The Clinical Characteristics of Fractures in Pediatric Patients Exposed to Proton Pump Inhibitors

*Nathan Fleishman, †Troy Richardson, and *Thomas Attard

ABSTRACT

Objectives: There are increasing concerns regarding proton pump inhibitor (PPI) use and the risk of fractures in adults. Few studies have evaluated this risk among pediatric patients. This study examined fractures and fracture location among pediatric patients exposed to PPI compared with those without documented exposure.

Study Design: Encounters for patients 6 months to 15.5 years were identified between July 1, 2011 to December 31, 2015 in the Pediatric Hospital Information System database. Exclusion criteria was applied for chronic illnesses, conditions or medications predisposing to fracture. Encounters were classified as PPI encounters if a charge for PPI was documented. PPI encounters were propensity matched to non-PPI encounters. Following initial encounter, patients were evaluated over a 2-year period for hospitalizations resulting from fracture.

Results: There was a statistically significant higher rate of fractures among the PPI-exposed group (1.4% vs 1.2%, $P = 0.019$). Adjusting for remaining differences in sex, race, encounter type, payer, and resource intensity after matching, the difference remained statistically significant ($P = 0.017$) with an adjusted odds ratio (95% CI) of 1.2 (1.0–1.4). Upper extremity was the most common location for fracture; however, the PPI cohort was more likely to suffer from lower extremity, rib, and spinal fractures ($P = 0.01$).

Conclusions: This study suggests an increased risk of fracture among pediatric patients taking PPI. Among patients hospitalized with a fracture, those with PPI exposure had a higher rate of lower extremity, rib, and spine fractures compared with controls. This appeared to be a class effect not related to individual PPI agent.

Key Words: bones, fracture site, fractures, pediatrics, proton pump inhibitor, side effects

(*JPGN* 2020;70: 815–819)

What Is Known

- Side effects related to proton pump inhibitor use in the adult population is increasingly being reported.
- Among these is the risk of fractures.
- Little research has addressed this particular area of concern in the pediatric population.

What Is New

- There is a significantly higher rate of fractures among pediatric patients with exposure to proton pump inhibitors compared with those without exposure.
- The location of fractures among proton pump inhibitor-exposed pediatric patients is statistically different than those patients without exposure, with lower extremity, spine, and rib fractures being more common.

Proton pump inhibitors (PPIs) have revolutionized the treatment of acid-peptic and other upper intestinal disorders in both pediatric and adult patients. They are one of the most widely prescribed classes of medications with annual sales of more than $13 billion worldwide (1–3). Although PPIs have historically been considered exceptionally safe, this class of medicines has become increasingly implicated in a broad spectrum of adverse events. The predominant areas of concern are infection risk, electrolyte disturbances, and fracture risk. Most of the literature related to adverse effects stems from adult patient studies; however, use of PPIs in pediatrics has come under increased scrutiny (4–8). Given their widespread use, including long-term use in the pediatric population, adverse effects of PPI in pediatrics is of increased relevance to clinical practice.

Concerns regarding fracture risk related to PPI use were initially addressed by Vesterdaard et al in 2006, which found PPI use within 1 year was associated with an increased risk of fractures whereas H2 antagonists were associated with a decreased risk of fracture (9). Subsequently, Yu et al (2) published a meta-analysis wherein PPI use was noted to modestly increase the risk of fractures. Another meta-analysis by Nassar et al reinforced this increased fracture risk with PPI exposure, which was amplified with longer duration of therapy. Interestingly, a large portion (12/33) of included studies in this analysis failed to note any increase in fracture risk or decreased bone mineral density associated with PPI use (10).

Although increased risk for fracture has been demonstrated in adult studies, the underlying mechanism of this effect remains unclear. Some have postulated a pathophysiologic mechanism of osteoclast inhibition whereas others hypothesized decreased absorption of calcium (7,11,12). An alternative theory postulates hormonal effects leading to increased bone turnover (7,11,12). Although decreased bone density and amplified osteoporosis mediated by PPI is implied by several investigators, this is far from an established effect (13). Further ambiguity stems from bone effects

Received August 5, 2019; accepted November 7, 2019.

From the *Children's Mercy Hospital, Kansas City, MI, and the †Children's Hospital Association, Lenexa, KS.

Address correspondence and reprint requests to Nathan Fleishman, Department of Pediatric Gastroenterology, Children's Mercy Hospital, 2401 Gillham Road Kansas City, MO 64108 (e-mail: nrfleishman@cmh.edu).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

The authors report no conflicts of interest.

DOI: 10.1097/MPG.0000000000002690

appearing to be more measurable in the elderly population leading some to hypothesize that younger patients better compensate for the effects of PPI on bone (14).

Pediatric fracture location and mechanism differ greatly from that of adults and this poses an issue with examining a risk of fractures among children using PPI. It is, therefore, important to evaluate fracture location when studying the pediatric population as they are likely to have a different pattern of presentation. A detailed analysis of pediatric fracture location in the setting of PPI has not been reported. Two studies assessing risk of fracture in children have yielded conflicting results. Freedberg in 2015 demonstrated no association between fracture risk and PPI use in children whereas Malchodi in 2019 noted an increased risk of fracture in early childhood in infants exposed to PPI and histamine blockade (15,16). The purpose of this study, therefore, is to assess the association of PPI use and fracture risk in children and a detailed analysis of related fracture location.

MATERIALS AND METHODS

We performed a retrospective propensity-matched analysis to compare the rate of fracture among pediatric patients receiving PPI with those patients who did not receive PPI using the Pediatric Health Information System (PHIS) database, an administrative database that contains discharge (eg, demographics, diagnostic codes, procedure codes) and billing data on inpatient, emergency department, ambulatory surgery, and observation encounters from 49 tertiary care, pediatric hospitals in the United States. PHIS hospitals are some of the largest and most advanced children's hospitals in America and constitute the most demanding standards of pediatric service in America. Data are maintained by Children's Hospital Association (Lenexa, KS), participating hospitals, and IBM Watson/Truven Health Analytics (Ann Arbor, MI). Data undergo a series of regular quality and reliability checks before being included in the database. Data are de-identified at the time of data submission; however, all children in the database are assigned a unique, encrypted patient identifier so that they can be followed across multiple encounters. This study was reviewed and approved with designation as nonhuman subject research by the Office of Research Integrity at Children's Mercy Hospital in Kansas City, Missouri.

Initial encounters for patients age 6 months to 15.5 years were identified between June 1, 2011 to December 31, 2015 in the PHIS database. Encounters for patients outside the stated age range, encounters carrying a diagnosis related to complex chronic conditions and encounters for patients with conditions or medications predisposing a patient to risk of fracture were excluded (17). Detailed description of diagnostic codes for CCCs and other conditions excluded can be found in Supplemental Table 1 (Supplemental Digital Content, *http://links.lww.com/MPG/B801*). Encounters were classified as PPI encounters if a charge for PPI was documented in the billing record. As patients were not randomly assigned to receive a PPI or not, we used propensity score matching to reduce potential confounding by indication and adjust for differences in characteristics among children who received a PPI during a PHIS hospitalization and those who did not. We created a propensity score using multivariable logistic regression to estimate the likelihood of receiving a PPI; we then used these propensity scores to perform a 1-to-1 propensity match between patients receiving a PPI and controls with the same number of encounters and no documentation of PPI. Variables in the final propensity model included hospital, age, race, sex, payer, encounter type, median household income quartile, hospitalization resource intensity score for kids (H-RISK) and 3M's All Patient Refined Diagnostic Related Group (APR DRG) (18). A caliper of 0.05 was used to identify appropriate matches, and balance of covariates was assessed after matching. Any covariate for which we failed to achieve balance after propensity matching was included in a multivariable logistic regression mixed model with a random hospital effect to account of clustering of discharges at the same hospital. This model was used to assess the association of PPI use with fracture after adjusting for any remaining demographic differences between cohorts. Following initial encounter, patients were evaluated over a 2-year period for hospitalizations resulting from fracture. Categorical variables for PPI encounters and non-PPI encounters were summarized as frequencies and percentages and compared using a chi-square test for association. Continuous variables were summarized using median and interquartile range and compared using a Wilcoxon rank-sum test. All analyses were conducted using SAS 9.4 (Cary, NC). *P*-values <0.05 were considered statistically significant.

RESULTS

Data from 32,001 healthcare encounters with documented PPI use were obtained and tracked over a 2-year period from the initial encounter. The demographic characteristics of the PPI exposed group and propensity matched controls with index hospitalizations having fracture within 24 months are shown in Table 1. Among all PPI encounters the median age was 4 years with a distribution of <1 years (32.7%), 1 to 3 years (16.1%), 4 to 8 years (15.2%), 9 to 13 years (23.9) and greater than 14 years of age (12.1%). 48.5% of the PPI cohort was female. The propensity matched control group did not differ statistically from the PPI exposed group in terms of age, sex, or median household income quartile. Statistical differences between PPI and non-PPI matches remained after matching for the following variables: race, payer, patient encounter location, and H-RISK. Of note, H-RISK is a classification system which was developed to provide a means of analyzing a resource utilization and illness severity in similar fashion to that of the MS-DRG used in adult medicare population (18). A higher proportion of the PPI cohort were noted to be Caucasian. The PPI cohort also had a higher proportion of commercial payers compared to more government-program payers in the propensity matched controls. The PPI cohort was more likely to have their initial encounter take place in the inpatient setting while emergency, ambulatory surgery, and observational settings were more likely in the PPI unexposed cohort. Finally, the PPI cohort demonstrated a slightly elevated resource-intensity score reflected in a higher H-RISK score, compared with the unexposed cohort.

There were a total of 1011 fracture encounters among both cohorts including repeat fracture. When analyzing fracture occurrence in the 2-year period of observation, the total number of fractures was 808 with 371 in the non-PPI cohort and 437 in the PPI cohort. The total number of fractures including multiple fractures in the PPI cohort was 581 compared with 453 in the non-PPI cohort. This equated to a statistically significant higher rate of fractures among the PPI-exposed group (1.2% in non-PPI vs 1.4% in PPI, $P = 0.019$). When looking at encounter for first fracture and adjusting for remaining differences in sex, race, encounter type, payer, and resource usage intensity after matching, this difference remained statistically significant ($P = 0.017$) with an adjusted odds ratio (95% confidence interval) of 1.2 (1.0–1.4). These data are summarized in Table 1.

In both cohorts, upper extremity (humerus, radius, ulna, wrist, or hand) was the most common location for fracture; however, the PPI cohort was statistically more likely to suffer from lower extremity (femur, tibia, fibula, or foot), rib, and spinal fractures compared with the control group ($P = 0.01$). Lower

TABLE 1. Propensity match summary

	No PPI	PPI	*P*-value
N, discharges	32,001	32,001	
Age in years, median (IQR)	4 (0–11)	4 (0–11)	0.830
Age group, N (Col %)			0.096
0–3 y	15,446 (48.3)	15,610 (48.8)	
4–8 y	5066 (15.8)	4870 (15.2)	
9–13 y	7728 (24.1)	7660 (23.9)	
14 + y	3761 (11.8)	3861 (12.1)	
Sex, N (Col %)			0.020
Female	15,216 (47.5)	15,509 (48.5)	
Male	16,785 (52.5)	16,492 (51.5)	
Race, N (Col %)			<0.001
White, NH	18,091 (56.5)	19,123 (59.8)	
Black, NH	4910 (15.3)	4374 (13.7)	
Hispanic	5537 (17.3)	5260 (16.4)	
Other	3463 (10.8)	3244 (10.1)	
Payer, N (Col %)			<0.001
Govt	18,055 (56.4)	17,898 (55.9)	
Commercial	12,513 (39.1)	12,842 (40.1)	
Other	1433 (4.5)	1261 (3.9)	
Patient type, N (Col %)			<0.001
Inpatient	17,849 (55.8)	19,265 (60.2)	
ED	3849 (12.0)	3854 (12.0)	
Ambulatory surgery	749 (2.3)	512 (1.6)	
Observation	9,554 (29.9)	8370 (26.2)	
Median HH income quartile, N (Col %)			0.329
Q1	7886 (24.6)	7769 (24.3)	
Q2	7652 (23.9)	7535 (23.5)	
Q3	7921 (24.8)	8044 (25.1)	
Q4	8542 (26.7)	8653 (27.0)	
Case mix index, mean (SE)	1.17 (0.01)	1.24 (0.01)	<0.001
Fracture following in the next 2 years, N (Col %)			0.019
No	31,630 (98.8)	31,564 (98.6)	
Yes	371 (1.2)	437 (1.4)	
% fracture (95% CI)*	0.9 (0.6–1.2)	1.1 (0.8–1.4)	0.017

Number of index hospitalizations in the study period (either PPI or non-PPI) with at least 1 hospitalization for fracture following in the next 24 months. CI = confidence interval; IQR = interquartile range; PPI = proton pump inhibitor; SE= standard error.
*Adjusted for remaining differences in sex, race, payer, patient type, case mix, and clustering by hospital.

extremity fractures accounted for 30.7% of the non-PPI cohort fractures while making up more than 33% of the fractures in the PPI-exposed patients. Rib, spine, and hip fractures accounted for 6.4% of the total number of fractures in the non-PPI group whereas they made up 11.2% of all fractures in the PPI-exposed population. After adjustment for multiple comparisons using Bonferroni correction, we found that fractures of ribs and femurs differed with statistical significance between cohorts with both being more likely to occur among the PPI-exposed cohort. A summary of fracture location distribution can be found in Table 2.

With regards to the age distribution of fractures, in the PPI cohort, the 1 to 3 range and the 9- to 13-year range had the highest percentage of total fractures with 27.5% and 33.2%, respectively. The same trend was seen in the non-PPI cohort with 25.2% of fractures occurring in the 1- to 3-year age and 36.4 percentage of fractures occurring among the 9- to 13-year group. The greatest total number of fractures occurred among 2-year olds in the PPI group representing 12.9% of fractures whereas the 1-year-old age range had the highest total number of fractures among the non-PPI cohort representing 13.5% of fractures. The grouped age distribution of fractures can be found in Table 3 with a more detailed comparison between cohorts illustrated in Supplemental Table 2

TABLE 2. Fracture distribution

	No PPI	PPI	*P*-value
N, discharges for fractures	453	581	
Fracture location			0.01
Upper extremity, N (Col %)	285 (62.9)	323 (55.6)	
Humerus	50 (11.0)	68 (11.7)	
Radius/ulna	128 (28.3)	154 (26.5)	
Wrist/hand	107 (23.6)	101 (17.4)	
Lower extremity, N (Col %)	139 (30.7)	193 (33.2)	
Femur	17 (3.8)	50 (8.6)	
Tibia/fibula	69 (15.2)	86 (14.8)	
Foot	53 (11.7)	57 (9.8)	
Other, N (Col %)	29 (6.4)	65 (11.2)	
Ribs	12 (2.6)	32 (5.5)	
Spine	9 (2.0)	25 (4.3)	
Hip	8 (1.8)	8 (1.4)	

P-value of 0.01 indicates a statistically significant difference in the location of fractures between the PPI-exposed cohort and the non-PPI-exposed cohort. This indicates a higher rate of lower extremity and ''other'' fractures in the PPI cohort. PPI = proton pump inhibitor.

TABLE 3. Age distribution of fractures

Age at fracture, years	Total (% of total)	No PPI, %	PPI, %
<1	44 (4.3)	19 (4.2)	25 (4.3)
1 to 3	274 (26.5)	114 (25.2)	160 (27.5)
4 to 8	197 (19.1)	73 (16.1)	124 (21.3)
9 to 13	358 (34.6)	165 (36.4)	193 (33.2)
≥14	161 (15.6)	82 (18.1)	79 (13.6)
Total	1034	453	581

Hospitalizations with fractures recorded by age and cohort.

(Supplemental Digital Content, *http://links.lww.com/MPG/B801*) and Figure 1.

Among all PPIs evaluated including esomeprazole, lansoprazole, pantoprazole, omeprazole, combination PPI use or other unspecified PPI, we found no correlation between fracture risk and individual PPIs ($P = 0.205$).

DISCUSSION

There are few studies examining the risk of fracture in the pediatric population among patients exposed to PPIs. In fact, only 2 studies to date have targeted this relationship. Freedberg et al performed a case control study looking at fractures and exposure to PPI in children without chronic conditions; however, they eliminated children <4 years of age from analysis. This was a large study, which evaluated more than 124,799 fracture cases from the THIN database, a general practitioner electronic medical record database in the UK. This study found a significantly increased risk of fractures among young adults but not with children. Children were broadly defined as <18 years of age; however, no specific age subgroups were characterized. The most common fractures among the pediatric cohort were wrist and hand (16).

A more recent cohort study by Malchodi et al in 2019 evaluated childhood fracture risk in infants exposed to PPIs and H2 Blockers in the first 6 months of life. This study used the Military Healthcare System and examined more than 874,000 children born between 2001 and 2013. This study excluded several conditions felt to predispose to fractures including osteogenesis imperfecta, child maltreatment, and prolonged NICU stays. It excluded pathologic fractures from analysis. The authors found children prescribed PPIs had a 22% higher fracture risk compared with those not prescribed a PPI. If prescribed both PPI and H2 blocker in the first 6 months of life, patients had a 31% higher risk of fracture. Histamine blocker exposure alone was not associated with an increased risk of fracture (15).

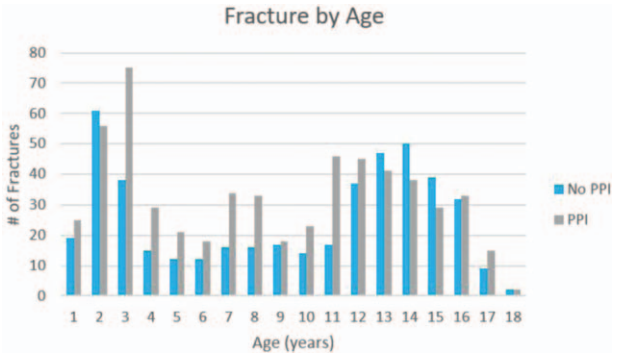

FIGURE 1. The number of fractures of each cohort distributed among age groups (by year). The blue bars represent PPI-exposed cohort whereas the gray bars represents the PPI-unexposed cohort. PPI = proton pump inhibitor.

Both the Freedberg and Malchodi studies addressed the fracture risk among the pediatric population but excluded a significant portion of this population from their analysis (15,16). Our retrospective propensity-controlled analysis examined whether exposure to PPI in multiple healthcare settings and among all pediatric age ranges is associated with increased occurrence of future fracture. Within the studied population, we observed a statistically higher incidence of fractures in patients exposed to PPIs compared with patients without exposure. There was no evidence of any individual PPI agent predisposing to fracture risk, suggesting a class effect. Our findings related to medication exposure and fracture occurrence conflicts with those findings of Freedberg but are consistent with those found in the Malchodi study. There is significant heterogeneity among the populations included in our study compared with the aforementioned including the age criteria defining our population.

Interestingly, we found that PPI-exposed patients had a higher rate of fractures involving lower extremities, ribs, and spine when compared with patients with no documented PPI exposure. Hip fractures, while few in number among both cohorts, were slightly more prevalent in the unexposed cohort, although this was not statistically significant. This finding is contrary to multiple studies, which have shown increased risk of hip fractures in adult PPI users. The reason for this difference is not within the scope of the present study. There is evidence that wrist and spinal fractures occur at a higher rate among this population (10,13,16,19). These locations, namely spine and hip, are much less common in the pediatric population. In children, forearm fractures predominate among patients presenting to the emergency department until the age of 15years at which time wrist and hand fractures become more predominate. Other common locations, depending on pediatric age group, include finger, hand, foot, and elbow (20). On the basis of our literature review, our study is the first to examine fracture location distribution in relation to PPI use.

The present study has several strengths as well as limitations. Using the PHIS database allowed us to obtain a large number of encounters from multiple hospitals across the country, which limits the geographic bias of our results. The PHIS database allowed us to track these patients over an extended period and in multiple settings (emergency, observation, surgical, and inpatient). Another strength of our study was our ability to limit confounding factors by using both diagnostic codes and CTC pharmaceutical codes to eliminate potential confounding conditions and medications, which may predispose to fractures. These criteria were applied to both our experimental group and the propensity matched controls. The propensity matched controls showed no statistically significant differences when matched on age, sex, and median household income. Although there were statistical differences in race, payer, and location of encounters, we did not feel these to be clinically significant. The fracture rate adjusted for these remaining differences remained statistically significant. No other study found during our literature search has classified subgroups for age including those less than 4 years in analysis of fracture risk and PPI use.

There are several limitations with our study. The retrospective nature limited ability to control for confounding factors, although we applied rigorous exclusion criteria and propensity matched controls. The PHIS database is strictly an administrative database, which captures billing and diagnostic codes. The ability of PHIS to capture more detailed information on duration of therapy is limited to the inpatient and observational settings. This is an inherent weakness in our study as it is possible exposure duration plays a significant role in the relationship between fractures and PPI use (13). Also, recently discontinued PPI treated patients, even if on long-term therapy were potentially included in our control group diluting the observed difference in fracture incidence in the 2

groups. Our study was not designed to account for these variables and the association between PPI and fractures is limited to exposure as deduced from billing for PPI administration. Although using the PHIS database allows for the capture of encounters among multiple hospitals, geographical location and hospital settings, it does not capture all hospitals or outpatient settings, such as a primary care provider office, urgent care, or specialty office. This may have led to a lack of continuity as our cohort was not in a ''closed system.'' Hence, underreporting of fractures, which were not seen in the above settings is clearly a possibility; however, this would likely impact both the PPI group and control group equally, which would underrepresent the fracture rate among both cohorts. Fractures not likely to be seen in settings captured by PHIS would include hand or foot fractures, which could be addressed in the outpatient setting only. Additionally, our study does not take into account prior PPI exposure preceding our captured time frame thereby likely underestimating PPI usage and hence underestimating the fracture occurrence rate among those exposed to PPIs in the past.

The same issue may lead to underreporting of PPI exposure as outpatient prescriptions or over the counter medications would not be captured. This may lead to underrepresentation of PPI exposure among those with fractures, which would have enhanced the non-PPI-exposed cohort fracture rate, diminishing the observed differences between our cohorts. PHIS captures data based on billing codes. The entry of billing code for the PPIs does not confirm compliance or administration of the medication. Finally, as mentioned, there were statistical differences in the 2 examined cohort in race, payer, patient type, and case mix index. Although these differences could affect the overall fracture rate between cohorts, they were felt to be clinically insignificant based on the distribution, which can be found in Table 1.

CONCLUSION

In conclusion, this study suggests an increased risk of fracture among otherwise healthy pediatric patients exposed to PPIs within a 2-year period of exposure. Among patients with a documented fracture, those with prior PPI exposure had a higher rate of lower extremity, rib, and spine fractures compared with controls. This difference persisted despite adjusting for multiple demographic factors and also appeared to be a class effect of the medications. Although our study examined a large cohort in various healthcare settings, it did not capture outpatient data including PPI prescriptions or over the counter purchases thereby limiting our ability to examine duration effects. Given the widespread use of PPIs and the findings of the present study, it is imperative that providers consider side effect risk including a potential risk for fractures when deciding to prescribe PPIs for pediatric patients. Future studies defining dosage and duration of use as well as mechanism are needed to further understand the relationship between PPIs and fractures in the pediatric population.

REFERENCES

1. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. *PLoS One* 2015;10:e0124653.
2. Yu EW, Bauer SR, Bain PA, et al. Proton pump inhibitors and risk of fractures: a meta-analysis of 11 international studies. *Am J Med* 2011;124:519–26.
3. De Bruyne P, Ito S. Toxicity of long-term use of proton pump inhibitors in children. *Arch Dis Child* 2018;103:78–82.
4. Stark CM, Nylund CM. Side effects and complications of proton pump inhibitors: a pediatric perspective. *J Pediatr* 2016;168:16–22.
5. Nehra AK, Alexander JA, Loftus CG, et al. Proton pump inhibitors: review of emerging concerns. *Mayo Clin Proc* 2018;93:240–6.
6. Hassall E, Kerr W, El-Serag HB. Characteristics of children receiving proton pump inhibitors continuously for up to 11 years duration. *J Pediatr* 2007;150:262–7267.e1.
7. Hansen KE, Jones AN, Lindstrom MJ, et al. Do proton pump inhibitors decrease calcium absorption? *J Bone Miner Res* 2010;25:2786–95.
8. Johnson DA, Oldfield ECt. Reported side effects and complications of long-term proton pump inhibitor use: dissecting the evidence. *Clin Gastroenterol Hepatol* 2013;11:458–64.
9. Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medications and the risk of fracture. *Calcif Tissue Int* 2006;79:76–83.
10. Nassar Y, Richter S. Proton-pump inhibitor use and fracture risk: an updated systematic review and meta-analysis. *J Bone Metab* 2018;25:141–51.
11. Costa-Rodrigues J, Reis S, Teixeira S, et al. Dose-dependent inhibitory effects of proton pump inhibitors on human osteoclastic and osteoblastic cell activity. *Febs j* 2013;280:5052–64.
12. Danziger J, William JH, Scott DJ, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. *Kidney Int* 2013;83:692–9.
13. 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;138:896–904.
14. Jo Y, Park E, Ahn SB, et al. A proton pump inhibitor's effect on bone metabolism mediated by osteoclast action in old age: a prospective randomized study. *Gut Liver* 2015;9:607–14.
15. Malchodi L, Wagner K, Susi A, et al. Early acid suppression therapy exposure and fracture in young children. *Pediatrics* 2019;144:pii: e20182625.
16. Freedberg DE, Haynes K, Denburg MR, et al. Use of proton pump inhibitors is associated with fractures in young adults: a population-based study. *Osteoporos Int* 2015;26:2501–7.
17. Feudtner C, Feinstein JA, Zhong W, et al. Pediatric complex chronic conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr* 2014;14:199.
18. Richardson T, Rodean J, Harris M, et al. Development of Hospitalization Resource Intensity Scores for Kids (H-RISK) and comparison across pediatric populations. *J Hosp Med* 2018;13:602–8.
19. Leontiadis GI, Moayyedi P. Proton pump inhibitors and risk of bone fractures. *Curr Treat Options Gastroenterol* 2014;12:414–23.
20. Naranje SM, Erali RA, Warner WC Jr et al. Epidemiology of pediatric fractures presenting to emergency departments in the United States. *J Pediatr Orthop* 2016;36:e45–8.