Proton-Pump Inhibitors: Do Children Break a Leg by Using Them?

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ABSTRACT

The risk of bone fracture in children under proton-pump inhibitors (PPI) treatment has been the subject of recent publications and naturally raises concerns among prescribing doctors, patients and their parents. Currently, there is no consistency in those risk claims according to the available evidence and an update on it is beneficial to reduce anxiety on one hand, and prompt for well-planned studies addressing the issue on the other. Furthermore, common sense and well-founded prescriptions must be the general rule for this as for any other therapeutic drug.

Key Words: drug, eosinophilic esophagitis, fracture, gastro-esophageal reflux, proton-pump inhibitors, side-effects, stomach

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Proton-pump inhibitors (PPI) are worldwide prescription best sellers. From the early 1990s, they have been used in an increased range of indications. In the 21st century, this trend replicated into paediatric field well beyond the very few indications that are expressed by strict recommendations in several paediatric societies. It is widely prescribed by general practitioners and is an over-the-counter medication not only to reflux disease but to a growing number of functional conditions. In paediatrics, omeprazole was the first PPI approved for clinical use, and still is the most studied PPI in basic and clinical research. New drugs emerged as is the case of esomeprazole, lansoprazole and pantoprazole, which, due to galenic composition and specific pharmacokinetic profile, are being preferred over omeprazole. In the adult population, the chronic use of PPI for decades, combined with multiple pharmacology prescription and coexistence of multiple health co-morbidities, led to physicians' concerns due to possible synergic side effects or antagonistic drug interactions. Several epidemiologic studies linked the PPI use to various side effects and warning reports regarding PPI toxicity have been published (1). Despite the plausibility of its occurrence, most of the recommendations regarding harmfulness of PPI use have been based on the rationale of chronic acid suppression effect or weak epidemiologic link, rather than robust research evidence from clinical trials.

What Is Known

- Proton pump inhibitors (PPI) chronic use is associated to vitamin and mineral deficits in adult population. Bone fracture in certain risk populations has been linked to PPI long time use.
- In paediatrics, there is scarce information regarding long time exposure.
- Paediatric retrospective cohorts have been identified augmented risk fractures in PPI exposure.

What Is New

- This is to the date the first analysis of published literature regarding PPI use in paediatrics and bone fractures. There is no consistent relationship to PPI use and fracture in paediatrics based on prospective unbiased evidence.
- Prospective studies are needed to confirm this observational hypothesis.

PPI effect is a strong acid secretion inhibition of receptors in the gastric parietal cells, rising the usual stomach pH of 2.5 to 6 for >19% in the 24 hours period (2). This alkaline trend could lead to diminished absorption derived from inhibition mechanisms dependent on acidic gastric environment to occur. In this case, mineral and vitamin bioavailability (iron, magnesium, calcium and vitamin B_{12}) are expectably diminished. Acid pH is crucial for release of ionized calcium from insoluble salts of dietary calcium (3,4). Hypergastrinemia derived from rise of gastric pH leads to parathyroid cell hyperplasia and enhances parathormone synthesis. This could stimulate osteoclast activation with consequent bone resorption. In theory, the combined effect of low calcium levels and increased parathormone should decrease bone density, as reviewed by Yang in 2012 focusing on calcium metabolism and PPI exposure between mixed studies in haemodialyzed patients, young healthy and post menopause females (5). In healthy patients, only one study showed malabsorption of calcium under fasting condition in the group of patients on omeprazole (2).

PPI block the H^+/K^+-ATPase not only in parietal cells but also in osteoclasts, an essential step in bone resorption, so the effects of PPI are also effective in osteoclasts. In this particular case, they seem to have a decreased osteoclastic activity, lowering bone resorption and consequently being osteoprotective (5).

Basic research at laboratory using cellular and animal models have been published and these molecular studies added important information about the effect of omeprazole in bone metabolism. Hyun et al (6). conducted a cell culture model and showed that

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omeprazole decreased the activation of osteoclasts but somewhat increased the activation of osteoblasts and this was replicated in later studies (7,8).

Joo et al (9) also used an experimental animal model and concluded that omeprazole combined with low calcium diet, but not alone, stimulates the expression of markers associated with osteoclastic activation.

In 2020, Yu-Xi et al (10) developed a murine model in which they examined the direct effect of pantoprazole on osteoclastic formation and bone resorption in an induced inflammatory model of bone loss. They concluded that pantoprazole prevented osteoclastic activity in vitro acting as a bone mass promoting drug.

STUDIES AND POTENTIAL ASSOCIATED HARM EFFECTS IN ADULTS

In the adult population there have been a considerable number of observational and epidemiological studies. Although in theory the result of acid suppression could be extremely deleterious, the reported data showed some minor associations from evidence-based results. The risk of side effects had very few prospective studies supporting them, and the found weak clinical associations did not prove a deterministic mechanism. The highlighted conditions are summarized below and there are some potential side effects that were not confirmed by epidemiological studies; however, some well conducted prospective studies clarified some pending questions as the elevated risk of myocardial infarction by interaction of PPI with other drugs. PPI had no association with myocardial infarction events in well-designed randomized studies (11). Meta-analysis with large number of adults showed weak association with fractures and other epidemiological studies confirming low-grade risk association with plausible co-morbidities to PPI exposure. There has been no association with cancer linked to prolonged hypergastrinemia nor carcinoid tumours over long term PPI use (12). In recent years, risk of dementia among long term PPI use was a global concern but was never demonstrated. Dementia risk hypothesis led to large populational studies and meta-analysis (13,14); however, mineral and vitamin malabsorption has been generally accepted and some expectable mineral deficits such as iron and vitamin B_{12} deficiency, as well as severe hypomagnesemia have been documented (15). Reversibility of these conditions is obtained with proper supplementation.

Recently, large meta-analysis regarding PPI use and the risk of bone fracture in adults were published:

In 2006, Yang et al (16) conducted a case–control study with >192,000 PPI users, showing that long-term PPI users had an increased risk of hip fracture. The risk significantly increased among patients on long-term and high-dose PPI (odds ratio [OR]: 2.65, 95% confidence interval [CI] 1.80–3.90); however, neither co-morbidities that may affect bone mass density or daily calcium supplementation were considered to analysis. Although recent meta-analysis are consistent with higher risk of fracture, Bone mineral density appears not to be directly related to the augmented risk, as shown in previous data by Nassar (17) and Liu (18).

A meta-analysis of selected 24 studies, including >2 million patients was published by Poly et al (19). Only studies that followed >500 patients for more than a year were selected. Despite variable heterogeneity among the different studies, it was concluded that patients on PPI had a higher risk of hip fracture than those without PPI therapy (Relative risk 1.20, 95% CI 1.14–1.28, $P < 0.0001$).

More recently, Hoff et al (20) conducted a Norwegian case-control study with 28,258 individuals and concluded that PPI use had no association with increased risk of fractures.

From these studies, it may be considered that, beyond risk of bias identified in most of published data, adult population may have a slightly higher risk of bone fracture among PPI users and this effect is positively correlated to duration of treatment.

PAEDIATRIC STUDIES AND POTENTIAL SIDE EFFECTS

In paediatric patients, PPI use has not been linked to major side effects in the clinical practice. Chronic use in paediatrics has been the exception rather than the rule; however, even short-term use in the first year of life may be challenging because there are very few reliable studies on safety and long-term effects. There are no standards supporting routine use of PPI in the newborn, as well as its use in infants without clear signs of reflux disease (21). Moreover, PPI prescription is absolutely discouraged for crying infants or to treat colic (22).

However, an increasing number of patients with other diseases, like eosinophilic oesophagitis or oesophageal atresia may still need PPI for a long time, so paediatricians have now their time for concerns. Despite the strict indications for the use of PPI in published clinical guidelines, its prescription has raised in the last decades. Prescriptions of antacid preparation to infants increased more than three times from 2009 to 2018 and this scenario has been well documented in an European national cohort of patients (23).

Microbiome diversity changes have been documented with PPI use and this is a sensitive topic. Microbiome diversity reaches its mature form at around three years of age and is dependent on environmental modulation. Microbiome changes are linked to gut ecosystem as well as predisposition to infection and immunity maturation. Some studies raised this possibility, and it is still impossible to predict how gastric acid suppression for a long period can be a modulator of immune system in the future. Iron and vitamin B_{12} deficiency also carry harm risk for the ones who need strong acid suppression for long periods.

Recently, another inflamed controversy emerged: the association of fracture risk with PPI use in paediatrics. What we learned from the adults is that the retrospective epidemiologic associations must be taken cautiously. As mentioned above, Yang et al (5) analysed a group of adults with long term use of high PPI doses and admitted the potential risk of bone fracture. This study raised some controversy for several years; after many publications, the pathway explanation for this theory remains to be proved.

Freedberg et al (24) studied a cohort of children and young adults ages 4–29 years and did not find association of PPI and bone fractures in children but a slight association among young adults.

The first alert in paediatrics was raised by an epidemiological study that linked PPI use and fracture episodes in a large national children cohort. Malchodi et al (25) retrospectively analysed a cohort, using pharmacy records of prescription of 851,361 children from a military health service from birth to 14 years old. They reported a higher fracture incidence in the group of children treated with PPI in the first year of life but not in a sub-group treated from 12 months to 2 years. The number of preterm and low birth weight children group was very large, as well as male sex, which add multiple risk factors for bone fracture. Children prescribed PPI in the first year of life had an increased risk of fracture, but when adjusted to different variables the association represented a minor risk. Interestingly in this study anti-epileptic drug prescription had no augmented fracture risk. This is puzzling as patients under anti-epileptic drugs are known to have risk of fracture by deleterious effect on bone metabolism, which has been confirm by recent meta-analysis in relation with valproate (26). Retrospective studies have limitations and may be biased as there is no robust characterization of the different groups: an example is seen in the large national cohort studies where fracture patterns, mechanism of injury or even maltreatment are not considered for analysis. More importantly, we

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TABLE 1. Summary of paediatric studies

Author (year)	Study type	Patients	Overall fracture risk (HR)	PPI dose related analysis	PPI duration related analysis (HR)	Bias
Freedman et al. (2015)	Nested case–control	4–29 y 124,799 cases (87,071 < 18 y) 605.643 controls 1 y follow up	1.13 (95% CI 0.92–1.39) < 18 y 1.39 (95% CI 1.26–1.53) 18–29 y	Cumulative dose was associated to fracture in adults only	Increased risk for 6 mo daily PPI exposure for adults	Prescription based analysis No daily dose No mechanism of injury No demographic or feeding data
Malchodi et al. (2019)	Retrospective cohort	7.998 PPI users PPI < 1 y 14 y follow up	1.23 (95% CI 1.15–1.32)	No	1.19 (1.11–1.29) < 30 days 1.20 (1.09–1.33) 30–60 days 1.23 (1.13–1.33) 60–150 days 1.41 (1.32–1.52) > 150 days	Prescription based analysis No daily dose No mechanism of injury No demographic or feeding data
Wang et al (2020)	Retrospective Case–control cohort	115,933 pairs < 18 y	1.11 (95% CI 1.06–1.15) Only > 6 y old	No	1.08 (95% CI 1.03–1.13) < 30 days 1.14 (95% CI 1.09–1.20) 31–364 days 1.34 (95% CI 1.13–1.58) > 365 days	Prescription based analysis No race/ethnicity, BMI or physical activity analysis No daily dose
Fleishman et al (2020)	Case–control cohort	32,001 pairs 6 mo to 15.5 y 24 mo follow up	1.2 (95% CI 1.0–1.4)	No	No	Private health care billing Inpatient patients only

BMI = body mass index; CI = confidence interval; HR = hazard ratio; PPI = proton-pump inhibitors.

do not know about daily light exposure or dietary type differences between the two groups (25).

Wang et al reported a small overall risk for fracture for children exposed to PPI (27). This effect was related to duration of therapy but no relation to daily dose as the cohort was based on prescription records, unreliable to define a daily dose. A possible relation was suggested for minor fractures (upper and lower limbs) but not spinal or head fractures in PPI exposed patients from this Swedish cohort. Interestingly, increased risk was significant only in the omeprazole prescribed children but not esomeprazole, pantoprazole or lansoprazole group. This large cohort found a correlation in children prescribed PPI at 6 years old or later. Age risk and fracture location were considerably different from other series, reinforcing the different results that may arise from varied large national retrospective cohorts.

Fleishman et al (28) reported a retrospective study based on payment of private accounts which considered PPI exposure based on the prescription receipt. This had the primary bias of a cohort from inpatient children in a private system, which does not represent the overall cohort, as this group may have different social and health resources. The billing and diagnostic recording codes were strictly an administrative database, and do not objectively describe the real exposure or the treatment duration with PPI by each patient. Furthermore, the inpatient recruitment of cases was naturally biased. In this cohort, femur and rib fractures were reported as the mostly associated with PPI use, perhaps because hand and wrist—the most frequent ones—can often be managed at ambulatory care, out of the scope of this database. In contrast to this report, adult series point out hip fracture as the commonly related type of fracture.

Based on these four divergent and partially biased retrospective studies, there emerged the general concept of the possibly increased fracture risk in children exposed to PPI (Table 1). Despite the proposed link of these two conditions, no relation to dose therapy or duration have been confirmed with any randomized controlled trial. The nature of the fracture and many other confounding variables should be analysed in parallel to the nature of PPI exposure. No diet considerations, calcium content in diet, vitamin D level, exercise habits were matched to the fracture risk. Corticosteroids have been the classic paediatric medication associated to loss of bone mineral density and increased risk of fracture. The pathway that could explain the association of PPI and bone fracture could be the decreased calcium absorption derived from chronic acid suppression. However, to date this has not been documented in paediatrics and several previous studies in adults did not confirm it either (29).

Iron and magnesium absorption issues are well documented as deficits linked to PPI use (15), but studies published to date aimed to evaluate PPI use and calcium absorption had results difficult to interpret or limited clinical applicability due to methodological limitations. Comparison of nutritional intake between children and adults cannot be simplified as aged adults are prone to any degree of gastric mucosa atrophy, which diminishes calcium absorption despite similar ingestions. Moreover, bone metabolism reabsorption derived from osteoclast activation has not been confirmed in a paediatric study (30).

SO, WHAT DO WE KNOW AND HOW SHOULD WE PREVENT PAEDIATRIC BONE DISEASE?

In paediatrics, bone density acquisition is a continuous process. Bone is a dynamic tissue that undergoes constant remodelling and increased density is the balance of bone-forming osteoblasts and bone-reabsorbing osteoclasts. Bone remodelling and growth occurs through infancy, childhood and adolescence until final stature is reached and bone mass peaks. Kocsis et al (30) did

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not find changes in biochemical parameters related to osteoclast or osteoblast in children exposed to short-time therapy. Bone densitometry is an easy way to determine osteopenia and may identify mild osteopenia accurately from 5% loss of bone mass. In a short-term use of PPI, substantial changes may not be visible on a bone scan or a significative *z* score deviation of bone density, but to date there are no studies addressing it. When faced with a bone fracture that cannot be explained by a high impact trauma, one should be aware of conditions that can predispose to loss of bone density. Biochemical and image analysis should be matched to possible risk factors, to explain the pathophysiology of the fracture.

Bone density standards can be used for clinical monitoring in a variety of patients with certain conditions such as *osteogenesis imperfecta*, metabolic diseases or under chronic corticosteroid use. Children with these conditions routinely need calcium absorption and excretion assay, vitamin D supplementation, as well as monitoring and bone density evaluation. Although no standards are defined for infants and young children, there are validated *z* scores adjusted for-the-age from 2 years onwards (31).

Some children with inflammatory gastrointestinal diseases have severe dietary restrictions and often need cow's milk avoidance. Nutritional imbalance of calcium and vitamin D deficiency may arise and be more noxious than any medication. Nutrition in digestive diseases is crucial and it is as important as drug prescription. Calcium derived from dairy products as milk and cheese have higher bioavailability for absorption and should be strongly recommended in daily diet. For children with feeding difficulties or dietary restrictions a personalized nutritional plan can be optimized through a nutrition team support. For example, in children in whom cow's milk avoidance is recommended, daily intake of other calcium sources should be encouraged. If needed, calcium supplements in patients under acid suppression should be prescribed as soluble form (calcium citrate) over calcium carbonate insoluble salts and preferably administered with meals.

When acid suppression needs to become a chronic medication, regular clinical assessment to define optimal duration of PPI use should be done and timely regular endoscopic examinations should not be delayed confirming the need for continued treatment.

Sunlight exposure and exercise are indicated by paediatric societies to prevent secondary osteoporosis and can be further stressed in the case of long-term PPI use. Physical activity is considered one of the most effective strategies to optimize peak bone mass during childhood particularly high impact activities like running or jumping (32,33).

Neurologically impaired patients are a special group that concerns not only paediatric gastroenterologists but also general paediatricians. These patients combine several risk factors for fracture as the lack of mobility, chronic anti-epileptic drugs use as well as long-term PPI use for reflux disease. These are high-risk patients for severe osteopenia and pathologic fractures. Therefore, bone density concerns are valid for the follow up of these patients and bone density mass should be regularly assessed.

Although there is no strong evidence to link PPI use and bone fractures in children, the strength of the large paediatric population analysed suggests that it is reasonable to monitor PPI long-term use, not only based on sole cumulative effect but the dosing effect per body surface. Treatment should be documented and monitored regularly to minimize the risk of bone disease, even if there is only a slight potential risk.

CONCLUSION

Acid suppression and gastro-oesophageal reflux medication have led to long discussion. Short-term use has been popular among paediatricians who provide a close follow up of infants, children and their caring anxious families. Functional diseases lead to most of the short use of PPI in the community from infancy to late adolescence. It should be addressed that pain relief can be managed with combined strategies and the mainstay of intervention should be non-pharmacological, diminishing the need for acid suppression. It is important to highlight the role of the physician skills to provide alternative ways to the easy drug therapy.

Chronic use of PPI should occur under supervision of a skilled specialist used to diagnose and follow digestive conditions whose prognosis can be clearly worsened without acid suppression.

In paediatric gastroenterology, there are groups of patients that will need PPI therapy for a part of their lives. These can start in early infancy like oesophageal atresia or be long-term users as in eosinophilic oesophagitis. Severe oesophageal motility disorders may even need PPI as a life-long treatment, as acid suppression has a relevant role in their clinical management. In this ongoing debate, clinical judgement should be careful to patients in whom other risk factors can be confounders of the reported observational effects.

In the real scenario of a paediatric patient who will need prolonged acid suppression, medication should be handled with care, concerning possible mineral deficits. This can be avoided through regular clinical examination and a bone metabolism profile determination before drug start, as is now standard of care to many other medications. Nobody expects that patients with severe reflux disease, oesophageal atresia or eosinophilic oesophagitis would not be treated because of a possible, though unproved, risk of fracture in the future. The benefit of such a medication should be balanced against proven side effects. This is the medical approach in general when a physician takes the option for corticosteroid treatment, for example.

Currently, there are no randomized studies regarding the type of harmful effect, relation with dose and/or duration of PPI treatment; however, when the suspicion arises it becomes urgent to reach solid evidence, based on prospective unbiased studies to clarify this topic. Currently, there is lack of a clear biologic mechanism that may prove a causal link between PPI use and bone fracture. As with other drugs, the sensible, appropriate use of PPI is the best recommendation for a beneficial outcome for our patients.

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