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Use of Proton Pump inhibitors is Associated with Fractures in Young Adults: A Population-Based Study

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Abstract

Purpose—Proton pump inhibitors (PPIs) are associated with fracture in adults with osteoporosis. Because PPI therapy may interfere with bone accrual and attainment of peak bone mineral density, we studied the association between use of PPIs and fracture in children and young adults.

Methods—We conducted a population-based, case-control study nested within records from general medical practices from 1994 to 2013. Participants were 4–29 years old with 1 year of follow-up who lacked chronic conditions associated with use of long-term acid suppression. Cases of fracture were defined as the first incident fracture at any site. Using incidence density sampling, cases were matched with up to 5 controls by age, sex, medical practice, and start of follow-up. PPI exposure was defined as 180 or more cumulative doses of PPIs. Conditional logistic regression was used to estimate the odds ratio and confidence interval for use of PPIs and fracture.

Results—We identified 124,799 cases and 605,643 controls. The adjusted odds ratio for the risk of fracture associated with PPI exposure was 1.13 (95% CI 0.92 to 1.39) among children aged < 18 years old and 1.39 (95% CI 1.26 to 1.53) among young adults aged 18–29 years old. In young adults but not children, we observed a dose-response effect with increased total exposure to PPIs (p for trend <.001).

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Conflict of interest: Daniel E. Freedberg, Kevin Haynes, Michelle R. Denburg, Babette S. Zemel, Mary B. Leonard, Julian A. Abrams, and Yu-Xiao Yang declare that they have no conflict of interest.

Conclusions—PPI use was associated with fracture in young adults but overall evidence did not support a PPI-fracture relationship in children. Young adults who use PPIs should be cautioned regarding potentially increased risk for fracture, even if they lack traditional fracture risk factors.

Keywords

proton pump inhibitors; histamine-2 receptor antagonists; acid suppression medications; pharmacoepidemiology; fracture; osteoporosis; bone mineral density; pediatrics; outcomes research

Introduction

Proton pump inhibitors (PPIs) have been associated with increased risk for hip fracture in older adults, while the relationship between PPIs and fracture in young adults and children has not been addressed [1]. In adults, PPIs are highly effective treatment for gastroesophageal reflux disease (GERD), but in children and young adults the effectiveness of PPIs is less clear [2]. Despite this, PPI use in children and young adults is rising with long-term PPIs increasingly prescribed to otherwise healthy children for non-specific symptoms [3,4].

In adults 50 years old or more, most fractures are related to osteoporosis or osteopenia [5]. The association between PPIs and fracture has been observed consistently in adults who are osteoporotic or at high risk for osteoporosis [6]. Yet the best available evidence suggests that PPIs do not cause osteoporosis. PPI use has not been associated with low bone mineral density (BMD) at sites of osteoporotic fracture, including the hip or the lumbar spine [7]. In a large, prospective cohort of women there was a modest association between PPIs and osteoporotic fracture, yet no baseline differences in BMD comparing PPI users to non-users, and no change in BMD after 3 years [8]. Even among subjects followed for osteoporosis by dual X-ray absorptiometry for up to 10 years, there was no decline in BMD comparing PPI users to non-users [9].

The period of rapid bone accrual is from 9 to 13 years old in females and from 11 to 15 years old in males, with increasing bone mass until the age of 30 [10]. Chronic PPI therapy may lead to hypochlorhydria with malabsorption of calcium and vitamin B12 and hypergastrinemia [11]. These mechanisms have the potential to interfere with bone growth in children and peak bone mass attainment in young adults, yet the relationship between PPIs and fracture has not previously been studied in these populations. To determine whether PPIs are a risk factor for fracture during years of life when bone mass is increasing, we conducted a nested case-control study among children and young adults within a large, outpatient database.

Methods

Study design

We conducted a population-based, case-control study nested within The Health Improvement Network (THIN) using data collected from 1994 to 2013.

Data source

THIN is a database of over 13 million electronic medical records maintained by general practitioners throughout the United Kingdom. For practitioners who use THIN, it represents the entire medical record, and THIN data has previously been validated for health outcomes research [12,13]. Because patients in the UK must register with a general practitioner to receive non-emergent medical care through the National Health Service, THIN broadly represents the population. THIN records contain demographic information, diagnoses, and complete prescribing information which is captured electronically.

Study population

All patients 4 through 29 years old with at least one year of follow-up in THIN were potentially eligible. We selected this age range because it encompasses the period of maximal bone growth velocity and because age 30 is the approximate peak of bone mass [14]. The epidemiology of fracture varies between toddlers, children, and young adults; to address this, we excluded toddlers < 4 years old and performed stratified analyses for children aged < 18 years old and for young adults aged 18 to 29 years old [15,16]. We excluded all subjects with unacceptable or incomplete medical records. To address potential confounding by indication, we also excluded those with chronic conditions associated with long-term acid suppression that may also be associated with fracture: neurocognitive and neuromotor disorders, tracheoesophageal anomalies, chronic pulmonary disorders including cystic fibrosis, diabetes, inflammatory bowel disease, celiac disease, short gut syndrome and other causes of malabsorption, hypo- and hyperparathyroidism, and malignancy [17]. Flow of patients into the study is shown in Figure 1. This study was approved by the Institutional Review Board of Columbia University.

Case selection

Cases of fracture were defined as eligible subjects with diagnoses for fracture within THIN. THIN diagnoses are linked to the Read code system, a hierarchical system of diagnostic codes [18], and Read coding for fracture has previously been validated within this dataset [19]. When subjects had multiple fractures, the first instance was selected.

Control selection

The control group was selected using incidence density sampling. The incidence density sampling design yields ORs interpretable as unbiased estimates of incidence rate ratios from a cohort study [20]. For each case, the control pool consisted of all eligible individuals without a diagnosis of fracture when the case had his or her first fracture. Up to 5 eligible control subjects were randomly matched with each case by age (within 1 year), sex, THIN practice, and start of follow-up (within 1 year). Controls were assigned the same index date as their matched case's date of fracture.

Exposure

The primary exposure was defined *a priori* as a minimum of 180 cumulative doses of PPIs prior to the index date. There is no data regarding the minimum threshold of PPI exposure associated with increased fracture risk in children and young adults, so we selected this cut-

off because 180 cumulative doses of PPIs is equivalent to six months of daily PPIs. Doses of PPI exposure was determined using THIN prescription records, which describe medications as they are actually dispensed. In order to evaluate for the possibility of an increased risk for fracture with increasing levels of PPI exposure, we classified PPI total exposure as none, 1–179 doses, 180–720 doses, and greater than 720 doses. In order to evaluate for the possibility of an increased risk for fracture based on relatively brief but high-intensity exposure to PPIs, we classified PPI maximal dose based on the highest frequency of dispensed PPIs regardless of duration (categories of none, daily or less, or more than daily).

Covariates

As potential confounders, we extracted information related to age, sex, body mass index (BMI, kg/m²), and use of medications other than PPIs that may be associated with fracture risk. To calculate BMI, we used height and weight measurements that were simultaneously recorded from the most recent visit prior to the index date. For subjects less than 18 years old, we calculated a sex-specific BMI Z-score (standard deviation score) relative to age based on growth charts and subjects' ages when data were recorded [21]. We classified subjects as overweight if they were at or above the 85th percentile for age (if under 18 years old) or had a BMI of 25 or more (if 18 or more years old). We classified subjects as underweight if they were at or below the 5th percentile for age (if under 18 years old) or had a BMI of 18.5 or less (if 18 or more years old). BMI for remaining subjects was classified as normal, or missing if no valid data was available. Use of medications other than PPIs was classified dichotomously based on whether a prescription was issued within 1 year before the index date. Medications examined included histamine-2 receptor antagonists, oral glucocorticoids, anti-epileptic drugs, calcium/vitamin D (excluding multivitamins), bisphosphonates, and opiates (excluding opiate-containing anti-tussants).

Statistical analysis

Categorical variables were analyzed using chi-square tests and continuous variables were analyzed using *t*-tests (for normally distributed data) or Wilcoxon rank sum tests. We used conditional logistic regression to estimate the multivariable adjusted odds ratios (ORs) and associated 95% confidence intervals (CIs) for fracture risk associated with PPI use. For the multivariable model, we selected variables that exerted a 10% change on the beta-coefficient representing PPIs in the PPI-fracture relationship or that had a significant independent relationship with fracture. The final model included the following variables: use of histamine-2 receptor antagonists, anti-epileptic drugs, opiates, and oral glucocorticoids. To assess for a dose-response effect, we used a non-parametric test for trend across ordered categories of exposure after excluding PPI non-users. All data were analyzed using Stata 12.1 (StataCorp, College Station, TX, USA) at the alpha 0.05 level of significance.

Results

Patient characteristics

A total of 124,799 cases and 605,643 controls were included in the study, with an average 4.85 controls matched for each case. Comparing cases to controls, there were no significant differences in duration of follow-up, age, and sex (Table 1). Among cases, the most

common fracture sites were wrist (24.9%) and hand (20.5%) for children and hand (32.5%) and foot (12.4%) for young adults. Hip fractures were less than 1% of all fractures in both age groups. Fracture site information is given in Supplementary Tables 1 and 2.

Exposure to proton pump inhibitors

Exposure to PPIs increased with increasing age. The proportion of those with 180 or more doses of exposure to PPIs was 0.1% among children compared to 1.1% among young adults ($p<.001$). This remained true when exposure to PPIs was classified as ever/never, with 0.5% of children ever exposed to PPIs compared to 5.5% of young adults ($p<.001$). To assess the dynamics of PPI exposure, we examined the median number of doses of PPIs and the time between the last exposure to PPIs and the index date. In subjects with low total PPI exposure (defined as 1–179 doses of PPIs), the median number of PPI doses was 28 (IQR 28–60) in children and 28 (IQR 28–63) in young adults. In these subjects, there was a median of 255 days (IQR 33–887) since the last exposure to PPIs in children and a median of 211 days (IQR 33–653) in young adults. In contrast, in subjects with high total PPI exposure (defined as >720 doses of PPIs), the median time since last exposure was 7 (IQR 0–201) in children and 0 (IQR 0–112) in young adults.

Multivariable analysis

The crude ORs for fracture and PPI exposure were 1.16 (95% CI 0.94 to 1.43) among children and 1.42 (95% CI 1.29 to 1.57) among young adults. In multivariable analysis, the adjusted ORs for fracture and PPI exposure were 1.13 (95% CI 0.92 to 1.39) among children and 1.39 (95% CI 1.26 to 1.53) among young adults. In the multivariable model, variables with independent associations with fracture among all ages were use of H2RAs, opiates, and steroids (Supplementary Table 3). There was no significant difference in the PPI-fracture relationship when BMI was added to the model classified as missing, underweight, normal, or overweight (OR 1.14, 95% CI 0.93 to 1.41 in children; OR 1.38, 95% CI 1.25 to 1.52 in young adults). Because BMI data was frequently missing, we performed a restriction analysis among the 233,102 subjects with simultaneously recorded height and weight. After adjusting for BMI, the PPI-fracture relationship remained the same among those with complete BMI data (OR 1.18; 95% CI 0.75 to 1.87 in children; OR 1.42, 95% CI 1.25 to 1.62 in young adults). We examined concurrent H2RA-PPI exposure by categorizing subjects as using no acid suppression, H2RAs alone, PPIs alone, or both H2RAs and PPIs (Supplementary Table 4). Exposure to concurrent H2RAs and PPIs was infrequent and there were no significant differences in ORs for fracture between users of PPIs alone compared to users of both H2RAs and PPIs in children (Fisher's $p=.144$) or young adults (chi-square $p=.221$).

Dose-response effect

To assess for an effect on fracture risk based on intensity and cumulative dose of PPIs, we classified PPIs by maximal dose and total exposure. In children there was no dose-response effect (Table 2, p for trend 0.188) whereas in young adults there was increased fracture risk when PPIs were given at higher intensity or when total exposure to PPIs was increased (Table 3, p for trend $<.001$).

Discussion

We found a significantly increased risk for fracture associated with prolonged use of PPIs in young adults but the preponderance of our data did not support an association between PPIs and fracture in children. In young adults but not children, there was a dose-response effect on fracture risk with increased PPI exposure. H2RAs, opiates, and steroids were independently associated with fracture in both age groups.

Use of PPIs is associated with fractures in older adults [1], yet evidence is lacking that bone density declines with PPIs, at least when bone density is measured by dual X-ray absorptiometry [7,9,8]. Our study focused on a population selected because it was well outside the window of osteoporosis. Kaye et al used restriction to exclude osteoporotic subjects and did not find an association between PPIs and fracture [22]. No prior study has examined the association between PPIs and fracture risk among children and young adults.

Falls are the most common cause of fracture in people of all ages [23]. However, compared to older adults, a larger proportion of fractures in children and young adults are related to sports and relatively high impact falls and other injuries [24]. In addition to force of impact, other mechanical factors influence risk for fracture after a fall. Fall direction, angle of impact, and underlying bone fragility all modulate risk for fracture after falling [25]. It is impossible to accurately classify these mechanical factors, but the results of this study support the possibility that PPIs increase overall fracture risk in a population where a large proportion of fractures are likely due to falls and other mechanical injuries.

There are several candidate mechanisms by which PPIs may increase bone fragility. PPIs have been associated with deficiencies in vitamin B12 and iron, findings best explained by PPI-induced hypochlorhydria [26,11]. In susceptible individuals, gastric hypochlorhydria from PPI use may similarly lead to the malabsorption of calcium salts with a deleterious effect on bone [27]. Studies in animals show that an acidic gastric environment is necessary for the dissolution of poorly water-soluble calcium salts, and patients with achlorhydria from pernicious anemia have increased fracture risk regardless of B12 therapy [28]. Among rats given high-dose PPIs and calcium phosphate, calcium absorption was blocked resulting in a decrease in bone mineral density [29]. In a factorial design, ovariectomized rats were assigned low-calcium versus normal diets, and PPIs vs placebo [30]. All rats assigned PPIs had increased markers of bone turnover but only the rats assigned to both a low calcium diet and PPIs also had biochemical evidence of increased bone resorption. When 7 days of omeprazole was given to women 65 years old or more, there was a marked 3-fold decrease in calcium absorption measured using radiolabeled calcium [31]. However, there is also other, contradictory data regarding the effect of PPIs on calcium absorption in humans. The effect of acid suppression on dietary calcium absorption in children and young adults is uncertain.

We observed increased risk for fracture associated with the equivalent of six months of exposure to daily PPIs. Population-based studies in older adults have found that acid suppression with either H2RAs or PPIs increases risk for fracture above baseline after the equivalent of several years of daily exposure [34]. However, no one has ever established a

similar minimum PPI exposure threshold in a population with increasing rather than decreasing bone mass (i.e., in a population similar to the one in our study). The mechanism linking PPIs and fracture is uncertain, so it is challenging to speculate on the likely threshold for PPIs and risk for fracture in our population or on how this threshold value may differ in children and young adults compared to older adults. PPIs may cause changes within bone structure—via hormonal or other mechanisms—with downstream effects on fracture felt after relatively brief exposures to PPIs, and felt disproportionately in children and young adults compared to older adults [35]. In our study, both PPIs and H2RAs were independently associated with increased fracture risk among subjects age 18 to 29 years old. PPIs are far more potent suppressors of gastric acidity than H2RAs, but the ability of acid suppression to induce calcium malabsorption may be modified by dietary calcium, timing of medication with meals, or other factors.

Mechanisms independent of gastric pH have also been proposed to explain the observed PPI-fracture relationship in older adults. These include: vitamin B12 deficiency leading to abnormal collagen cross-linking in bone; PPI-induced hypergastrinemia causing hyperparathyroidism; and a direct effect of PPIs on vacuolar osteoclasts where binding of PPIs to H^+/K^+ -ATPases blocks acidification of osteoclast resorption lacunae. Studies addressing these mechanisms by measuring bone turnover using urinary or serum metabolites are inconclusive. A controlled study of adults with a history of peptic ulcer disease taking H2RAs showed a decrease in urinary markers of bone turnovers after subjects were switched to PPIs [36]. On the other hand, a recent study in which healthy males 18–50 years old took PPIs for 12 weeks showed no change in bone metabolism [33].

This study has several strengths. We used a large, population-based dataset that has been extensively validated for health outcomes [12,13]. This dataset, THIN, is fundamentally different from an insurance claims database; it is an electronic medical record maintained for the purpose of providing care. We used restriction to exclude subjects who had GERD-predisposing conditions that may also associate with fracture [17]. And we assessed for alternative explanations for increased risk for fracture among PPI users, such as concurrent use of steroids and opiates.

Our study has limitations. During childhood, fracture incidence rises during the adolescent growth spurt [15], but the study was not powered to detect increased fracture risk related to PPIs within this age-specific subgroup of children. Because exceedingly few fractures occurred at locations classically associated with osteoporosis, we were unable to stratify fractures as occurring at osteoporotic versus non-osteoporotic sites. Read codes do not describe fracture etiology, so we were also unable to determine which fractures were related to high-impact events (such as automobile accidents) versus low-impact events. Fracture incidence varies by race [37], but this information is not available within the THIN database. THIN medication records do not capture over-the-counter (OTC) PPI use. However, best evidence indicates that OTC PPI use is minimal in the United Kingdom, especially among children who receive prescription medications for free [38]. If present, OTC PPI use would likely be non-differentially distributed between cases and controls and would bias results towards the null. We could not assess PPI use outside of THIN records, including non-adherence to prescribed PPIs and use of PPIs prior to inclusion in the dataset. Use of PPIs

for GERD can be intermittent [39]. Use of PPIs prior to inclusion in the dataset would result in left-censoring, with subjects exposed to PPIs misclassified as PPI non-users. Such an effect would be seen disproportionately in children as opposed to young adults, because providers are encouraged to discontinue PPIs in children and because children have a shorter duration of time at risk. If present, left-censoring could cause false negative results especially among those less than 18 years old.

The modestly elevated fracture risk associated with H2RAs, which are weaker acid suppressants than the PPIs, raises the possibility of confounding by indication. We excluded from the study population patients with comorbidities that might be associated with the use of acid suppressive therapy and fracture risk in this population [17]. Besides these comorbid conditions, the primary indication for acid suppressive therapy in this population would be GERD or dyspepsia, neither of which are likely to be an important confounder in this context because neither has a known direct effect on fracture risk [4]. Residual confounding is always a possibility in observational studies, but randomized study designs to address the question of whether PPIs increase fracture risk in young people would be unethical as well as unfeasible. As described above, this study used a combination of restriction, matching, and statistical adjustment to reduce residual confounding. The observed PPI-fracture relationship in young adults persisted despite these measures, with an apparent dose response relationship between higher levels of PPI exposure and increased fracture risk.

We observed that PPI use was associated with increased risk for fracture in young adults but not children. The highest risk for fracture was seen among young adults who received prolonged or high-intensity PPIs. Use of PPIs continues to expand, with a concerning expansion of use among children and young adults. Our results suggest the possibility that PPIs act on bone to increase fracture risk through mechanisms that are independent of osteoporosis. The long-term bone health consequences of PPI use early in life are unknown, and future studies should explore mechanisms that may mediate PPI use and fracture in this population. In the short-term, physicians should prescribe PPIs with caution to young adults even if they lack risk factors for fracture.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow of subjects into the study.

Table 1

Characteristics of study subjects.

Characteristic	Cases (n=124,799)	Controls (n=605,643)	p-value
Duration of follow-up (mean years, SD)	5.0 (3.3)	5.0 (3.3)	.116
Age at index date (%)			.079
< 18 years old	87,071 (69.8)	424,066 (70.0)	
18 years old	37,728 (30.2)	181,577 (30.0)	
Sex (%)			.130
Male	81,906 (65.6)	396,129 (65.4)	
Female	42,893 (34.4)	209,514 (34.6)	
Body Mass Index (%)			<.001
Overweight*	13,201 (10.6)	62,165 (10.3)	
Normal	24,539 (19.7)	117,742 (19.4)	
Underweight**	2,440 (2.0)	13,015 (2.2)	
Missing	84,619 (67.8)	412,721 (68.2)	
Medications (%)			
Histamine-2 receptor antagonists	364 (0.3)	1,319 (0.2)	<.001
Anti-epileptic drugs	710 (0.6)	2,253 (0.4)	<.001
Bisphosphonates	1 (0.0)	11 (0.0)	.421
Calcium-Vitamin D	29 (0.0)	125 (0.0)	.565
Opiates	1,705 (1.4)	5,722 (0.9)	<.001
Oral glucocorticoids	874 (0.7)	3,464 (0.6)	<.001

SD: Standard deviation.

* Overweight: Body Mass Index (BMI) ≥ 25 if ≥ 18 years old or BMI ≥ 85 th percentile if < 18 years old.** Underweight: BMI ≤ 18.5 if ≥ 18 years old or BMI ≤ 5 th percentile if < 18 years old.

Dose and total exposure relationship between proton pump inhibitors and fracture among subjects < 18 years old.

Table 2

Proton pump inhibitors	Cases	Controls	Crude OR (95% CI)	Adjusted OR* (95% CI)
Maximal dose	86,578	422,162	Reference	Reference
None	424	1,651	1.25 (1.12–1.40)	1.22 (1.09–1.36)
Daily or less	69	253	1.33 (1.00–1.74)	1.30 (1.00–1.70)
> Daily				
Cumulative exposure				
None	86,578	422,162	Reference	Reference
1–179 doses	379	1,427	1.30 (1.15–1.45)	1.26 (1.12–1.41)
180–720 doses	61	278	1.07 (0.78–1.42)	1.03 (0.78–1.37)
> 720 doses	53	199	1.30 (0.94–1.77)	1.29 (0.95–1.74)

OR: Odds Ratio; CI: Confidence Interval; IQR, interquartile range.

* Adjusted for prior use of histamine-2 receptor antagonists, anti-epileptic drugs, opiates, and oral glucocorticoids.

Table 3

Dose and total exposure relationship between proton pump inhibitors and fracture among subjects 18 years old.

Proton pump inhibitors	Cases	Controls	Crude OR (95% CI)	Adjusted OR* (95% CI)
Maximal dose				
None	35,137	172,044	Reference	Reference
Daily or less	2,231	8,327	1.31 (1.25–1.38)	1.28 (1.22–1.35)
> Daily	360	1,206	1.46 (1.30–1.65)	1.43 (1.27–1.61)
Cumulative exposure				
None	35,137	172,044	Reference	Reference
1–179 doses	2,044	7,674	1.30 (1.24–1.37)	1.28 (1.21–1.34)
180–720 doses	343	1,147	1.46 (1.29–1.66)	1.43 (1.26–1.62)
> 720 doses	204	712	1.40 (1.20–1.64)	1.39 (1.18–1.62)

OR: Odds Ratio; CI: Confidence Interval; IQR, interquartile range.

* Adjusted for prior use of histamine-2 receptor antagonists, anti-epileptic drugs, opiates, and oral glucocorticoids.