REVIEW ARTICLE

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Proton Pump Inhibitors and Fracture Risk

True Effect or Residual Confounding?

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Abstract

Fracture is a major contributor to human morbidity and mortality, especially in the elderly. It has been discussed in the literature that conditions associated with decreased stomach acidity may lead to a decrease in intestinal calcium absorption and, consequently, to an increased fracture risk. In recent years, several observational studies reported a slightly increased fracture risk in association with the use of proton pump inhibitors (PPIs) and/or histamine H_2 receptor antagonists. It was the objective of this review to critically assess the available evidence linking PPI use to an increased fracture risk. A MEDLINE and EMBASE search from 1960 to June 2010 was performed to identify the relevant articles using predefined search terms. Because (i) there is no proven mechanism, (ii) the reported magnitude of the risk elevation associated with the use of PPIs was only weak, and (iii) the likelihood of residual confounding despite adjustment for known co-morbidities and drug use cannot be ruled out, we conclude that the currently available literature does not support the notion that the use of PPIs is causally related to a materially increased fracture risk in humans.

Fracture is a known major contributor to morbidity and mortality in the elderly. It has been shown that hip fracture is an important predictor of death in patients older than 66 years; after 2 years of follow-up, 38% of patients hospitalized due to a hip fracture died.[1] In another study, the

risk of death among elderly patients (mean age 78 years) with a hip fracture was 3.8-fold higher than in age- and sex-matched hospitalized control patients.[2] Elderly people, particularly postmenopausal women, are vulnerable to deleterious effects of drugs on their skeletal system.[3,4] Any drug known to affect bone mineral density or skeletal health in general should be prescribed with caution and based upon a prior benefit-risk evaluation. Recently, the widely used acid-suppressant proton pump inhibitors (PPIs) have been associated with an increased risk of fracture in several observational studies.[5-13] Randomized controlled trials addressing the risk of fracture in users of PPIs are currently lacking. Given the widespread use of PPIs and the enormous burden of fracture-related costs on our healthcare systems, a causal association between the use of PPIs and fracture risk would be of outstanding importance and clinical relevance. The main aim of this narrative review article is to describe the existing literature on observational studies on this issue, discussing whether the available evidence does or does not support the notion of a possible causal effect between PPI use and fracture risk. In addition, we briefly review the underlying mechanisms by which PPIs may exhibit detrimental effects on skeletal health.

1. Search Strategy

To identify relevant articles, we performed a MEDLINE and EMBASE search from 1960 to June 2010. We used the search terms 'fractures', 'bones', 'calcium absorption', 'osteoporosis', 'proton pump inhibitors' (and the individual drug names 'omeprazole', 'pantoprazole', 'lansoprazole', 'rabeprazole' and 'esomeprazole'), 'H_2 histamine receptor antagonists', 'vitamin B_{12} deficiency', 'homocysteine', 'hyperhomocysteinaemia'. We also included recent abstracts from conferences in 2009 reporting results from trials that were not yet published and therefore not available in MEDLINE or EMBASE. We included all articles written in English, French, German or Spanish in our analyses. Reference lists from retrieved articles were reviewed to ascertain inclusion of all relevant articles.

2. The Possible Role of Proton Pump Inhibitors in Skeletal Metabolism

Insufficient daily intake or absorption of calcium from the gut is associated with an increased risk of osteoporosis and fractures.[14-17] Among other factors, it has been suggested that stomach acid may play an important role in calcium absorption;[18] however, evidence from the literature is scarce.[19] Any condition that decreases stomach acidity, such as achlorhydria[20] and the use of PPIs or histamine H_2 receptor antagonists, may be related to diminished calcium absorption mainly due to the formation of insoluble calcium compounds. Unfortunately, no long-term studies are available in the literature investigating the effect of PPIs on intestinal calcium absorption. Available reports from short-term studies vary greatly with regard to study population and design used to assess calcium absorption. Recently, Insogna[21] reviewed the available literature on the effect of PPIs on mineral metabolism and concluded that current evidence from the literature is insufficient to conclude that PPIs decrease calcium absorption. In the following section, the relevant studies are briefly discussed.

To our knowledge, only two studies assessed direct effects of PPIs on bone metabolism in adults. Mizunashi et al.[22] intended to investigate whether omeprazole suppresses bone resorption by inhibiting osteoclast proton pump *in vivo*; however, the obtained results have been conflicting and no final conclusion could be drawn whether PPI use is associated with a significantly altered bone turnover. Adachi et al.[23] found no difference in bone mineral density among long-term users of H_2 receptor antagonists in comparison with healthy controls not using this drug class.

Graziani et al.[24] assessed the post-meal increment in serum calcium among 30 patients undergoing haemodialysis (age range 34–65 years) following a test meal with or without omeprazole in a crossover design. Although the authors did not assess the intestinal calcium absorption directly, a decreased rise of serum calcium was observed with concomitant omeprazole administration. In a similar crossover study among 16 haemodialysis

patients (mean age 61.4 years), calcium carbonate was administered together with or prior to a standardized meal, and the effect of omeprazole was assessed. Again, rise in serum calcium was decreased among users of omeprazole.[25] Although these studies suggest that omeprazole may decrease calcium absorption to some degree, no direct assessment of intestinal calcium absorption has been done. Furthermore, haemodialysis patients are known for alterations in the vitamin D and parathormone metabolism (secondary and tertiary hyperparathyroidism) and for differences in skeletal metabolism. Therefore, these results cannot be generalized and do not provide convincing evidence for a direct effect of PPIs on calcium absorption in the general population.

In another study, Graziani et al.[26] further examined the effect of omeprazole on the rise of serum calcium in eight healthy young men (age range 36–52 years) following a test meal containing 1 g of elemental calcium. Post-ingestion calcium rose significantly in subjects taking placebo but did not change after omeprazole use. In contrast to these findings, Serfaty-Lacrosniere et al.[27] could not demonstrate an effect of omeprazole on intestinal calcium absorption using whole gut lavage methodology in 13 healthy volunteers (age range 30–71 years) who received a test meal. O'Connell et al.[28] studied the effect of omeprazole on calcium absorption using ^{45}Ca-tracer methodology. In 18 healthy women and men aged 65–89 years, fractional intestinal calcium absorption was reduced in subjects using omeprazole; however, the absolute difference in calcium absorption was relatively small, averaging −5.5% (−41% relative reduction).[28] Finally, in a crossover study in healthy young men, no change in intestinal calcium absorption could be demonstrated in relation to the use of an H_2 receptor antagonist.[29] Of importance, a recently published observational study investigating a possible association of PPI use and osteoporosis and bone mineral density failed to demonstrate that PPI use was related to accelerated loss of bone mineral density or osteoporosis.[30]

Prolonged PPI use has been associated with vitamin B_{12} deficiency.[31] Vitamin B_{12} deficiency is linked to hyperhomocysteinaemia, which in turn has been linked to an increased risk of fractures in elderly patients[32,33] and was associated with osteoporosis in patients with Crohn's disease.[34]

Taken together, only limited data are available linking short-term use of PPIs or other acid suppressive drugs to decreased calcium absorption or to direct effects on skeletal metabolism, such as development of osteoporosis or accelerated bone loss. In addition, no long-term studies have been carried out so far. However, despite the rather weak evidence for a substantial effect of acid suppression on calcium and bone metabolism, one cannot rule out that PPI use may lead to a certain alteration of calcium absorption. As already suggested by Insogna,[21] a well designed, long-term, randomized, placebo-controlled trial enrolling middle-aged and elderly people would be necessary to elucidate in more depth whether PPIs may decrease calcium absorption in a clinically significant manner. Whether vitamin B_{12} deficiency and hyperhomocysteinaemia associated with PPI use is indeed causally linked to an increased risk of fractures remains unproven given the scarce data available in the literature.

3. Proton Pump Inhibitor Use and the Risk of Fracture

To date, several population-based epidemiological studies have been published in the literature[5,6,8-13] or are currently available as abstracts[7] assessing the risk of fracture in association with PPI use. Most of these investigations were case-control studies (table I), with the exception of de Vries et al.[6], Gray et al.[9] and Roux et al.,[13] who conducted cohort studies. In 2006, Yang and co-workers[12] reported the results of a case-control analysis using the UK-based General Practice Research Database (GPRD). Cases were patients with a recorded diagnosis of hip fracture at above the age of 50 years between 1997 and 2003. The authors identified all cases with an incident diagnosis of hip fracture, and up to ten controls, matched to cases on age, sex, index date and time in the database prior to the index date (i.e. the date of the hip fracture). The relative risk (expressed as odds ratio [OR]) of having a

Table I. Use of proton pump inhibitors (PPIs) and fracture risk: summary of observational studies

Study (years of study)	Setting	Cases	Controls	OR (95% CI) for current PPI use	OR (95% CI) by PPI dose	OR (95% CI) by duration of use	OR (95% CI) for use of histamine H_2 receptor antagonists
Yang et al.[12] (1987–2003)	UK-based GPRD, patients aged ≥50 y	2722 hip fractures in patients taking PPIs >1 y and 10 834 hip fractures in patients not taking acid suppression	135 386 controls, matched for sex, age, calendar time and follow-up time prior to fracture	1.44 (1.30, 1.59)	≤1.75 dd: 1.40 (1.26, 1.54) >1.75 dd: 2.65 (1.80, 3.90)	1 y: 1.22 (1.15, 1.30) 2 y: 1.41 (1.28, 156) 3 y: 1.54 (1.37, 1.73) 4 y: 1.59 (1.39, 1.80)	1.23 (1.1.4, 1.39)
Vestergaard et al.[11] (2000)	Denmark, whole population	124 655 fractures, no exclusion criteria applied		Last use ≤1 y ago: 1.18 (1.12, 1.43) Last use >1 y ago: 1.01 (0.96, 1.06)	<25 dd: 1.16 (1.06, 1.26) 25–99 dd: 1.34 (1.26, 1.42) >99 dd: 1.14 (1.09, 1.19)	Not reported	Last use ≤1 y ago: 0.88 (0.82, 0.95) Last use >1 y ago: 1.02 (0.97, 1.07)
Targownik et al.[10] (1996–2004)	Manitoba, Canada, patients aged ≥50 y	15 792 cases of osteoporosis-related fractures	47 289 controls, matched for sex, age, co-morbidities and ethnic background	Not reported	Not reported	≥1 y: 0.99 (0.90, 1.11) ≥2 y: 0.94 (0.82, 1.07) ≥3 y: 0.92 (0.78, 1.07) ≥4 y: 1.05 (0.86, 1.27) ≥5 y: 1.16 (0.91, 1.46) ≥6 y: 1.28 (0.93, 1.77) ≥7 y: 1.92 (1.16, 3.18)	See text for details
Kaye and Jick[35] (1995–2005)	UK-based GPRD, patients aged 50–79 y	1098 fractures in patients taking PPIs. Cases free of major risk factors for fracture	10 923 controls with same age, sex and index date distribution	OR for any PPI prescription: 0.9 (0.7, 1.1)	Not reported	0 Rx: reference 1 Rx: 1.0 (0.7, 1.4) 2–9 Rx: 1.0 (0.7, 1.3) 10–29 Rx: 0.9 (0.6, 1.4) ≥30 Rx: 0.5 (0.3, 0.9)	Not reported
Gray et al.[9] (1993–2005)	Women's Health Initiative	21 247 fractures		Hip: 1.00 (0.71, 1.40)[a] Spine: 1.47 (1.18, 1.82)[a] Wrist/forearm: 1.26 (1.05, 1.51)[a]	Not reported	<1 y: 1.27 (1.13, 1.44)[a] 1–3 y: 1.19 (1.05, 1.35)[a] >3 y: 1.30 (1.03, 1.64)[a]	1.08 (1.02, 1.14)[a]
Corley et al.[5] (1995–2007)	Kaiser Permanente, Northern California	33 752 hip/femur fractures	130 471 controls with same age, sex, duration of membership, race/ethnicity and first year of membership	1.30 (1.21, 1.39)	<0.74 pills/day: 1.12 (0.94, 1.33) 1.5 pills/day: 1.41 (1.21, 1.64)	Cumulative dosage was not associated with an increased risk of fractures	1.18 (1.08, 1.29)

a Reported values are hazard ratios (95% CI).

dd = defined daily dose; **GPRD** = General Practice Research Database; **OR** = adjusted odds ratio; **Rx** = prescriptions.

fracture increased with increasing duration of previous use of PPIs. The adjusted OR was already statistically significantly increased for patients who used PPIs for 1 year (OR 1.22; 95% CI 1.15, 1.30; crude OR 1.43; 95% CI 1.35, 1.52) and increased with increasing exposure duration, yielding an adjusted OR of 1.59 (95% CI 1.39, 1.80) and crude OR of 2.17 (95% CI 1.93, 2.45) for patients who used PPIs for 4 years. The risk estimates were adjusted for a large number of potential confounders, encompassing some ten drug classes (among others, antidepressants, anxiolytics and corticosteroids) and 15 diseases (including alcoholism), whereby almost all of them were independently positively associated with an altered risk of developing a hip fracture, and only few being protective. It is interesting and important to note that the crude ORs were higher than the adjusted ORs. Thus, adjusting for co-morbidities reduced the OR towards the null, suggesting that the large number of co-morbidities and concurrently used drugs were associated both with an increased fracture risk and with a higher likelihood of PPI use. To further elucidate whether bias by indication may have been an explanation for the observed increased ORs, the authors restricted their analysis to patients with gastro-oesophageal reflux disease. In this sensitivity analysis, the point estimate changed only negligibly, suggesting that bias by indication may not be a major source of confounding. In addition, the authors reported a dose-dependent increase in the OR in patients using PPIs for 1 year. Again, the risk estimates decreased considerably after adjustment for potential confounders. Finally, the fracture risk was also increased among users of H_2 receptor antagonists in comparison with non-use of this respective drug class. Taken together, these results suggest a possibly increased fracture risk in patients using long-term acid suppressive therapy. However, the question remains whether adjusting for co-variates effectively and completely controlled for confounding, or whether adjusting was only partially successful, yielding risk estimates in association with PPI use that were still distorted to some degree by residual confounding (i.e. analyses not adjusted for use of vitamin D, calcium supplementation or use of opioids).

Another observational study from Denmark was published by Vestergaard et al.[11] in 2006. The authors analysed a large dataset of 124 655 fracture cases and 373 962 controls. They did not apply any exclusion criteria; thus, patients with known strong risk factors for fractures, such as a previous fracture or alcoholism, were kept in the analysis. The authors assessed the OR for a large number of potential confounders and displayed these co-morbidities and drugs (e.g. corticosteroids or antiepileptic drugs) in a separate table, yielding rather high and statistically significant ORs for fractures for most of these potential confounders. Unfortunately, the authors did not report crude ORs, so it is not possible to compare unadjusted and adjusted ORs. Use of PPIs in the year prior to the index date (i.e. the date of the fracture in cases) was associated with an adjusted OR of 1.18 (95% CI 1.12, 1.43) for all fractures combined, with slightly higher risk estimates for the subgroups of hip or spine fractures. Increasing daily doses and increasing cumulative doses (based on defined daily doses) were not associated with increasing ORs. In addition, use of H_2 receptor antagonists was not associated with an increased risk of fractures; on the other hand, the OR for use of H_2 receptor antagonists in the year prior to the index date was even reduced below 1.0, yielding an OR of 0.88 (95% CI 0.82, 0.95). Taking into account that this study observed neither a dose-dependent nor a duration-dependent fracture risk associated with PPI use, these findings do not support the hypothesis that a reduction of gastric acidity and an elevation of gastric pH by acid-suppressing drugs may increase the fracture risk. The authors concluded that the fracture risk may be slightly increased in users of PPIs, but that the risk increase may be of limited clinical importance.

In August 2008, another case-control analysis on the association between PPI use and the risk of fracture was published by Targownik and coworkers.[10] The authors included case patients at or above the age of 50 years who had a fracture recorded between 1996 and 2004 in an administrative claims database called Population Health Research Data Repository from Manitoba, Canada. In addition to patients with hip frac-

tures, the authors also identified patients with osteoporotic fractures of the vertebrae or the wrist. They matched three controls to each case on age, sex and co-morbidities, using the Johns Hopkins aggregated diagnosis groups (0, 1–2, 3–5 or 6+ diagnoses).[36] Overall, the authors analysed 15 792 fracture cases and 47 289 control patients, whereby about one-third had more than 5 years of previous history recorded in the database. Again, the authors presented a long list of drugs and co-morbidities that were independent risk factors for fractures. The findings were similar to the ones reported by Yang et al.,[12] with a statistically significantly increased relative risk estimate of fractures overall associated with long-term use of PPIs of ≥7 years (≥5 years for hip fracture). As opposed to the findings of Yang et al.,[12] however, the OR of having a fracture was not materially increased for patients who used PPIs for <7 years. The adjusted OR for PPI use of ≥7 years was 1.92 (95% CI 1.16, 3.18) and, again, all adjusted ORs were lower than the crude ORs. Use of H_2 receptor antagonists was associated with a decreased unadjusted OR for all fractures combined in the 1-year exposure group and in patients who used H_2 receptor antagonists for ≥3 years. Given the possible mechanism of action (suppression of stomach acid secretion), it seems unlikely that use of the less potent H_2 receptor antagonists is associated with an increased fracture risk compared with more potent PPIs. In addition, there is some inconsistency in the data provided by these authors related to short-term exposure.[10] Recently in 2010, Gray and co-workers[9] reported their results on PPI use, hip fracture and changes in bone mineral density using the data from the Women's Health Initiative. 130 487 women were prospectively followed-up for a mean of 7.8 years. In total, 21 247 fractures occurred during the study period. The authors reported multivariate-adjusted hazard ratios (HR) for current use of PPI and hip fracture (1.00; 95% CI 0.71, 1.40), spine fracture (1.47; 95% CI 1.18, 1.82), forearm/wrist fracture (1.26; 95% CI 1.05, 1.51) and total fracture (1.25; 95% CI 1.15, 1.36). Of importance, cases and controls differed significantly in relation to important risk factors for fractures (among others, osteoporosis, diabetes mellitus, hormone replacement therapy), which were overrepresented in PPI users. The authors adjusted their analyses for 5 (model 1) and an additional 20 potential confounders (model 2). Of interest, the HR invariably tended towards the null result for all different fracture sites when using model 2, and remained marginally statistically significant for total fractures, spine fractures and wrist/forearm, but not hip fracture. Similarly, the results for use of H_2 receptor antagonists became statistically insignificant after adjustment for multiple risk factors (model 2) for every fracture site except total fractures.

In another recent study from 2010, Corley and colleagues[5], using the Northern California Kaiser Permanente database, reported that ≥2 years of PPI use and ≥2 years of use of H_2 receptor antagonists were associated with an increased OR of hip fracture in patients with at least one predefined risk factor for hip fracture (1.30; 95% CI 1.21, 1.39, and 1.18; 95% CI 1.08, 1.29, respectively). However, in patients without one of these predefined risk factors, acid suppression therapy was not related to an altered risk of fracture. Of note, the risk of fracture was increased with higher daily dosage but not with cumulative duration of acid suppressive therapy. The analyses were adjusted for multiple risk factors for fractures, and many of these were more abundant among cases than controls (e.g. diabetes and alcohol consumption). However, in contrast to Gray et al.,[9] analyses were not adjusted for other important risk factors, such as use of psychotropic medication, calcium consumption and hormone replacement therapy. In addition, the authors noted that the OR was already increased for short-term use of PPIs (<1 year), suggesting a selection bias or residual confounding rather than a causal, duration-dependent effect of PPI use.

So far, in most of these observational studies discussed here[5,9,10,12] long lists of drugs and co-morbidities were reported to be associated with an increased risk of fracture. The authors adjusted the multivariate analyses on PPI use and fracture risk for these parameters (using 0 [parameter absent] or 1 [parameter present]), and the crude ORs went down towards the null (where available); however, some ORs remained statis-

tically significantly increased, leading to the conclusion that long-term PPI use may increase the fracture risk. In addition, only the studies by Yang et al.[12] and Corley et al.,[5] and, in part, the studies by Targownik et al.[10] and Gray et al.,[9] provided some data indicating a higher risk of fracture among users of H_2 receptor antagonists. Therefore, the question remains whether residual confounding may be responsible for the increased relative risk estimates seen in users of PPIs.

To address this question in more detail, Kaye and Jick[35] from the Boston Collaborative Drug Surveillance Program used the GPRD for another study on this topic. The authors initiated the study in a similar manner to the authors of the previously described studies,[10-12] but they added a second analysis restricted to cases and controls who had no major risk factors for fractures recorded. The study included patients between the ages of 50 and 79 years who had an incident hip fracture recorded between 1995 and 2005. In the first step, they found 4414 cases of incident hip fracture and identified at random up to ten controls per case, matched to cases on age, sex and index date. They used the electronic patient records to identify all co-morbidities with a prevalence of ≥1% that were associated with an OR of ≥2.0. Again, they came up with a long list of co-morbidities fulfilling these criteria, since many diseases are direct or indirect risk factors for fractures. However, as opposed to analysing the association between PPI use and the hip fracture risk, and adjusting for this long list of co-morbidities, they excluded in a second step all cases with such co-morbidities being associated with an increased fracture risk. This reduced the group of potential fracture cases from 4414 to 1098, and they matched a new set of controls to these remaining cases who also had no history of such diagnosed risk factors for fractures recorded. The final case-control set encompassed 1089 fracture cases and 10 923 controls, all of them free of direct risk factors for fractures. Within this study population, they analysed the association between PPI use and the fracture risk and found no evidence for an elevated fracture risk associated with long-term PPI use, with an OR of 0.5 (95% CI 0.3, 0.9) for patients who had 30 or more PPI prescriptions recorded.[35] This finding should not be interpreted as a possibly reduced fracture risk associated with long-term PPI use, but it can be interpreted as evidence that PPI use is not associated with a substantially increased risk of fracture. If a causal association between PPI use and relevant fracture risk indeed existed to a clinically relevant degree, one would expect to find this association also in this group of patients with a low *a priori* fracture risk. However, it cannot be concluded that PPI use is not associated with an altered fracture risk in patients at high risk of fractures, as this part of the study population was no longer studied. In addition, exclusion of patients with direct risk factors for factures, such as previous fracture and osteoporosis, can be problematic if these diseases are on the causal pathway and not necessarily confounders.

The results of additional observational studies have been reported at conferences and are available as abstracts. In a Dutch study based on the PHARMO database, de Vries et al.[7] compared PPI use of 6763 hip fracture cases with up to four controls per case, matched on age, sex and region. Overall, current use of PPIs was associated with a slightly increased relative fracture risk (OR 1.20; 95% CI 1.04, 1.40). However, when the authors stratified by exposure duration, the OR was higher for those who used PPIs for ≤3 months (OR 1.26; 95% CI 0.94, 1.68) than for patients who used PPIs for 1–3 years (OR 1.09; 95% CI 0.81, 1.47). This inverse duration effect is not consistent with the proposition that use of PPIs is causally associated with an increased fracture risk. Since this study is currently only available as an abstract, it is not possible to comment on the methods in detail. In an additional retrospective cohort analysis, de Vries et al.[6] analysed data from the GPRD, the database used by Yang et al.,[12] and reported a slightly increased fracture risk for long-term users of PPIs. The authors identified a large number of PPI users, users of H_2 receptor antagonists and users of bisphosphonates, and assessed the fracture risk during current or past use of these study drugs using a Cox proportional hazards model. This study is difficult to interpret, as certain issues related to the methodology remain unclear. In addition, as opposed to excluding

patients with osteoporosis and previous fractures, the authors included a group of users of bisphosphonates, which makes the findings especially vulnerable to bias by indication, since these patients are of course at high risk of developing a fracture, with or without use of PPIs. The authors reported an overall slightly increased relative risk (RR) for current users of PPIs as compared with past users of PPIs (RR 1.15; 95% CI 1.10, 1.20), while no such effect was seen for users of H_2 receptor antagonists. The risk was higher during the first year of use (RR 1.18; 95% CI 1.10, 1.27) than for use of ≥3 years (RR 1.11; 95% CI 1.03, 1.20). Again, this finding is not consistent with the hypothesis of a causal association between PPI use and an increased fracture risk.

A study was recently conducted in a small group of women who were enrolled in a bone mineral density screening programme in France.[13] All information regarding co-morbidities and drug use by these women came from questionnaire-based self-reporting, and this exposure assessment only referred to the actual study period, but did not take any previous use of PPIs or of other drugs into account. The study encompassed 1211 women, of whom only 61 (5%) used omeprazole at baseline. As the authors describe in detail, omeprazole users were more likely to have a history of a low trauma fracture and to be users of thiazides and calcium or vitamin D preparations. The latter two drugs are prescribed to women who are at high risk of osteoporosis, and previous fractures are known to be a direct risk factor for fractures. Despite all these limitations, the authors conducted a multivariate analysis and concluded that omeprazole use was associated with an "independently increased fracture risk" in the multivariate analysis (RR 3.10; 95% CI 1.14, 8.44). Again, this study only partially adjusted for confounding, and any increased fracture risk associated with omeprazole use is readily explained given the different characteristics of PPI users and non-users at baseline.

4. Discussion

All observational studies conducted so far have been stimulated by the hypothesis that decreased stomach acidity may cause lower calcium absorption, stimulate bone resorption and lead to decreased bone mineral density, which may ultimately result in an increased fracture risk. Importantly, this hypothesis is based on some small studies in humans with conflicting results[19,22-27,29] and is not supported by a recent large observational study.[30] As the available observational studies assessing the risk of fracture and use of PPIs or H_2 receptor antagonists differ in their findings, this association is currently far from being well established. Whereas the results in the studies by Yang et al.[12] and Corley et al.[5] seem to be the most consistent, other studies lacked a dose- or time-dependent relationship. Furthermore, some studies could not demonstrate a similar, dose- and/or time-dependent relationship for H_2 receptor antagonists.[9-11] Some studies suffered from considerable methodological drawbacks and have to be interpreted with care, as mentioned in section 3.[6,13]

All discussed reports on PPI use and fractures carry the risk of residual confounding. Adjusting for co-morbidities that are direct and independent risk factors for an outcome of interest does not always adequately adjust for confounding in observational studies, particularly since these potential confounders can present with various levels of severity. For example, a history of dementia was associated with an increased fracture risk in four studies reporting an increased fracture risk associated with PPI use.[5,10-12] Adjusting for dementia using a 0/1 variable may oversimplify the situation, as patients may have severe late-stage dementia or an early mild form of a cognitive disorder. Severe dementia is associated with impaired coordination as well as with multiple drug use (e.g. antipsychotic or antidepressant drugs), both known to increase the risk of falls and fractures. On the other hand, mild forms of dementia may not impair body coordination and may not yet be treated with drugs affecting the CNS; thus, patients with mild forms of dementia may not be at a higher risk of falls and fractures. It is possible that PPI use is more likely to occur in patients with severe dementia (for example, due to polymedication) than in patients with mild dementia, and it is also conceivable that exposure duration

may be longer for patients with a longer term history of severe dementia than for those with an early form of mild dementia. Thus, adjusting the analysis on the association between PPIs and fracture risk for a history of dementia using a simple 0/1 variable may adjust the relative risks only partially, but residual confounding is likely to be present.

On the other hand, the technique applied by Kaye and Jick[35] (i.e. excluding all patients with diagnosed dementia of any severity) eliminates potential confounding by this parameter to a much higher degree. Thus, excluding patients with clinical risk factors for the outcome of interest increases the likelihood of detecting an association of interest between a drug of interest (e.g. PPIs) and the risk of developing a certain outcome of interest (e.g. fractures). The fact that PPIs were no longer associated with an increased fracture risk in an analysis restricted to patients free of diagnosed clinical risk factors for fractures in the studies by Kaye and Jick[35] and Corley et al.[5] provides strong evidence that use of PPIs *per se* does not substantially alter fracture risk, and that residual confounding by co-morbidities and drugs may explain the findings of published observational studies so far. However, it has to be acknowledged that, owing to exclusion of high-risk patients from the analysis, the generalizability of these findings is reduced and a possible effect of PPIs in vulnerable populations at high fracture risk cannot be excluded and was observed by Corley et al.[5] Kaye and Jick[35] did not report results on dose-response effects. Therefore, it cannot be excluded that high daily PPI doses may have been associated with an increased risk of fractures in their study population. In addition, if PPIs truly affected bone mass and increased the risk of fracture, excluding patients with a previous history of osteoporosis may be problematic, as osteoporosis would be on the causal pathway rather than a true confounder.

Of note, some of the more recent studies[5,9,12] reported an increased fracture risk for patients with short-term PPI use, suggesting that the observed increase in fracture risk may not be the result of long-term exposure to PPIs, but of selection bias, residual confounding or confounding by co-morbidities and multiple drug use.

5. Conclusions

PPIs are widely used, often on a long-term basis. Concerns related to their safety must be taken seriously. In this context, the various observational studies assessing the fracture risk in association with use of PPIs are welcome and need to be discussed; however, there is evidence that the observed increased relative fracture risks associated with PPI use may be the result of residual confounding rather than a causal effect. The fact that several observational studies reported elevated fracture risks for PPI users does not mean that the original hypothesis of possibly reduced calcium absorption and subsequent increased fracture risk is necessarily correct. This hypothesis is mainly based on small short-term studies with conflicting results. Therefore, the current evidence suggests that the association between the use of PPIs and increased fracture risk is not likely to be causal. Nevertheless, it is important that PPIs are used with caution and that a careful benefit-risk assessment should precede any prescribing of a PPI. Currently, there is not enough evidence to support the notion that all patients receiving long-term PPI therapy should be screened for osteoporosis. Clinicians should be judicious in their use of PPIs, and patients who require long-term PPI therapy should be encouraged to ensure they receive the recommended daily intake of calcium and vitamin D. Use of pharmacological treatment for skeletal protection for long-term PPI users in the absence of other indications does not seem to be justified or warranted.

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References

1. Soderqvist A, Ekstrom W, Ponzer S, et al. Prediction of mortality in elderly patients with hip fractures: a two-year prospective study of 1,944 patients. Gerontology 2009; 55 (5): 496-504

2. Vestergaard P, Rejnmark L, Mosekilde L. Has mortality after a hip fracture increased? J Am Geriatr Soc 2007; 55 (11): 1720-6
3. Bodmer M, Meier C, Kraenzlin ME, et al. Risk of fractures with glitazones: a critical review of the evidence to date. Drug Saf 2009; 32 (7): 539-47
4. Meier C, Kraenzlin ME, Bodmer M, et al. Use of thiazolidinediones and fracture risk. Arch Intern Med 2008; 168 (8): 820-5
5. Corley DA, Kubo A, Zhao W, et al. Proton pump inhibitors and histamine-2 receptor antagonists are associated with hip fractures among at-risk patients. Gastroenterology 2010; 139 (1): 93-101
6. de Vries F, Cooper AL, Cockle SM, et al. Fracture risk in patients receiving acid-suppressant medication alone and in combination with bisphosphonates. Osteoporos Int 2009; 20 (12): 1989-98
7. de Vries F, van Staa TP, Leufkens HGM, et al. Use of proton pump inhibitors and risk of hip fracture. EULAR 2009 Jun 10-13. Copenhagen
8. Fournier MR, Targownik LE, Leslie WD. Proton pump inhibitors, osteoporosis, and osteoporosis-related fractures. Maturitas 2009; 64 (1): 9-13
9. 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 (9): 765-71
10. Targownik LE, Lix LM, Metge CJ, et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ 2008; 179 (4): 319-26
11. 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 (2): 76-83
12. Yang YX, Lewis JD, Epstein S, et al. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006; 296 (24): 2947-53
13. Roux C, Briot K, Gossec L, et al. Increase in vertebral fracture risk in postmenopausal women using omeprazole. Calcif Tissue Int 2009; 84 (1): 13-9
14. Ali T, Lam D, Bronze MS, et al. Osteoporosis in inflammatory bowel disease. Am J Med 2009; 122 (7): 599-604
15. Cashman KD. Diet, nutrition, and bone health. J Nutr 2007; 137 (11 Suppl.): 2507-12S
16. Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. Osteoporos Int 2008; 19 (8): 1119-23
17. Tang BM, Eslick GD, Nowson C, et al. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007; 370 (9588): 657-66
18. Straub DA. Calcium supplementation in clinical practice: a review of forms, doses, and indications. Nutr Clin Pract 2007; 22 (3): 286-96
19. Wood RJ, Serfaty-Lacrosniere C. Gastric acidity, atrophic gastritis, and calcium absorption. Nutr Rev 1992; 50 (2): 33-40
20. Goerss JB, Kim CH, Atkinson EJ, et al. Risk of fractures in patients with pernicious anemia. J Bone Miner Res 1992; 7 (5): 573-9
21. Insogna KL. The effect of proton pump-inhibiting drugs on mineral metabolism. Am J Gastroenterol 2009; 104 Suppl. 2: S2-4
22. Mizunashi K, Furukawa Y, Katano K, et al. Effect of omeprazole, an inhibitor of H+,K(+)-ATPase, on bone resorption in humans. Calcif Tissue Int 1993; 53 (1): 21-5
23. Adachi Y, Shiota E, Matsumata T, et al. Bone mineral density in patients taking H2-receptor antagonist. Calcif Tissue Int 1998; 62 (4): 283-5
24. Graziani G, Badalamenti S, Como G, et al. Calcium and phosphate plasma levels in dialysis patients after dietary Ca-P overload: role of gastric acid secretion. Nephron 2002; 91 (3): 474-9
25. Hardy P, Sechet A, Hottelart C, et al. Inhibition of gastric secretion by omeprazole and efficiency of calcium carbonate on the control of hyperphosphatemia in patients on chronic hemodialysis. Artif Organs 1998; 22 (7): 569-73
26. 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 (8): 1376-80
27. 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 (4): 364-8
28. 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 (7): 778-81
29. 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 (3): 640-7
30. Targownik LE, Lix LM, Leung S, et al. Proton-pump inhibitor use is not associated with osteoporosis or accelerated bone mineral density loss. Gastroenterology 2010; 138 (3): 896-904
31. 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 (4): 422-8
32. McLean RR, Jacques PF, Selhub J, et al. Plasma B vitamins, homocysteine, and their relation with bone loss and hip fracture in elderly men and women. J Clin Endocrinol Metab 2008; 93 (6): 2206-12
33. McLean RR, Jacques PF, Selhub J, et al. Homocysteine as a predictive factor for hip fracture in older persons. N Engl J Med 2004; 350 (20): 2042-9
34. Roblin X, Phelip JM, Genevois M, et al. Hyperhomocysteinaemia is associated with osteoporosis in patients with Crohn's disease. Aliment Pharmacol Ther 2007; 25 (7): 797-804
35. Kaye JA, Jick H. Proton pump inhibitor use and risk of hip fractures in patients without major risk factors. Pharmacotherapy 2008; 28 (8): 951-9
36. Leslie WD, Anderson WA, Metge CJ, et al. Clinical risk factors for fracture in postmenopausal Canadian women: a population-based prevalence study. Bone 2007; 40 (4): 991-6

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