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Association of Long-term Proton Pump Inhibitor Therapy with Bone Fractures and effects on Absorption of Calcium, Vitamin B12, Iron, and Magnesium

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Abstract

Proton pump inhibitors (PPI) are now one of the most widely used classes of drugs. PPIs have proven to have a very favorable safety profile and it is unusual for a patient to stop these drugs because of side effects. However, increasing numbers of patients are chronically taking PPIs for gastroesophageal reflux disease and a number of other common persistent conditions, therefore the long-term potential adverse effects are receiving increasing attention. One area that is receiving much attention and generally has been poorly studied, is the long-term effects of chronic acid suppression on the absorption of vitamins and nutrients. This area has received increased attention because of the reported potential adverse effect of chronic PPI treatment leading to an increased occurrence of bone fractures. This has led to an increased examination of the effects of PPIs on calcium absorption/ metabolism as well as 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 well as the studies of the effects of chronic PPI usage on VB12, iron and magnesium absorption. In general the studies in each of these areas have led to differing conclusions, but when examined systematically, a number of the studies are showing consistent results that support the conclusion that long-term adverse effects on these processes can have important clinical implications.

Keywords

PPI; proton pump inhibitor; acid suppression; H⁺K⁺ATPase inhibitor; omeprazole; lansoprazole; rebeprazole; pantoprazole; esomeprazole; hip fractures; vitamin B12; cobalamin; iron deficiency anemia; hypomagnesemia; hypocalcemia; osteoporosis; Zollinger-Ellison syndrome

I. Introduction

A number of animal and human studies support the conclusion that gastric acid secretion can affect the absorption of a number of nutrients, vitamins and drugs[1–4]. Its affect on absorption of vitamin B12, iron, calcium and magnesium is receiving particular attention recently, because of the widespread maintenance use of the potent acid suppressants, proton pump inhibitors [PPIs](H⁺K⁺ ATPase inhibitors) (omeprazole, lansoprazole, pantoprazole, esomeprazole,

rabeprazole)[5,•6,7,•8,9–10]. These drugs generate more than \$13.5 billion in sales (3rd largest selling drug class) and in 2009 more than 119 million PPI prescriptions were written in the US, therefore they are very widely used, and many patients continue to take them for extended periods of time[5,11,12]. This is particularly true in patients with gastroesophageal reflux disease (GERD) which occurs monthly in up to 40% of American adults, and in the proportion with moderate to severe GERD, long term maintenance treatment with PPIs is needed to control symptoms[2,5,12,13]. Many studies show the risk of minor adverse effects from PPI is low with rates of withdrawal in various studies of <1–2% [10]. Furthermore, the risk of longer-term adverse events in most large reports is low, however, because of the large numbers of patients taking these drugs long-term and their known effects on nutrient absorption, their possible long-term affects in this area are receiving increasing attention. These studies are reporting conflicting results, particularly the possibility that long term PPI use increases the occurrence of bone fractures (possibly by decreasing calcium absorption)[•8,9,10,14–20]; can result in vitamin B12 deficiency[2,4,9,10,17,21–23] and cause lead to iron deficiency[2–4,9, 10,24–26]. The recent results in each of these controversial areas are briefly reviewed in this article, concentrating on published articles within the last few years.

II. Long-term use of PPIs and effects on vitamin B12(VB12) absorption(Table 1)

It is well established that gastric acid secretion is needed for dietary VB12 absorption from foods [2,4,27,28]. VB12 is an essential nutrient that must be acquired from the diet, is present in foods bound to protein, and the presence of gastric acid is needed for the pancreatic proteases to cleave the VB12 from the protein, allowing its reassociation with intrinsic factor (IF) and eventual absorption in the terminal ileum [2,4,23,27,28]. In short-term studies various acid suppressants (histamine H2-receptor antagonists, PPIs) have been reported to decrease the absorption of VB12 from foods, but not to decrease absorption of crystalline VB12 which is not protein bound [2,23,29–31].

The most recent study examined 34 long-term care patients aged 60-80 years [•32](Table 1) (17 taking long-term PPIs, 19 not taking PPIs) and the effect of a VB12 nasal spray for 8 weeks on the VB12 status. At baseline the chronic PPI users had lower serum VB12 levels, higher methylmalonic acid levels(MMA) and a greater percentage were VB12 deficient (75 vs. 11%, p=0.006). After 8 weeks of VB12 nasal spray (500mcg/once per week), there was a significant increase in serum VB12 levels compared to pretreatment in the chronic PPI users, and a significant decrease in the frequency of VB12 deficiency in the chronic PPI uses from pretreatment (75 to 24%, p=0.012)(Table 1) [•32]. These authors conclude that older individuals who are long-term PPI users are at increased risk of VB12 deficiency and should be more systematically screened for VB12 deficiency than is 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 included.

In 2008 three studies evaluated the effects of PPIs on VB12 status and came to different conclusions(Table 1)[21,33,34]. Two were cross sectional studies on elderly patients (pts) [21,33](Table 1) and one a longitudinal study in patients with Zollinger-Ellison syndrome (ZES)[34]. In the first cross sectional study(Table 1)[33], the effects of chronic use[over 6 yrs] of H2 receptor antagonists (H2R) (150 pts), PPIs (141 pts) or neither (251 pts) were examined in elderly patients in nursing homes or the community ambulatory care facilities (Table 1). In 20% of the nursing home patients and 29% of the community care patients low/marginally low VB12 status was found which is consistent with a number of other studies reporting 25% in such patients with a range of 3–40%[22,33,35]. VB12 deficiency can cause neurological disorders including neuropathy, spinal cord degeneration, gait disorders leading to falls, depression and dementia, which if diagnosed in time are reversible [35,36]. These results

demonstrate VB12 deficiency is a problem in the aged and therefore any participating factor that contributes to it is important to identify. In the first cross sectional study (Table 1) [33] PPI usage, but not H2R usage was associated with lower VB12 levels, the percentage decrease in VB12 levels correlated with the time of PPI usage, and concomitant use of oral VB12 did not prevent this decrease, it only delayed it. In the second cross sectional study (Table 1) [21] serum VB12 levels as well as homocysteine levels and MCV were compared in 125 aged [>65 yrs] long term PPI users and their partners not taking PPIs (Table 1). No differences in serum VB12, serum HCY levels or MCV were detected (Table 1). These two studies differed in populations studied with the patients being older in the 1st study [33] (81 vs. 73 yrs), percentage female patients (63 vs. 50%) and possibly ethnicity. Whether these factors contributed to the differences in results is unclear [35].

The third 2008 study (Table 1) [21] was a longitudinal study of patients with Zollinger-Ellison syndrome (ZES), who are curable by surgery long-term in only 40% [37,38], and thus require life-long acid antisecretory treatment of which PPIs are now the drugs of choice [39,40]. In this study of 61 acid hypersecretors (46 ZES) treated long-term (up to 12 yrs) with PPIs, 10% had low VB12 levels and 31% normal levels with VB12 deficiency (increased HCY/MMA with normal folate). No decrease with duration of PPI treatment in serum VB12 levels was seen. Potential deficiencies in this study is that it was not clear that all patients had all studies yearly, there was no control group not taking PPIs and no correction was made for possible multivitamin usage. This study's results differ from a previous prospective study [23] involving 130 ZES patients followed for a mean of 4.5 years, in which patients treated with PPIs developed lower levels of VB12, but not folate, the lower levels correlate with the presence of PPI induced hypersecretion and the duration of PPI treatment correlated inversely with VB12 levels ($P=0.013$). A limitation of the latter study was that serial HCY/MMA levels were not measured so that the true level of VB12 deficiency may have been higher.

Two older case control studies which also deal with this subject are included in Table 1 [22, 41]. In a case control study in 2004 (Table 1) [22] in a geriatric population (≥ 65 years) the usage of H2R/PPIs and a number of other variables were compared in 53 patients with vitamin B12 deficiency to 212 controls (matched for age, gender, multivitamin use, frequency of *Helicobacter pylori* infection). The current chronic use of H2R/PPIs was associated with significant increase in risk of VB12 deficiency (OR 4.45) and no association was found with past or short-term H2R/PPI usage. The authors conclude their results supported an association between chronic use of H2R/PPIs by older adults and the development of VB12 deficiency. In a second case control study from 2003 (Table 1) [41] of 10844 state-wide Medicaid patients, 125 patients who had parenteral VB12 supplementation started were identified, and the frequency of chronic H2R/PPI usage and a number of other variables compared to 500 age and gender matched controls (Table 1) [41]. For the patients requiring VB12 supplementation, 18% had been exposed to chronic suppressive acid therapy (>12 mos H2R/PPI) compares to 11% of the control group which was significant difference ($p=0.025$, OR 1.82, CI 1.08-3.09). It was concluded in this study that there is an association between the need for parenteral VB12 supplementation and chronic suppressive gastric acid therapy.

While many of the studies summarized in Table 1 suggest an association between the prolonged, chronic use of gastric acid suppressant drugs, particularly PPIs, and the development of lower VB12 levels, and an increased frequency of VB12 deficiency, especially in the aged, at present this is still not firmly established, is not widely acted on, and thus remains controversial. Randomized trials are needed, but would be costly, adequate control groups difficult to define and thus it is not apparent they will be forthcoming. With the available information, it would seem appropriate to evaluate VB12 status at appropriate intervals in long term users of PPIs, especially the aged who may have poorer nutrition and lower body stores

initially and unique groups of patients requiring life-long PPI treatments, such as those with Zollinger-Ellison syndrome or other gastric acid hypersecretory states.

II. Long-term use of PPIs and effects on calcium absorption/metabolism and bone fractures (Table 2)

The effect of PPIs on calcium absorption/metabolism has received much attention recently and is even more controversial than its possible effect on VB12 status reviewed in the preceding paragraphs. This has occurred because of two 2006 studies by Yang et al [•8] and Vestergaard et al [•42] (Table 2). Yang [•8] reported long-term PPI therapy, particularly at high doses, is associated with and increased risk of hip fractures. Yang's study (Table 2) [•8] was a nested case control study using the General Practice Research database from the United Kingdom. The study cohort consisted of PPI users and non-users of acid suppression drugs who were >50 years old and included all patients with an incident hip fractures between 1987–2003 (Table 2) [•8]. Both PPIs (OR 1.44, 95% CI-1.3–1.59) and H2Rs (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 H2Rs (AOR for >1 yr of use 1.34, 95% CI-1.14–1.38). The adjusted rate of hip fractures was significantly higher in patients prescribed long-term high dose (>1.75 average daily dose) PPIs (AOR 2.65) and the risk progressively increased with the duration of PPI treatment [•8]. The positive association with hip fractures and PPI therapy was stronger in men (OR 1.78, 95% CI-1.42–2.22) than women. The results of this study were consistent with another 2006 study (Table 2), a Danish study by Vestergaard et al [•42] which was a case-control study in a Danish population, which showed that PPI use was associated with an increased risk of hip fractures (OR, 1.45, 95% CI-1.28–1.65). In contrast to the Yang study [•8], the Vestergaard study [•42] observed neither a PPI dose-response effect nor duration-response affect of PPI usage with hip fractures. It has been proposed [•8] this difference may be due to the difference in follow-up in the two studies, with a long follow-up of 15 years in the Yang study [•8] and only 5 years in the Vestergaard study [•42]. These studies has resulted in number of subsequent studies showing differing results, which are reviewed in Table 2 and will be discussed after the next paragraph.

Limited animal and human studies show that gastric acid secretion can facilitate calcium absorption and that acid suppressants such as PPIs can decrease calcium absorption and decrease bone density [•6,•8,17,18,43–47]. An acidic environment in the stomach facilitates the release of ionized calcium from insoluble calcium salts, and the calcium solubilization is thought to be important for calcium absorption [•6,•8,17,18,43–47]. A number of conditions that cause hypo/achlorhydria in humans including gastrectomy, pernicious anemia and atrophic gastritis are associated with and increased occurrence of osteoporosis and bone fracture, and it is assumed that this is secondary to the effect of low gastric acid levels on calcium absorption [•6,•8,17,18,43–45,48]. Limited experimental evidence indicate that PPIs may also potentially affect bone resorption by inhibiting the osteoclastic proton transport system, and this affect may ameliorate the negative affect of PPIs increasing osteoporosis by decreasing calcium absorption [•8,48–50].

As pointed out above the two large, case control studies of Yang [•8] and Vestergaard [•42] (Table 2) in 2006 led to considerable interest in the possibility that chronic PPI use could lead to an increase in bone fractures and speculation of the possible mechanisms involved [7,11, 14,17,18,51–55]. These studies and others reviewed below (Table 2) aroused sufficient attention to lead in May 2010, the US Food and Drug Administration to issue 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).

Five studies (Table 2) [••19,•42,46,52,56] since 2006 have reported long-term PPIs usage is associated with an increase occurrence of bone fractures, whereas two studies (Table 2) [16, 20] report no association. Only the study by Roux et al [••57] prospectively studied the affect of PPIs on bone fractures, whereas the others were either nested control studies, cross sectional studies, or cohort studies (Table 2). Roux et al's [••57] study was confined to 1211 postmenopausal females who were studied at baseline and at the end to a 6-year period for vertebral fractures assessed by X Rays with a correlation with PPI usage (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 yrs) (Table 2). This increase is larger than the 18% risk of any fracture, 45% increase for hip fracture and 60% for spine fracture reported with chronic PPI use reported by Vestergaard [•42]; the 23% increase reported for hip fractures by Yang et al [•8]; the 34% increase reported for women in nonspinal fractures by Yu et al [11]; the 92% increase reported by Targownik et al [52]; the 30% increase reported by Corley et al [56] and 47% increase reported for spine and 26% for total fractures reported by Gray et al [••19] (Table 2).

In the study by Yang et al (Table 2)[•8] there was evidence of both an increasing affect of higher doses of PPIs on hip fractures and an increasing affect with longer durations of chronic PPI usage. Similar results were reported by Corley et al [56] and, in the 2008 study by Targownik et al [58] a time-dependent affect was seen, because PPI usage ≤ 6 yrs was not associated with an increased occurrence of all fractures, however PPI use > 6 years was associated with a 92% increase in all fractures and PPI use > 5 years with a 62% increase in hip fractures (Table 2). In contrast no dose affect was seen in the study of Vestergaard (Table 2)[•42]. These results raise the possibility that one factor that could be contributing to the variability in these different studies, besides the different methodical approaches used, frequently different populations studied and different methods of assessing fracture rate, is a failure to clearly define the daily amount of PPI usage as well as the duration of such usage in the patients studied. This is particularly a problem now that PPIs are available over the counter and can be missed as a patient medication even with careful questioning.

While most of the above studies support the conclusion that chronic PPI usage is associated with an increase occurrence of bone fractures, at present, the likely mechanism of this affect, is not at all clear [7,16,17,46,47,51,54,57]. 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 [7,16,17,46-48,51,54,57]. Each of these findings is controversial, even the affect of PPIs on calcium absorption. Calcium is though 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 [•6,•8,17,18,43-47]. Animal studies show that PPIs, H2Rs and achlorhydria can reduce and/or acid increased calcium absorption [43,51]. Short-term studies in humans have provided conflicting results. In some studies PPIs, H2Rs or achlorhydria have been shown to decreased calcium absorption [44,48,59-61] with omeprazole causing a 41% decrease in one study [44], whereas in other studies they have had not decreased calcium absorption (Table 2)[47,48,62-65]. The recent 2010 study by Wright et al (Table 2) [47] is particularly well done using dual stable isotope state of the art methods to assess changes in serum and urinary calcium in a study which was placebo-controlled, double-blind, cross-over in design in 12 healthy volunteers, with or without treatment for a three days with omeprazole (20 mg BID). 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 (Table 2) [47]. At present the factors that contribute to these markedly different results are unclear, although it has been proposed one important variable in these studies is whether they are done fasting or in a fed state [47]. Furthermore, the effects of PPIs on skeletal metabolism have not been well

studied and the studies available give differing results. In some studies markers of bone turnover have been altered by PPI treatment in humans suggesting PPIs alter bone resorption, whereas in other studies no effect on bone turnover was seen [48,49,66,67].

The ability of PPIs to alter bone mass and/or cause osteoporosis is also unclear. In animal studies the PPI omeprazole reduced bone density [68,69]. 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 at causing osteoporosis [67]. Four studies reviewed in Table 2 also investigated PPIs effects on bone mineral density and gave differing results [15,16,19,46]. In the 2010 Gray study [19] the use of PPIs for >3 yrs was associated with a marginal decrease in hip BMD, but not at other sites. In a study of chronic renal dialysis patients, those who chronically used PPIs had lower BMDs at all sites ($p=0.01-0.04$). In the Yu study (Table 2)[46] women, but not men, chronically using PPIs had lower BMD(hip, femur)($P<0.01$) and no increased rate of bone loss was seen in PPI/H2R users($p=0.09$). In the 2010 study by Targownik (Table 2) [16] chronic PPI usage 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. This study [16] concludes the association between PPI use and hip fracture was probably related to factors independent of osteoporosis.

Other possible explanations have been raised for an effect of PPI on bone fractures and bone metabolism include PPI induced hypergastrinemia resulting in parathyroid hyperplasia/hypertrophy and increased PTH secretion [51,66]; the ability of PPIs to alter the osteoclastic-based vacuolar proton pump may contribute to alterations in bone turnover and contribute to fracture risk [42,70]; an increased occurrence of co-morbidities (i.e., thiazide use, different BMI, different alcohol intake, etc) that contribute to the development of bone fractures, may be present in PPI users in some studies [16,57]; low VB12 levels may be caused by the PPIs which has been associated with a lower BMD [57,71,72]; PPI users may have a different diet because intolerances secondary to gastritis [42]; or the bone alterations may be related to PPI aggravation of gastric disease, particularly that due to *H. pylori*[42].

III. Long-term use of PPIs and effects on Iron absorption

There are relatively few studies assessing directly the long-term effect of chronic PPI use on iron absorption and the results of the studies available are controversial.

Numerous animal, as well as human support the conclusion that the absorption of iron is affected by gastric acidity [2,30,73,74]. Dietary iron is present in food as either non-heme (66%) or heme iron(32%), and the non-heme iron's absorption is markedly improved by gastric acid. Gastric acid helps the non-heme iron containing food sources to dissociate the iron salts, helps to solubilize the iron salts which allows them to be reduced to the ferrous state, which allows the formation of complexes with ascorbate, sugars and amines which in turn, facilitates absorption [2,30,73,74]. 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 [2,3,30,73,74]. In rats, PPI treatment decreased iron absorption in animals taking a low iron diet [74]. In some studies of patients with long-term PPI use evidence for decreased iron absorption has been found which was attributed to the PPI (decreased ferritin, iron levels, iron deficiency anemia) [25], whereas in other studies no effect was seen [26,75]. The former study [25] 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 [25] leading the authors to attribute the failure to respond to oral iron replacement due to malabsorption from secondary to PPI use. In contrast, in one study involving 109 patients with ZES who require life-long PPI treatment, and had

continuous PPI treatment for at least 6 years, over a 4 year period, no evidence of iron deficiency or decreased absorption and decreased iron stores was found, although decreased VB12 level were found in many of these patients [23]. Patients with hereditary hemochromatosis are treated with frequent phlebotomies, which increase intestinal iron absorption [•76]. In a study of 7 such patients [•76], 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 [•76].

IV. Long-term use of PPIs and effects on magnesium absorption

Hypomagnesemia has been reported with PPI use in <25 cases [77–84]. In a recent review of 10 cases [•81], the patients had been taking PPIs a mean of 8.3 yrs; they presented with severe symptomatic hypomagnesemia (≤ 0.54 mmol/l); and there was significant morbidity (fatigue, unsteadiness, parenthesis, tetany, seizures, cardiac arrhythmias, hospitalizations). The hypomagnesemia resolved when the PPI therapy was stopped and recurred if the PPI therapy was re-introduced [77,78,81]. In some cases the hypomagnesemia is accompanied by hypokalemia and/or hypercalcemia [79,81,82].

At present the mechanism(s) of the PPI induced hypomagnesemia is not clear. One study tested the hypothesis that it occurs in poor metabolizers of PPI, but that was not the case [82]. It was concluded in one study that it 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 [82]. It was proposed that PPI-induced hypomagnesemia is likely due to gastrointestinal magnesium loss, although this is unproven at present [78,81,82].

V. 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 B12, iron and magnesium. In general, the studies in each of these areas have led to differing conclusions, but when examined systematically, a number of the studies are showing consistent results that support the conclusion that long-term adverse effects on these processes can have important clinical implications. What are badly needed for each of these nutrients, as well as studies of bone fractures, are more prospective studies. Furthermore, whereas the clinical implications in a number of cases are being 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, mineral) and studies of the PPI's mechanism(s) at inducing clinical problems potentially related to these processes (fractures, anemia, VB12 deficiency manifestations, hypomagnesemia) are badly needed.

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Table 1

Long-term studies of effects of PPIs on vitamin B12 (VB12)

Year Study	Number, Pts(Pt)	Type Patient	Type Study	Study Design	Results	Ref
2010	17 (long-term PPI)/ 19 (no PPI)	Age 60–80 yrs Long-term care	Prospective	Baseline VB12, MMA levels and after 8 wk treatment with VB12 nasal spray in PPI users	1. At baseline long-term PPI users had lower VB12, Inc MMA and inc % VB12 deficiency (75% vs. 11%, p=0.006). 2. Nasal V12 spray Inc VB12, dec VB12 deficiency	[*32]
2008	659 141 PPIs, 150 H2R, 271 neither, over 72 mo time (Ave=18 mos)	Pts (age 60– 102 yrs)- Long-term care and community	Cross sectional sample	Serum VB12, demographics, VB12 history, multivitamin use	1. H2R usage did not influence VB12 levels but PPIs users had lower levels (p=0<0.00005). 2. Oral VB12 slowed but did not prevent decrease in VB12 levels 3. VB12 status low/marginal in 20% nursing home and 29% community elderly patients.	[33]
2008	125 long-term (>3yrs) PPI uses, 125 partners (non PPI users)	Aged ≥ 65 yrs	Cross sectional sample	Serum VB12, homocysteine levels (HCY), MCV	1. No difference in VB12 levels for PPI users, nonusers 2. 3% of users and 2% nonusers had low VB12 levels 3. No difference in HCY levels or mean MCV.	[21]
2008	61 acid hypersecretors (46 ZES, 15 other) taking PPIs	Acid hypersecretors (BAO>15 mEq/hr)	Longitudinal study	Yearly VB12 levels, 41 pts HCY and MMA levels determined (in	1. 10% had low VB12 levels without signs VB12 deficiency 2. 31% normal VB12 levels but inc MMA/HCY with normal folate levels 3. Concluded acid dec not explain VB12 deficiency.	[34]
2004	53 VB12 deficient pts compared to 212 controls for H2R/PPI use	Aged ≥ 65 yrs	Case control study	Control for age, gender. Multivitamin use, HP infection rate, compare chronic current use of H2R/PPIs	1. Chronic current use of PPIs/H2R's associated inc VB12 deficiency (OR 4.45) 2. No association with short-term or past H2R/PPI use found 3. Suggest Chronic use H2R/PPI associated with higher VB12 deficiency.	[22]
2003	125 pts requiring VB12 supplementation compared to 500 controls	State-wide Medicaid population (109,444 pts)	Case control study	Controls matched for age, gender.	1. 18% of VB12 supplemented patients exposed to chronic acid suppression (>12 mos PPI/H2R0 compared to 11% of control group (p=0.025) 2. Conclude initiation of VB12 treatment is associated with chronic gastric acid suppressive therapy	[41]

Abbreviations. PPI-proton pump inhibitor; H2R-Histamine H2-receptor antagonist; wk-weeks; mo-month; yr-year; MMA-methylmalonic acid, HCY-homocysteine, MCV-mean corpuscular volume; Ave – average; inc-increase; dec-decrease

Table 2
Long-term studies of effects of PPIs on calcium absorption/metabolism and/or bone fractures)

Author(Yr) Study	Number. Pts(Pt)	Type Patient	Type Study	Study Design	Results	Ref
Wright (2010, in press)	12 healthy volunteers	Healthy volunteers	Placebo- controlled, double blind, cross-over study	Purpose: to evaluate the acute effect of OMEP on intestinal calcium absorption	1. Neither calcium absorption nor urinary calcium levels differed between PPI use (3 days) and placebo group, despite marked difference in gastric acid suppression	[47]
Gray (2010)	130,487 females, enrolled in WHI Observations study with mean F/U of 7.8 yrs	Age 50–79	Prospective	F/u 7.8 yrs, compare drug information with main outcomes self-reported fractures, and for subsample 3 year change in BMD	1. Multivariate adjusted hazard ratios 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. Use of PPIs associated with marginal effect on 3 yr BMD change at hip (p=0.05), but not other sites.	[••19]
Targownik (2010)	1. 2193 pts (hip)[3956 spine] with dec BMD compared to 5527 (hip) [10257 spine] controls without. 2. 2193 longitudinal BMD study	Pts from Manitoba Bone Mineral Density Database (MBMDD)	Cross sectional and longitudinal study	1. Pts in MBMDD with hip/lumbar dec BMD (t score ≤ -2.5) compare 3 controls 2. Compare all pts who had 2 BMD between 2001–6 (n=2549).	1. PPI usage 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) for PPI use of >1500 doses over 5 yrs 2. In the longitudinal study PPIs did not cause significant decrease in BMD at either the hip or lumbar spine	[16]
Corley (2009)	33,592 pts with hip fracture matched to 130,741 control (Kaiser database)	All patients with hip fracture matched to control (age, gender, ethnicity)	Nested control study	Identified all cases hip fracture in Kaiser database and then matched to 4 controls with similar age, gender, ethnicity. Analyzed PPI/H2R use	1. Pts using PPI $\geq$ 2yrs had 30% inc risk of hip fracture (OR, 1.3, 95% CI-1.21–1.39) and H2R 18% inc 2. Higher doses for longer time had greater risk (>1.5 pills PPI for 8–10 yrs, OR39, CI 1.4–4.08. 3. Greatest risk for pt 50–59 yrs of age, OR, 2.31, CI 1.67–3.19. 4. Risk of hip fracture inc with time /dose of PPI	[56]
Roux (2009)	1211 postmenopausal women	Postmenopausal women in Osteoporosis and Ultrasound study	Prospective study	At baseline and end of 6yr F/u vertebral fractures assessed by X-Ray 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 yrs for nonusers (RR 3.41)(p=0.009) 3. Multivariate analysis risk factors include omeprazole use (RR 3.10, p=0.027), age >65 (RR2.34, p=0.44), low lumbar spine BMD (RR-2.38, p=0.04)	[••57]
Kirkpantur (2009)	68 maintenance hemodialysis pts (Group 1–36 PPI users, Group 2 (32, PPI nonusers)	Maintenance hemodialysis pts	Cohort study	Radius, hip, and spine BMD assessment and correlated with PPI use and other variables	1. Mean duration of PPI use was 27 ± 5 mos. 2. PPI users had lower BMD at all sites(p=0.019–0.04) 3. Serum Ca, PTH, phosphate similar two groups	[15]

Author(Yr) Study	Number, Pts(Pt)	Type Patient	Type Study	Study Design	Results	Ref
Kaye (2008)	1. Phase 1: 4414 pts each matched to up to 10 controls 2. Phase 2: 1098 cases vs. 10923 controls	Aged 50–79 from United Kingdom General Practice Research Database (GPRD)	Two phase, matched, nested control study	Phase 1: Match cases with hip fracture between 1995–2005 to controls Phase 2: match cases and control without major risk factors for hip fracture	4. Multivariable analysis for > 18 mos PPI use, was 1.31 for low BMD in the radius, 0.98 femoral neck, 0.94 trochanter, 1.19 in lumbar spine 1. Phase 1: PPIs usage did not increase risk of hip fracture (OR, 0.9, 95% CI 0.7–1.1) 2. No evidence for association of hip fracture with increased PPI dose or with a specific PPI	[20]
Tangownik (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 1999–2004	Retrospective, matched cohort study	Compared PPI use and other variables in those with or without fractures	1. PPI use ≤6 yrs not associated with inc fractures 2. PPI use >6 yrs associated with inc risk of fractures (AOR, 1.92 95% CI-1.16–3.18, p=0.011) 3. PPI use ≥5 yrs associated with inc risk hip fracture (AOR, 1.62, CI-1.02–2.58, p=0.04) and after ≥7yrs even higher risk (AOR, 4.55, CI-1.68–12.39, P=0.002)	[58]
Yu (2008)	5,755 men and 5,339 women >65 from the Osteoporotic Fractures of Men study (MrOS) and Study of Osteoporotic fractures (SOF) study	Age >65 with SOF women recruited 1986–1988, men 2000–2 community dwelling.	Cohort study and prospective	Compared PPI use and other variables to BMD and BMB change with time	1. On multivariate analysis men, not women, using either PPIs/H2R had lower BMD (hip, femur)(P<0.01) 2. PPIs in women inc nonspinal fracture rate (RH, 1.34, CI-1.10–1.64) 3. PPIs in men not taking calcium supplements had inc nonspinal fracture rate (RH, 1.49, CI-1.04–2.14) 4. No inc rate of bone loss with time in PPI/H2R users (p=0.09)	[46]
Yang (2006)	13,556 hip fracture cases and 13,5386 controls from GPRD UK database	Age>50 yrs	Nested case control study	Compared characteristics including PPI/H2R use in patients with/without hip fractures	1. Overall adjusted OR for hip fracture on PPIs>1 yr was increased at 1.44 (95% CI-1.30–1.59) 2. Risk hip fracture increased in both H2R (OR 1.23) and PPI users > 1 yr (OR 1.44) 3. Risk increased with duration of PPI use and higher with high PPI dose (>1.75 average)(AOR 2.65).	[•8]
Vestergaard (2006)	124,655 with fracture and 373,962 controls from Danish population for the years 2000	All cases with any fracture and controls (age/gender matched)	Case control study	Compared characteristics with primary endpoint. Use of PPI/H2R/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; and OR-1.60, CI 1.25–2.04 for spine fracture. 2. H2R associated with a decreased risk if used within last year. 3. Antacids did not change risk overall, but increased risk for hip and spine fractures 4. No dose-response was seen with PPIs	[•42]

Abbreviations. See Table 1. Inc-increase; dec-decrease; RR-relative risk; WHI-women's Health Initiative Observation Study and Clinical Trials; F/u-follow-up; BMD-bone mineral density measured by densitometry; MBMDD -Manitoba Bone Mineral Density Database ; OR-Odds ratio, CI-confidence interval; AOR-adjusted Odds ratio;