M, Turgan C: **Proton pump inhibitor omeprazole use is associated with low bone mineral density in maintenance haemodialysis patients**. *Int J Clin Pract* 2009, **63:**261–268.
12. Targownik LE, Lix LM, Leung S, Leslie WD: **Proton-pump inhibitor use is not associated with osteoporosis or accelerated bone mineral density loss**. *Gastroenterology* 2010, **138:**896–904.
13. Insogna KL: **The effect of proton pump-inhibiting drugs on mineral metabolism**. *Am J Gastroenterol* 2009, **104(Suppl 2):** S2–S4.
14. •• Gray SL, LaCroix AZ, Larson J, et al.: **Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative**. *Arch Intern Med* 2010, **170:**765–771. *This article describes a recent prospective study demonstrating that PPI use is associated with increased occurrence of bone fractures*.
15. Kaye JA, Jick H: **Proton pump inhibitor use and risk of hip fractures in patients without major risk factors**. *Pharmacotherapy* 2008, **28:**951–959.
16. den Elzen WP, Groeneveld Y, de Ruijter W, et al.: **Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals**. *Aliment Pharmacol Ther* 2008, **27:**491–497.
17. Valuck RJ, Ruscin JM: **A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults**. *J Clin Epidemiol* 2004, **57:**422–428.
18. Termanini B, Gibril F, Sutliff VE III, et al.: **Effect of long-term gastric acid suppressive therapy on serum vitamin B_{12} levels in patients with Zollinger-Ellison syndrome**. *Am J Med* 1998, **104:**422–430.
19. Nand S, Tanvetyanon T: **Proton pump inhibitors and iron deficiency: is the connection real?** *South Med J* 2004, **97:**799.
20. Sharma VR, Brannon MA, Carloss EA: **Effect of omeprazole on oral iron replacement in patients with iron deficiency anemia**. *South Med J* 2004, **97:**887–889.
21. Stewart CA, Termanini B, Sutliff VE, et al.: **Assessment of the risk of iron malabsorption in patients with Zollinger-Ellison syndrome treated with long-term gastric acid antisecretory therapy**. *Aliment Pharmacol Ther* 1998, **12:**83–98.
22. Festen HP: **Intrinsic factor secretion and cobalamin absorption. Physiology and pathophysiology in the gastrointestinal tract**. *Scand J Gastroenterol* 1991, **26:**1–7.
23. Dutta SK: **Editorial: vitamin B_{12} malabsorption and omeprazole therapy**. *J Am Coll Nutr* 1994, **13:**544–545.
24. Koop H: **Review article: metabolic consequences of long-term inhibition of acid secretion by omeprazole**. *Aliment Pharmacol Ther* 1992, **6:**399–406.
25. Steinberg WM, King CE, Toskes PP: **Malabsorption of protein-bound cobalamin but not unbound cobalamin during cimetidine administration**. *Dig Dis Sci* 1980, **25:**188–191.
26. • Rozgony NR, Fang C, Kuczmarski MF, Bob H: **Vitamin B(12) deficiency is linked with long-term use of proton pump inhibitors in institutionalized older adults: could a cyanocobalamin nasal spray be beneficial?** *J Nutr Elder* 2010, **29:**87–99. *A recent prospective study demonstrated a marked increase of VB_{12} deficiency in elderly institutionalized participants using chronic PPIs and demonstrated the effectiveness of a VB_{12} nasal spray.*
27. Dharmarajan TS, Kanagala MR, Murakonda P, et al.: **Do acid-lowering agents affect vitamin B12 status in older adults?** *J Am Med Dir Assoc* 2008, **9:**162–167.
28. Hirschowitz BI, Worthington J, Mohnen J: **Vitamin B12 deficiency in hypersecretors during long-term acid suppression with proton pump inhibitors**. *Aliment Pharmacol Ther* 2008, **27:**1110–1121.
29. Norton JA, Fraker DL, Alexander HR, et al.: **Surgery to cure the Zollinger-Ellison syndrome**. *N Engl J Med* 1999, **341:**635–644.
30. Gibril F, Jensen RT: **Zollinger-Ellison syndrome revisited: diagnosis, biologic markers, associated inherited disorders, and acid hypersecretion**. *Curr Gastroenterol Rep* 2004, **6:**454–463.
31. Metz DC, Jensen RT: **Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors**. *Gastroenterology* 2008, **135:**1469–1492.
32. Force RW, Meeker AD, Cady PS, et al.: **Ambulatory care increased vitamin B12 requirement associated with chronic acid suppression therapy**. *Ann Pharmacother* 2003, **37:**490–493.
33. Vestergaard P, Rejnmark L, Mosekilde L: **Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture**. *Calcif Tissue Int* 2006, **79:**76–83.
34. Chonan O, Takahashi R, Yasui H, Watanuki M: **Effect of L-lactic acid on calcium absorption in rats fed omeprazole**. *J Nutr Sci Vitaminol (Tokyo)* 1998, **44:**473–481.
35. O'Connell MB, Madden DM, Murray AM, et al.: **Effects of proton pump inhibitors on calcium carbonate absorption in**

women: a randomized crossover trial. *Am J Med* 2005, **118:**778–781.
36. Sipponen P, Harkonen M: **Hypochlorhydric stomach: a risk condition for calcium malabsorption and osteoporosis?** *Scand J Gastroenterol* 2010, **45:**133–138.
37. Yu EW, Blackwell T, Ensrud KE, et al.: **Acid-suppressive medications and risk of bone loss and fracture in older adults**. *Calcif Tissue Int* 2008, **83:**251–259.
38. Wright MJ, Sullivan RR, Gaffney-Stomberg E, et al.: **Inhibiting gastric acid production does not affect intestinal calcium absorption in young healthy individuals: a randomized, crossover controlled clinical trial**. *J Bone Miner Res* 2010 (Epub ahead of print).
39. Wright MJ, Proctor DD, Insogna KL, Kerstetter JE: **Proton pump-inhibiting drugs, calcium homeostasis, and bone health**. *Nutr Rev* 2008, **66:**103–108.
40. Tuukkanen J, Vaananen HK: **Omeprazole, a specific inhibitor of H+-K+-ATPase, inhibits bone resorption in vitro**. *Calcif Tissue Int* 1986, **38:**123–125.
41. Sheraly AR, Lickorish D, Sarraf F, Davies JE: **Use of gastrointestinal proton pump inhibitors to regulate osteoclast-mediated resorption of calcium phosphate cements in vivo**. *Curr Drug Deliv* 2009, **6:**192–198.
42. Yang YX: **Proton pump inhibitor therapy and osteoporosis**. *Curr Drug Saf* 2008, **3:**204–209.
43. Johnson DA: **Safety of proton pump inhibitors: current evidence for osteoporosis and interaction with antiplatelet agents**. *Curr Gastroenterol Rep* 2010, **12:**167–174.
44. Cote GA, Howden CW: **Potential adverse effects of proton pump inhibitors**. *Curr Gastroenterol Rep* 2008, **10:**208–214.
45. Laine L: **Proton pump inhibitors and bone fractures?** *Am J Gastroenterol* 2009, **104:**S21–S26.
46. Moayyedi P, CAG Clinical Affairs Committee: **Hip fracture and proton pump inhibitor therapy: position statement**. *Can J Gastroenterol* 2008, **22:**855–858.
47. Corley DA: **Proton pump inhibitor, H2 antagonists, and risk of hip fracture: a large population-based study [abstract]**. *Gastroenterology* 2009, **136:**A70.
48. •• Roux C, Briot K, Gossec L, et al.: **Increase in vertebral fracture risk in postmenopausal women using omeprazole**. *Calcif Tissue Int* 2009, **84:**13–19. *This article describes the only prospective study examining the effects of chronic PPI use on bone fractures, demonstrating a threefold increase in risk of vertebral fractures with chronic PPI use in postmenopausal females*.
49. Targownik LE, Lix LM, Metge CJ, et al.: **Use of proton pump inhibitors and risk of osteoporosis-related fractures**. *CMAJ* 2008, **179:**319–326.
50. Recker RR: **Calcium absorption and achlorhydria**. *N Engl J Med* 1985, **313:**70–73.
51. Graziani G, Como G, Badalamenti S, et al.: **Effect of gastric acid secretion on intestinal phosphate and calcium absorption in normal subjects**. *Nephrol Dial Transplant* 1995, **10:**1376–1380.
52. Bo-Linn GW, Davis GR, Buddrus DJ, et al.: **An evaluation of the importance of gastric acid secretion in the absorption of dietary calcium**. *J Clin Invest* 1984, **73:**640–647.
53. Serfaty-Lacrosniere C, Wood RJ, Voytko D, et al.: **Hypochlorhydria from short-term omeprazole treatment does not inhibit intestinal absorption of calcium, phosphorus, magnesium or zinc from food in humans**. *J Am Coll Nutr* 1995, **14:**364–368.
54. Knox TA, Kassarjian Z, Dawson-Hughes B, et al.: **Calcium absorption in elderly subjects on high- and low-fiber diets: effect of gastric acidity**. *Am J Clin Nutr* 1991, **53:**1480–1486.
55. Heaney RP, Smith KT, Recker RR, Hinders SM: **Meal effects on calcium absorption**. *Am J Clin Nutr* 1989, **49:**372–376.
56. Mizunashi K, Furukawa Y, Katano K, Abe K: **Effect of omeprazole, an inhibitor of H+, K(+)-ATPase, on bone resorption in humans**. *Calcif Tissue Int* 1993, **53:**21–25.
57. Cui GL, Syversen U, Zhao CM, et al.: **Long-term omeprazole treatment suppresses body weight gain and bone mineralization in young male rats**. *Scand J Gastroenterol* 2001, **36:**1011–1015.
58. Tolia V, Boyer K: **Long-term proton pump inhibitor use in children: a retrospective review of safety**. *Dig Dis Sci* 2008, **53:**385–393.
59. Tucker KL, Hannan MT, Qiao N, et al.: **Low plasma vitamin B12 is associated with lower BMD: the Framingham Osteoporosis Study**. *J Bone Miner Res* 2005, **20:**152–158.
60. Morris MS, Jacques PF, Selhub J: **Relation between homocysteine and B-vitamin status indicators and bone mineral density in older Americans**. *Bone* 2005, **37:**234–242.
61. Miret S, Simpson RJ, McKie AT: **Physiology and molecular biology of dietary iron absorption**. *Annu Rev Nutr* 2003, **23:**283–301.
62. Koop H, Bachem MG: **Serum iron, ferritin, and vitamin B_{12} during prolonged omeprazole therapy**. *J Clin Gastroenterol* 1992, **14:**288–292.
63. • Hutchinson C, Geissler CA, Powell JJ, Bomford A: **Proton pump inhibitors suppress absorption of dietary non-haem iron in hereditary haemochromatosis**. *Gut* 2007, **56:**1291–1295. *This article describes a well-done recent study demonstrating that PPIs can decrease the absorption of iron in patients with primary hemochromatosis and that its chronic use can decrease the frequency of phlebotomies needed to maintain body iron stores at correct levels*.
64. Epstein M, McGrath S, Law F: **Proton-pump inhibitors and hypomagnesemic hypoparathyroidism**. *N Engl J Med* 2006, **355:**1834–1836.
65. Cundy T, Dissanayake A: **Severe hypomagnesaemia in long-term users of proton-pump inhibitors**. *Clin Endocrinol (Oxf)* 2008, **69:**338–341.
66. Kuipers MT, Thang HD, Arntzenius AB: **Hypomagnesaemia due to use of proton pump inhibitors—a review**. *Neth J Med* 2009, **67:**169–172.
67. Shabajee N, Lamb EJ, Sturgess I, Sumathipala RW: **Omeprazole and refractory hypomagnesaemia**. *BMJ* 2008, **337:**a425.
68. • Mackay JD, Bladon PT: **Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series**. *QJM* 2010, **103:**387–395. *This recent report of the characteristics of 10 cases of PPI-induced hypomagnesemia emphasizes its refractory nature, severity of manifestations, and disappearance when the PPI is stopped.*
69. Hoorn EJ , van der Hoek J, de Man RA, et al.: **A case series of proton pump inhibitor-induced hypomagnesemia**. *Am J Kidney Dis* 2010, 56:112–116.
70. Francois M, Lévy-Bohbot N, Caron J, Durlach V: **Chronic use of proton-pump inhibitors associated with giardiasis: a rare cause of hypomagnesemic hypoparathyroidism? [in French]**. *Ann Endocrinol (Paris)* 2008, **69:**446–448.
71. Broeren MA, Geerdink EA, Vader HL, van den Wall Bake AW: **Hypomagnesemia induced by several proton-pump inhibitors**. *Ann Intern Med* 2009, **151:**755–756.