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ORIGINAL ARTICLE

Effects of calcitriol on bone mineral density in patients treated with esomeprazole

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Abstract

Context: Proton pump inhibitor (PPI) increases the risk of decrease in bone mineral density (BMD). However, whether calcitrol improves this situation is unknown.
Objective: The current study investigates the effects of calcitriol on BMD in patients with esomeprazole therapy.
Materials and methods: Three hundred and eighty-six participants with gastrointestinal ulcerations were enrolled and randomly assigned into controlled and supplemented groups. Participants in the controlled group were prescribed esomeprazole (20 mg/qd), while the supplemented group was prescribed esomeprazole (20 mg/qd) and calcitriol (2.5 μg/qd). BMD, serum levels of calcium, carboxy-terminal collagen crosslinks (CTX), and alkaline-phosphatase (ALP) were assessed.
Results: (1) No significant between-group difference of age, gender, smoking, previous glucocorticoid use and hemoglobin level was found; (2) after 10.6 ± 0.8 d of PPI therapy, BMD *T* score in the controlled group was slightly increased compared with initial (−1.25 ± 0.08 versus −1.28 ± 0.06, $p = 0.084$), while there was no change in the supplemented group (−1.25 ± 0.05 versus −1.26 ± 0.03, $p = 0.308$); (3) during study termination, calcium level in the supplemented group was slightly higher than the controlled group (2.05 ± 0.03 mmol/L versus 2.01 ± 0.05 mmol/L, $p = 0.073$), while no significant differences of CTX (366.57 ± 43.71 pg/mL versus 373.15 ± 50.23 pg/mL, $p = 0.036$) and ALP were found among these two groups (50.47 ± 9.32 U/L versus 52.23 ± 10.45 U/L, $p = 0.075$).
Conclusion: Patients with gastrointestinal ulcerations with esomeprazole therapy, calcitriol supplement showed no efficacy on BMD changes.

Keywords

1,25-Dihydroxyvitamin D, alkaline phosphatase, bone mineral density, carboxy-terminal collagen crosslinks, duodenal ulceration, gastric ulceration, proton pump inhibitor

History

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Introduction

Proton pump inhibitor (PPI), one of the most important and efficacious medications, is commonly used in the prevention and management of gastric or duodenal ulceration and other gastrointestinal diseases (Federico et al., 2012; Sanchez-Delgado et al., 2012). However, some observational studies and meta-analyses indicated that long-term use of PPI is associated with the increased risk of osteoporosis and fracture (Eom et al., 2011; Jung, 2010; Talley et al., 2007; Vestergaard, 2012; Yang et al., 2006). The underlying mechanisms are still ambiguous, and moreover, some of these findings might be confounded by other factors such as older age, smoking, anemia, and other co-morbidities. Unfortunately, there has been no prospective and randomized clinical trial to investigate the effects of PPI on bone micro-architecture change currently. Therefore, before the relationship of PPI use and the incidence of osteoporosis and fracture being documented clearly, being cautious of the potentially undermining effects of PPI on osteoporosis and fracture is quite necessary and reasonable.

1,25-Dihydroxyvitamin D, namely calcitriol, an active form of vitamin D_3, is an efficient and commonly used medication for increasing calcium absorption and deterring osteoporosis progress in the elderly population (Anderson et al., 2013; Lerchbaum & Obermayer-Pietsch, 2012). In this regard, it is reasonable to postulate that the supplement of calcitriol may be beneficial for patients with PPI use, because increased calcium absorption with calcitrol may offset the effects of PPI on diminishing calcium absorption in the gastrointestinal tract. Taken together, in order to investigate the relationship between the incidence of osteoporosis in Chinese populations with PPI use, and also to evaluate the effects of calcitriol supplement on bone mineral density (BMD) change, our present study enrolled subjects with gastric or duodenal ulceration demonstrated by gastric endoscopy and pathological biopsy, and conducted the following randomized and controlled trials but not blinded trial.

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Materials and methods

Study population

Three hundred and eighty-six patients diagnosed with gastric or duodenal ulceration demonstrated by gastric endoscopy and pathological biopsy were enrolled from January 2011 to March 2012, and randomly assigned into two groups, namely controlled group and supplemented group. Demographic information of all the participants was collected and informed consent was obtained before the trial. The current study was approved by the ethical committee of the Second Affiliated Hospital of Shantou University. All participants were closely monitored and no adverse side effects related to medications have been found.

Study protocol

One hundred and ninety-three patients in the controlled group were orally given esomeprazole (20 mg/qd, Astrazeneca), while 193 patients in the supplemented group were prescribed esomeprazole (20 mg/qd, orally) and calcitriol (0.25 μg/qd, Roche Diagnostics, Indianapolis, IN). Therapeutic course was terminated when the patient's symptom and sign were improved. BMD of femoral neck was evaluated by dual-energy X-ray absorption-metry (DXA) in the initial and termination stage of this trial. *T* score, a parameter of BMD severity, was used to evaluate the change of BMD between these two groups. Serum levels of calcium, carboxy-terminal collagen crosslinks (CTX), and alkaline phosphatase (ALP) were also assessed. Participants were not prescribed with calcium, except those with severe hypo-calcemia (less than 1.9 mmol/L or with associated symptoms such as muscle seizure).

Study endpoint

The endpoints of the present study were used to evaluate the effect of PPI on BMD change, and the effect of calcitriol on BMD change in patients with short-term use of PPI was also evaluated.

Statistical analysis

Continuous variable was presented as mean ± SD or median appropriately, and compared by Student's *t*-test when data were normally distributed, otherwise compared by the Wilcoxon rank-sum test. Categorical data were showed as percentage and compared by the χ^2 test. Statistical analyses were performed using SPSS software version 16.0 (SPSS, Inc., Chicago, IL). A value of $p < 0.05$ was considered significant.

Results

Characteristics of study populations

All participants enrolled in the current study were from Shantou, a city located in the east of Guangdong province, China. As shown in Table 1, the vast majority of our study subjects were approximately 44-years-old, which is earlier than the natural period of osteoporosis progression. Our participants were predominantly male, which accounted for 63.9%, and among the female, only a minority (5.7% versus 6.7%) in both groups were of post-menopausal stage. Eight and nine participants in the controlled and supplemented groups had a short-term history of glucocorticoid use previously, and all were due to asthma. Some participants (2.1% versus 3.1%) with previous history of fracture were due to trauma or injury. Body mass index in these two groups were comparable (21.8 ± 2.4 kg/m^2 versus 21.4 ± 2.1 kg/m^2, $p = 0.198$). Smoking in both groups was 20.7% and 19.7%, respectively, and previous calcium supplement in both groups was 21.8% and 23.3%. Hemoglobin concentrations (125.6 ± 8.1 g/L versus 127.4 ± 10.4 g/L, $p = 0.264$) in these two groups were at normal range and were comparable.

Table 1. Characteristics of study populations.

Variables	Controlled group ($n = 193$)	Supplemented group ($n = 193$)	*p*
Age (years)	43.8 ± 5.6	44.3 ± 4.1	0.187
Female (%)	68 (35.2)	71 (36.8)	0.334
Current smoking (%)	40 (20.7)	38 (19.7)	0.078
Glucocorticoid used history (%)	8 (4.1)	9 (4.7)	0.165
Fracture history (%)	4 (2.1)	6 (3.1)	0.263
Post-menopause (%)	11 (5.7)	13 (6.7)	0.087
Body mass index (kg/m^2)	21.8 ± 2.4	21.4 ± 2.1	0.198
Past calcium supplement (%)	42 (21.8)	45 (23.3)	0.336
Hemoglobin level (g/L)	125.6 ± 8.1	127.4 ± 10.4	0.264

Table 2. Comparisons of mean BMD *T* score.

Mean BMD *T* score	Controlled group	Supplemented group	*p*
Femoral neck (before administration)	-1.25 ± 0.08	-1.25 ± 0.05	0.244
Femoral neck (after termination)	-1.28 ± 0.06	-1.26 ± 0.03	0.108
p	0.084	0.308	

Comparison of BMD between these two groups

As presented in Table 2, the mean BMD *T* scores of femoral neck in both groups before PPI administration were comparable (-1.25 ± 0.08 versus -1.25 ± 0.05, $p = 0.244$). After 10.6 ± 0.8 d of PPI treatment, the mean BMD *T* score in the controlled group was slightly but not significantly increased when compared with the initial score (-1.25 ± 0.08 versus -1.28 ± 0.06, $p = 0.084$). Nevertheless, in the supplemented group, the BMD *T* score did not change change after 12.7 ± 1.1 d of PPI treatment (-1.25 ± 0.05 versus -1.26 ± 0.03, $p = 0.308$). Additionally, the difference of femoral mean BMD *T* score between these two groups before and after PPI use was evaluated, and statistically significant difference was not found (Table 2).

Indices comparison between these two groups

As shown in Table 3, during trial termination, the serum calcium level in the supplemented group was slightly higher than that in the controlled group (2.05 ± 0.03 mmol/L versus 2.01 ± 0.05 mmol/L, $p = 0.073$), and seven and eight participants with hypo-calcemia in each group were prescribed with 10% calcium gluconate and the doses used were comparable

Table 3. Comparisons of indices.

Indices	Controlled group	Supplemented group	*p*
Serum calcium (mmol/L, before administration)	2.08 ± 0.04	2.07 ± 0.05	0.365
Serum calcium (mmol/L, after termination)	2.01 ± 0.05	2.05 ± 0.03	0.073
Serum CTX (pg/mL, before administration)	355.63 ± 46.32	361.40 ± 52.43	0.427
Serum CTX (pg/mL, after termination)	373.15 ± 50.23	366.57 ± 43.71	0.086
Serum ALP (U/L, before administration)	49.65 ± 7.07	50.26 ± 12.24	0.083
Serum ALP (U/L, after termination)	52.23 ± 10.45	50.47 ± 9.32	0.075

(118.6 ± 10.4 mL versus 107.5 ± 8.6 mL, $p = 0.158$). Serum levels of CTX and ALP, sensitive indicators for bone turnover, were comparable between these two groups before PPI administration and after trial termination (Table 3).

Other associated clinical events and economic expenditure

No side effects related to esomeprazole or calcitriol use have been reported in the current study, also no fracture was observed. Notably, the expenditure for esomeprazole use in the controlled group was marginally lower than the supplemented group (117.8 ± 8.6 Yuan versus 140.5 ± 10.7 Yuan, $p = 0.48$), which was due to the extra-cost of calcitriol.

Discussion

The outcomes from the current study indicated that after a short-term treatment of esomeprazole in patients with gastrointestinal ulceration, the mean BMD *T* score of femoral neck was slightly increased in the controlled group while no change of BMD *T* score in the supplemented group was observed, indicating that the supplement of calcitriol might somewhat abolish the unfavorable effect of PPI on BMD decrease, although in our present study the difference of BMD *T* score between controlled and supplemented groups was statistically insignificant, which we believed might be partially ascribed to the small number of participants enrolled in the current study.

Proton pump inhibitor plays a critical role in the prevention and management of multiple gastrointestinal diseases such as gastrointestinal ulceration by decreasing the gastric acid secretion through the irreversible inhibition of H^+–K^+ ATPase ion ex-changer (Bardou et al., 2012; Sanchez-Delgado et al., 2012). Notably, owing to its high quality of safety profile, PPI has been broadly used due to its high-quality safety profile. However, recently some diseases reported outside the gastrointestinal tract were associated with the use of PPI, and one of the most frequently reported critical conditions is the increased incidence of osteoporosis and fracture in patients with the long-term application of PPI (Madanick, 2011; Vakil, 2012; Vestergaard et al., 2006). Accordingly, osteoporosis or fracture is largely associated with BMD decrease in the elderly subjects. It is also well known that calcium is one of the most important components in maintaining the BMD in an appropriate level. Therefore, continuous decrease in serum calcium level decrease would finally result in BMD decrease, and subsequently cause osteoporosis and fracture. Many factors influencing the homeostasis of calcium have been documented literally; among them, calcium absorption in gastrointestinal tract is of paramount importance. Notably, calcium absorption in the gastrointestinal tract is largely dependent on the acidic environment produced by gastric acid. Thereby, the reduction of gastric acid by PPI use or other anti-acidic medications could potentially lead to decrease in calcium absorption, decrease and finally undermine calcium homeostasis (de Vries et al., 2009; Eom et al., 2011; Yu et al., 2008). Subsequently, the osteoclasts will be activated so as to re-establish and maintain calcium homeostasis. As is well known, the most important mechanism by which the osteoclasts elevate the serum calcium level results in increasing bone re-absorption (Targownik et al., 2010). In a short term, such compensation could be beneficial and crucial to maintain calcium homeostasis. However, in the long run, continuous bone re-absorption will eventually lead to BMD decrease, osteoporosis, and fracture. Theoretically, this might be one of the explanations with respect to the side effects of long-term use of PPI on BMD change.

Nevertheless, the relationship between the short-term application of PPI application with and BMD change is still unclear. Our present study reveals that in patients with gastrointestinal ulceration, after 10.6 ± 0.8 d therapy, esomeprazol slightly but insignificantly increased BMD *T* score when compared with the initial score (-1.28 ± 0.06 versus -1.25 ± 0.08, $p = 0.084$). While in the supplemented group, BMD *T* score was without any change after 12.7 ± 1.1 d of therapy (-1.26 ± 0.03 versus -1.25 ± 0.05, $p = 0.308$). To the best of our knowledge, such difference might be ascribed to the use of calcitriol. Supplement of calcitriol, an active form of vitamin D_3 which is quite important for increased calcium absorption, might somewhat help improve calcium absorption in gastrointestinal tract, especially in patients with gastrointestinal ulceration, and the use of PPI might simultaneously diminish calcium absorption.

The difference of BMD changes in both group was comparable when study termination which we believed might be in part due to the short term of our present study, and which might also indirectly indicated that short term of PPI use was safe with respect to the BMD decrease and osteoporosis progress as evidenced by the serum levels of CTX and ALP in both groups were comparable. Additionally, the small sample of current study might also be accountable for the insignificant difference of outcomes.

Conclusions

Our present study showed that the short-term use of PPI in patients with gastric or duodenal ulceration was safe, and

combined with the short-term use of calcitriol, had no solid benefits in terms of maintaining BMD at the present time. Whether prolonged calcitriol use in patients who need long-term use of PPI is beneficial needs further investigation.

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Declaration of interest

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