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Proton pump inhibitors have no measurable effect on calcium and bone metabolism in healthy young males: A prospective matched controlled study

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ABSTRACT

Objectives. Proton pump inhibitors (PPIs) are associated with an increased risk of bone fractures. This study sought to evaluate the effect of PPIs on biochemical markers of calcium and bone metabolism.

Methods. Prospective matched controlled study involving healthy adult males (age 18–50 years) suffering from frequent heartburn. Patients received standard-dose PPI for 12 weeks and were matched by age with healthy controls. Blood studies were taken at 0, 1 and 3 months for biochemical markers of mineral and bone metabolism. Two-way (time and PPI treatment) repeated measures analysis of variance (RM-ANOVA) and multiple linear regression were used for analysis.

Results. A total of 58 participants (29 per group) completed the study. Mean age of participants was 33.2±7.5 years. Baseline characteristics and biomarkers were similar for both groups except for higher BMI (28.6 vs. 25.6 kg/m^2, p=0.008) and serum C-terminal cross linked telopeptides of type I collagen [CrossLaps, (300 vs. 228 pg/ml, p=0.028)] in the PPI group. There was no difference in parathormone (PTH), ionized calcium, vitamin D, osteocalcin and CrossLaps between the PPI and control subjects (all non-significant; 2-way RM-ANOVA). Multiple linear regression modeling showed no effect of PPIs on any of the studied calcium or bone metabolism biomarkers.

Conclusion. PPI intake for 12 weeks has no measurable effect on calcium or bone metabolism in healthy young males.

Abbreviations: PPI, Proton Pump Inhibitor; PTH, Parathyroid Hormone; CrossLaps, C-terminal cross-linked telopeptides of type I collagen; CV, Coefficient of Variance; RM, repeated measures; ANOVA, Analysis of Variance; NNH, Number Needed to Harm; BMD, Bone Mineral Density.

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1. Introduction

Proton pump inhibitors (PPIs) are amongst the most widely used drugs worldwide. Because of a favorable side-effect profile and proven efficacy in the treatment of common gastric acid-related problems, PPIs are widely prescribed and purchased over the counter with estimated global sales of $26.5 billion in 2008 [1]. However, the increasing prevalence of their chronic use has raised several concerns about potential drug-related long term adverse events as a result of prolonged inhibition of acid production by gastric parietal cells [2]. Recently, many observational case–control and cohort studies have shown a modest increase in spine, hip, and total fractures with chronic PPI intake [3,4]. Other studies have, however, failed to substantiate this association [5,6]. As a result, the US Food and Drug Administration issued in May 2010 an alert that PPIs may enhance the rate of bone fractures without adding a black box warning [7]. Given the heterogeneous nature of available studies and the diverging results, several meta-analyses were implemented that again led to conflicting conclusions [8,9]. While some estimated that as many as 4.7% of hip fractures might be attributable to PPI use, others found no or only a modest association without any evidence for an effect of duration, thus raising doubts whether the observed epidemiologic association is causal or the result of unmeasured confounders[8,9].

Importantly, the pathophysiologic mechanisms underlying this putative increased risk in fractures remain unclear. Possible explanations include hypochlorhydria-induced decreased calcium absorption [10], and/or a direct effect of PPIs on H^+-K^+ pumps in osteoclasts [11]. Clinical trials have described conflicting results regarding the effect of acid suppression on biochemical measurements of bone resorption in humans as well as discordant effects on bone mineral density. However, any of the aforementioned mechanisms should, in principle, result in perturbation of calcium homeostasis with changes in serum ionized calcium and consequently in parathyroid hormone and markers of bone turnover. To address this question, we designed a prospective matched controlled study to evaluate the effect of PPI use on serum markers of calcium and bone homeostasis.

2. Materials and methods

2.1. Population

The study population consisted of 2 groups, the first included healthy men aged 18 to 50 years complaining of frequent heartburn and who had not received any prior PPI therapy in the preceding year, while the second consisted of age-matched (±2 years) healthy men without heartburn or dyspepsia. Patients were recruited by advertisement and all efforts were made to complete recruitment in the fall and winter period to minimize the effect of sun exposure on serum 25-hydroxy vitamin D levels. Exclusion criteria included female gender to avoid confounding effect of various phases of menstrual cycle on bone metabolism [12]. Men more than 50 years of age were also excluded in order to avoid impact of confounders that are usually present in the elderly population and that can affect mineral metabolism like drugs, age, and concomitant diseases. Lastly, subjects were excluded in case of known allergy to PPIs, regular beach seekers (more than once a week), known small intestinal disease, recent fracture (within the past six months), history of kidney stones, and ongoing or recent (within 1 year) intake of vitamin D or calcium supplements, anticonvulsants, glucocorticoids, and PPIs or H_2 receptor antagonists. Patients were also not allowed to have any of these supplements and medications once they were enrolled in the study and compliance was checked on every study visit. Once a patient with heartburn was enrolled in the study, he was directly matched by age (±2 years) with a healthy volunteer control that underwent blood studies within 2 weeks from the enrollment of the patient he was matched to. All subjects completed a baseline semi-quantitative food frequency dietary questionnaire, modified from a previously validated food frequency questionnaire developed by our group, at the time of recruitment [13]. The study was approved by the Institutional Review Board and was registered as a clinical trial, ClinicalTrial.gov identifier: NCT01139645. All patients and matched controls gave written informed consent.

2.2. Intervention

Participants with heartburn were randomized to receive a standard dose of one of three commercially available PPIs, taken once daily 30 min before breakfast for a period of 3 months. The PPI used was either esomeprazole at a 40 mg dose (Nexium®, AstraZeneca, London, England), rabeprazole at a 20 mg dose (Pariet®, Janssen-Cilag, Beerse, Belgium), or lansoprazole at a 30 mg dose (Lanzor®, Sanofi-Aventis, Paris, France). The medications were provided free and at monthly installments, with return of medication packages at each visit for pill count, to assess and ensure proper adherence and compliance. The matched volunteers in the control group were not given PPI or placebo. Participants in both groups had non-fasting blood studies at the time of recruitment and after 1 month, and 3 months. All blood studies were drawn before noon, between 8 am and 12 pm. These included total serum calcium, ionized calcium, phosphorus, albumin, parathormone (PTH), 25-OH-vitamin D, C-terminal cross-linked telopeptides of type I collagen (CrossLaps), and osteocalcin. In addition, serum creatinine was measured once at baseline. Serum calcium and phosphorus were measured by standard calorimetric methods, using the Hitachi 912 analyzer (Mannheim, Germany). Serum 25-OH-vitamin D level was measured by RIA using the IDS (Immunodiagnostic System Limited, UK) and serum PTH by ELISA-PTH immuno-radiometric assay (CisBio International, Gif-Sur-Yvette, Cedex, France). For PTH, the detection limit of the assay was 0.7 pg/ml and the normal range of the kit was 8–76 pg/ml. For 25-OH-vitamin D, the normal range of the kit was 20–60 ng/ml. The intra-assay and inter-assay variability for 25-OH-vitamin D and PTH is below 10%. Our institution has been a participant of the Vitamin D External Quality Assessment Scheme (DEQAS), which evaluates the performance of participating laboratories quarterly, for several years (www.deqas.org). Serum CrossLaps were measured by ECLIA (electro-chemi-luminescence immuno-