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ORIGINAL ARTICLE

Short Term Omeprazole Use and Markers of Calcium Homeostasis

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ABSTRACT

Introduction: Several studies indicate a higher prevalence of fracture following long term utilization of proton pump inhibitors, among them omeprazole is the most widely used. However, the exact mechanisms lead to this complication are largely unknown. We studied short term effects of omeprazole on some markers of calcium metabolism. **Materials and Methods:** In thirty young adult patients with gastroesophageal reflux, omeprazole was prescribed at 20 mg twice daily for thirty days. Baseline characteristics as well as data after treatment with omeprazole were compared. We also measure important parameters in sixty age and sex match healthy individuals at baseline. **Results:** Mean age of patients was 31.8 year and there was no significant difference regarding age, sex, body mass index, serum calcium, serum alkaline phosphatase and parathyroid hormone between cases and controls. Although, most of the patients were vitamin D deficient (mean = 29.7 nmol/l); compared to controls serum 25 OH Vitamin D was higher (P= 0.005) and serum phosphate was lower (P= 0.001) in patients. In addition, there was significant increase in alkaline phosphatase (P=0.01) and borderline decrease in serum calcium (P= 0.057), thirty days after treatment with omeprazole. **Conclusions:** High dose omeprazole after thirty days in the presence of vitamin D deficiency affects bone turnover probably by decreasing calcium absorption.

INTRODUCTION

Omeprazole is the most widely used proton pump inhibitors (PPIs) (1,2). Several lines of evidence indicate that there is higher prevalence of fracture among users of omeprazole (3-7).

A number of mechanisms have been proposed to explain this phenomenon. Although direct effect of omeprazole on bone may be a plausible mechanism (8-11), the most attractive theory is decrease in calcium absorption due to omeprazole induced hypochlorhydria. In this regard, A number of studies showed decreased intestinal calcium absorption (12-16) while others not (17,18). However, the exact mechanisms by which omeprazole affects bone and calcium metabolism remained to be identified.

The aim of present study was to determine effects of omeprazole on markers of calcium homeostasis in young adults treated for gastroesophageal reflux disease.

MATERIALS AND METHODS

In a prospective study thirty young otherwise, healthy adults with diagnosis of gastroesophageal reflux disease (GERD) were enrolled. Baseline clinical and laboratory characteristics were recorded using a structured questionnaire. Exclusion criteria were: previous treatment with any gastric acid suppressant (e.g. PPIs, H2 blockers, Antacids), long duration of symptoms, use of any drug that affects bone and calcium metabolism (e.g. calcium, vitamin D (vit D), bisphosphonates, steroids), smoking, pregnancy, previous gastrointestinal (GI) surgery, malabsorption syndromes, cancers and any disorder that may disturb bone or calcium homeostasis e.g. renal disease. Omeprazole was prescribed at 20 mg twice daily on empty stomach. We conducted a positive pill count to ensure compliance. Thirty days after initiation of treatment the clinical and laboratory data were recorded. A control group consists of sixty age and sex matched healthy individuals were included in study. 5 ml blood was obtained at baseline (patients and controls) and thirty days after treatment (patients) by venipuncture. Sera were extracted and freezes at -80°C until further analysis.

Height and weight were measured by stadiometer and clinical scale and body mass index was calculated as weight/height2. Serum parathyroid hormone (PTH) and 25 OH vit D were measured by Chemiluminescent assay (CLIA) (Diasorin Inc. USA) with intra assay coefficients of variation less than 5%

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and 13% respectively. Serum calcium, phosphate, alkaline phosphatase, magnesium and urinary calcium and creatinine were measured using available commercial kits.

Statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, Ill). Data were expressed as mean±SE for continuous variables and absolute numbers for categorical variables. Student t test and chi squared test were used for comparison of continuous and categorical variables between groups respectively. Paired sample t test and Wilcoxon sign rank test were used to compare variables at baseline and after intervention. P≤0.05 was set to be considered as significant.

The study protocol was approved by medical ethics committee of Zahedan University of Medical Sciences and informed written consent was obtained from all of participants.

RESULTS

Thirty adult individuals with mean age of 31.8 were included in this study. Female to male ratio was 2:1. Adherence to treatment was more than 96% and none of the patients reported significant side effects. Compared to control group mean serum phosphate was higher (*P*=0.001) and mean serum 25 OH vit D was lower (*P*=0.005) in patients (Table 1). 98% of all of subjects were vit D deficient (Serum 25 OH vit D < 50 nmol/l). Clinical and laboratory findings before and one month after treatment with omeprazole are depicted in Table 2. There were no significant changes in body mass index, serum concentrations of PTH, Phosphate, 25 OH vit D and magnesium and urinary calcium/urinary creatinine (Uca/Ucr) before and after intervention. However, serum concentrations of alkaline phosphatase (ALP) were significantly higher after treatment with omeprazole (*P*=0.01). There was also a trend towards decrease in serum calcium after receiving omeprazole (*P*=0.057).

DISCUSSION

Although, there were no significant changes in serum PTH, 25 OH vit D, Magnesium (Mg), Phosphate (P) and Uca/Ucr, we found a significant increase in serum ALP activity and a trend to decreasing serum calcium after one month of treatment with omeprazole which may be due to a decrease in intestinal absorption of calcium. However, due to high prevalence of vit D deficiency in this region consistent with our previous report (19), these results should be interpreted differently. As calcium plays a critical role in metabolic processes, its plasma concentrations should be kept in a narrow range. In the face of vit D deficiency -due to decreased intestinal calcium absorption- a compensatory rise in PTH causes near normalization of calcium albeit in the expense of bone resorption. In this situation omeprazole further impairs intestinal calcium absorption (by inducing hypochlorohydria), and causes a decrease however non-significant in serum calcium. On the other hand, further increase in parathyroid hormone leads to increase bone turnover which manifested as a significant rising in serum alkaline phosphatase.

In a study by Kocsis et al. treatment with 20 mg omeprazole daily for 2 weeks in children caused no significant changes in bone turnover (20). However, the study was too short to expect significant changes in bone take place. Furthermore, doses of omeprazole were lower and the patients were heterogeneous.

A number of studies focused on hypochlorohydric effect of omeprazole on intestinal calcium absorption; most of them showed a decrease in calcium absorption (12,13,16). However, these studies were of small sample size and short duration.

Recently, Hansen et al. showed no statistically significant alteration in calcium absorption following 30 days use of omeprazole in postmenopausal women by calculating true fractional calcium absorption (TFCA) using dual isotope study (17). Although, isotope studies designated as standard mode of TFCA the calcium preparation is calcium chloride that is more bioavailable than natural calcium salts in diet. In addition, this study showed increased isotope absorption after treatment with omeprazole which may be due to decrease in absorption of endogenous calcium. Finally, most of these subjects were overweight or obese and it is well known impact of obesity on calcium kinetics (21,22).

In a similar study Wright et al. investigated effects of esomeprazole on calcium absorption in 12 healthy subjects using TFCA (18). This study was of short duration and small sample size compared to our study. Furthermore, there is some evidence that indicates omeprazole may cause not only decreased calcium absorption but also a more generalized malabsorption syndrome (23-27).

Strengths and Weaknesses

Our study has a large sample size of almost young individuals. Duration of study and dosage of omeprazole are also acceptable. In addition, we include vit D status in this study which is the most important marker of calcium absorption. There are a number of limitations in our study too. Lack of measurement of bone resorption markers and high prevalence of vit D deficiency that may affect our results are the most important weaknesses of study.

Table 1

Clinical and Laboratory characteristics of patients versus control

	Patients (N=30) Mean±SE	Controls (N=60) Mean±SE	*P*
Sex (M/F)	10/20	20/40	1.0
Age (Years)	31.8±1.6	31.4±1.0	0.8
BMI (Kg/m^2)	24.3±0.8	24.3±0.6	0.9
Serum Calcium (mmol/l)	2.4±0.02	2.4±0.01	0.5
Serum P (mmol/l)	1.2±0.3	1.3±0.02	0.001
Serum ALP (IU/L)	172.8±9.4	193.7±8.6	0.1
Serum PTH (ng/l)	69.0±4.6	61.6±3.1	0.1
Serum 25 OH Vit D (nmol/l)	29.7±4.5	15.7±0.5	0.005

Abbreviations;
SE: standard error, M/F: male/female, BMI: body mass index, P: Phosphate, ALP: Alkaline Phosphatase, PTH: parathyroid hormone, 25 OH Vit D: 25 OH Vitamin D

Table 2

Clinical and laboratory findings before and thirty days after treatment with omeprazole

	Before intervention (Mean±SE)	After intervention (Mean±SE)	*P*
BMI (Kg/m^2)	24.3±0.88	24.3±0.89	0.8
Serum ALP (IU/L)	172.8±9.4	180.3±10.8	0.01
Serum Ca (mmol/l)	2.4±0.02	2.4±0.01	0.057
Serum P (mmol/l)	1.2±0.3	1.2±0.03	0.3
Serum PTH (ng/l)	69.0±4.6	72.7±5.5	0.4
Serum Mg (mmol/l)	0.8±0.008	0.8±0.01	0.4
Serum 25 OH Vit D (nmol/l)	29.7±4.5	26.4±2.7	0.1
Uca/Ucr (mmol/mmol)	0.08±0.009	0.07±0.007	0.2

Abbreviations;
SE: standard error, BMI: body mass index, P: Phosphate, ALP: Alkaline Phosphatase, PTH: parathyroid hormone, 25 OH Vit D: 25 OH Vitamin D, Ca: Calcium, Mg: Magnesium, Uca/Ucr: urinary calcium/urinary creatinine

CONCLUSION

In conclusion, we showed that following thirty days, omeprazole affects bone and calcium metabolism through decreased intestinal calcium absorption. Further prospective studies with longer durations and more focus on vit D status are suggested.

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AUTHOR CONTRIBUTIONS

All authors contributed equally

CONFLICT OF INTERESTS

None.

ETHICAL STANDARDS

Written informed consent was obtained from the patients.

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