

Impact of Long-term Use of PPI on Bone Mineral Density

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ABSTRACT

Proton pump inhibitors (PPIs) are commonly prescribed for the treatment of various gastrointestinal conditions. However, extended use of these medications has been linked to potential alterations in bone mineral metabolism. This study aims to assess the impact of PPIs on bone mineral density (BMD) and identify associated risk factors among individuals using PPIs. A cross-sectional study was conducted at the Rheumatology Consultancy Clinic of Baghdad Teaching Hospital/Baghdad Medical City from November 1, 2017, to October 31, 2018. The study included 100 patients, with 50 using PPIs and 50 not using them. BMD was measured using dual-energy X-ray absorptiometry (DXA). PPI users showed significantly lower levels of serum calcium, vitamin D, and serum inorganic phosphorus, as well as increased alkaline phosphatase activity. DXA results, including T-scores, Z-scores for L2-L4, and total scores, were all significantly lower in PPI users compared to non-users ($P < 0.05$). Prolonged use of PPIs adversely affects bone mineral density, contributing to the development of osteoporosis and osteopenia, particularly in the lumbar spine.

Keywords: proton pump inhibitors, DEXA scan, Ca mineral, Vitamin D, phosphorus

INTRODUCTION

Proton pump inhibitors (PPIs) are commonly prescribed to treat conditions such as duodenal ulcers and reflux esophagitis¹. These drugs are generally well tolerated when used as directed, and have become a mainstay in clinical practice for both acute and long-term management, although there has been ongoing debate about their long-term use. The precise mechanism by which PPI use leads to decreased bone mineral density and increased fracture risk remains unclear². Several hypotheses have been put forward to explain how PPIs may contribute to fracture risk. One such hypothesis suggests that the acidic environment of the stomach is necessary for effective calcium absorption. Calcium in food is usually insoluble at neutral pH and bound to proteins³. However, in an acidic environment, calcium is released from these proteins and becomes soluble, facilitating absorption⁴. Therefore, decreased gastric acidity due to PPIs may impair calcium absorption, leading to decreased serum calcium levels, secondary hyperparathyroidism, and increased bone resorption^{5,6}. Another possible mechanism involves elevated levels of the hormone gastrin, which may influence fracture risk. Recent epidemiological studies have suggested that long-term use of proton pump inhibitors (PPIs) significantly increases the risk of osteoporosis and hip fractures, particularly in patients with gastroesophageal reflux disease (GERD)⁷⁻¹², thereby impairing calcium and phosphate absorption and disrupting bone metabolism. In addition, PPIs may inhibit bone resorption by osteoclasts^{13,14}.

PATIENTS AND METHOD

1. Approval was taken from the committee of scientific Council of Clinical Pharmacy, and the Iraqi board for medical specializations.
2. An informed consent was taken from selected patient.

Study design and settings: This study is a cross-sectional study conducted in the Rheumatology Consultancy Clinic of Baghdad Teaching Hospital/Baghdad Medical City during the period from 1st of November, 2022 to 31st of October, 2022.

Study population: All patients presented to the Rheumatology Consultancy Clinic of Baghdad Teaching Hospital and referred to DEXA scan were the study population.

Inclusion criteria for proton pump inhibitor (PPI) users:

1. Adults (age >18 years).
 2. Reflux esophagitis.
 3. Patients who are using higher than over the counter (OTC) doses of PPIs. (20mg).
 4. The duration of PPIs use by patients for 6 months and more.
- Exclusion criteria for PPI users:
1. Shorter duration of PPI use (<6month)
 2. Smokers.
 3. Alcohol consumption.

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4. Any disease that may affect bone mineral density (BMD):

- a. Cushing syndrome
- b. Addison's disease
- c. Hypogonadism

5. Drugs that may affect BMD:

- a. Glucocorticoids
- b. Aromatase inhibitors
- c. Gonadotropine-releasing hormone agonists
- d. High-dose thyroxine
- e. Calcineurin inhibitors
- f. Anticonvulsants
- g. Heparin
- h. Oral anticoagulants
- i. Benzodiazepine, MAOIS, atypical antipsychotics

6. Body mass index (BMI) less than 19 Kg/m².

7. Other diseases:

Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), Ankylosing spondylitis (AS), Malabsorption, Chronic kidney disease, Chronic Liver disease, Chemotherapy & Menopause.

Sampling of patients: A total of 100 patients were selected for the study, with 50 patients using proton pump inhibitors (PPIs) and 50 patients not using PPIs.

Data Collection: The data was collected from each patient by the researcher and filled in a prepared questionnaire, which was designed by the researcher. The questionnaire included the followings:

1. Demographic Characteristics of Patients: Age and gender distribution were recorded.
2. Body mass index (BMI) of patients.
3. Social characteristics of patients: smoking and alcohol consumption.
4. Investigations findings of patients: serum calcium, total alkaline phosphatase (ALP) activity, vitamin D and inorganic phosphorus.
5. Proton pump inhibitor (PPI) drugs characteristics, use, type, dose, duration and frequency.
6. Dual X-ray absorptiometry (DEXA) scan results of patients: L2-L4 T score, L2-L4 Z score, total T score and total Z score.

Assessment of patients: Proper history and examination for all patients were done by the researcher. The included patients were referred by the clinician to DEXA scan of Baghdad Teaching Hospital. The DEXA scan examination was done by the physical therapist under the supervision of the Rheumatologist. Regarding maneuver of DEXA scan examination, any patient came to the BMD unit undergo the following step for each examination:

1. Patient's name should be recorded, age, sex, history of corticosteroid use, weight, height, BMI and age of menopause (if female patient).
2. During DEXA scan examination, the input dose of radiation (1.95µSv/41µGY) applied to the spine area of patient, and then T- and Zscores were automatically reported.
3. Regarding DXA scan machine's name was TRACTOS from DMS group \French-made.
4. Regarding chemical agents and kit used in this study showed as following:

A-kit's name of serum calcium(Ca⁺ ,phosphorous(Phos) and Alkaline phosphatase(ALP) were Flex reagent cartridge from SIEMENS company\Germany.

B-kit's name of vitamin D was Elabscience from Euroimmun\Germany. The measured T scores were classified according the World Health Organization (WHO) criteria for the diagnosis of osteopenia and osteoporosis as follows:

- 1-T-score less than (-2.5 SD) considered osteoporosis.
- 2-T-score between (-2.5 and -1) defined as osteopenia.
- 3-T-score greater than or equal to (-1) considered normal.

For Z score, it was classified to:

1-Below expected normal range (≤ -2 SD).

2-Within normal range (> -2 SD).

Besides, serum calcium, alkaline phosphatase (ALP), inorganic phosphorous levels were measured for each patient included in this study in Baghdad Teaching Hospital Laboratories; but serum vitamin D level was measured in AL-Nader specialized Medical Laboratory(private laboratory).

Normal limit values (7):

1-Serum calcium 8.5-10.5 mg\dl.

2-Serum phosphorous 2.5-5 mg\dl.

3-Serum alkaline phosphatase (ALP) 46-116 U\L.

4- Serum vitamin D level30-100ng\ml

Statistical analysis: Data analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 20 by a community medicine specialist. Descriptive statistics were presented as means $\pm$ standard deviations (SD) and frequencies as percentages (%). Multiple contingency tables were created, and appropriate statistical tests were applied¹⁵. Chi-square tests were used for categorical variables, with Fisher's exact test employed when expected frequencies were less than 5. Linear logistic regression analysis was performed to identify predictors influencing the T-score. A significance level of $P < 0.05$ was considered, and the results were presented in tables and/or graphs¹⁶.

RESULTS AND DISCUSSION

This study included 100 patients (50 PPI users and 50 PPI non-users) presented for DEXA scan with mean age of 42.9 ± 10.9 years;9% of patients were in age group less than 30 years, 33% of them were in age group 30-39 years, 39% of them were in age group 40-49 years,14% of them were in age group 50-59 years and 5% of them were in age 60 years and more. Male patients were equal to female patients with male to female ratio as 1:1. Most (85%) of patients were living in urban areas while 15% of them were living in rural areas. The mean BMI of patients was 27.5 ± 5.3 Kg/m² ; 29% of them had normal BMI, while

Table 1. Sociodemographic characteristics of patients presented for dual-energy x-ray absorptiometry (DEXA).

Variable	No. of patients	%
Age mean $\pm$ SD (42.9$\pm$10.9 years)		
<30 years	9	9.0
30-39 years	33	33.0
40-49 years	39	39.0
50-59 years	14	14.0
≥ 60 years	5	5.0
Total	100	100.0
Gender		
Male	50	50.0
Female	50	50.0
Total	100	100.0
Residence		
Urban	85	85.0
Rural	15	15.0
Total	100	100.0
BMI mean $\pm$ SD (27.5$\pm$5.3 Kg/m²)		
Normal	29	29.0
Overweight	38	38.0
Obese	33	33.0
Total	100	100.0

Table 2. Serum -calcium, -total alkaline phosphatase (ALP) activity, -vitamin D, and -inorganic phosphorus levels in studied group of patients.

Variable	PPI user	PPI non-user	P
	Mean $\pm$ SD	Mean $\pm$ SD	
Serum calcium (mg/dl)	7.5 $\pm$ 0.6	9.1 $\pm$ 0.5	<0.001*S
Total ALP activity (U/L)	127.9 $\pm$ 36	74.4 $\pm$ 19.4	<0.001*S
Vitamin D(ng/ml)	35.7 $\pm$ 26.3	48.1 $\pm$ 33.9	0.04*S
Inorganic phosph. (mg/dl)	2.7 $\pm$ 0.7	3.5 $\pm$ 0.56	<0.001*S

Table 3. Distribution of dual energy X-ray absorptiometry (DEXA) scan scores (T-score and Z-score) in proton pump inhibitor (PPI) users compared to proton pump inhibitor (PPI) non-users.

Variable	PPI user	PPI non-user	P
	Mean $\pm$ SD	Mean $\pm$ SD	
T-score L2-L4	-2.4 $\pm$ 0.89	-0.15 $\pm$ 0.75	<0.001*S
Z-score L2-L4	-2.22 $\pm$ 1.17	0.44 $\pm$ 1	<0.001*S
Total T-score L1-L4	-2.53 $\pm$ 0.9	-0.25 $\pm$ 0.74	<0.001*S
Total Z-score L1-L4	-2.25 $\pm$ 1.15	0.34 $\pm$ 1	<0.001*S

Table 4. Linear regression analysis of variables in relation to Tscore of PPI users.

Variable	B	SE	t	P
Constant	-6.07	1.9	-3.1	0.003
Residence	0.81	0.26	1.2	0.2
BMI	-0.1	0.02	4.7	<0.001
Serum calcium	0.24	0.18	1.3	0.1
Serum inorg. Phsph.	0.008	0.14	0.05	0.9
Dose	-0.03	0.01	-1.1	0.3
Duration	-0.08	0.03	-2.1	0.03
Frequency of dose	-0.55	0.21	-2.5	0.01

38% of them were overweight and 33% of them were obese. All these findings were shown in Table 1.

The results of table 2 showed that, a high significant reduction in mean serum calcium level in PPI patients users ($P<0.001$) compared to the corresponding levels in non-PPI users. Mean serum calcium level being respectively, 7.5 $\pm$ 0.6 mg/dl and 9.1 $\pm$ 0.5 mg/dl. Moreover, a high significant elevation in mean total ALP activity in PPI users ($P<0.001$) compared to the corresponding levels in non-PPI users; mean total ALP activity being respectively, 127.9 $\pm$ 36 U/L and 74.4 $\pm$ 19.4 U/L as shown in table 2. Moreover, the results of table 2 showed that, a significant reduction in mean vitamin D level in PPI patients users($P<0.04$) compared to the corresponding levels in non-PPI users. Mean vitamin D level being respectively, 35.7 $\pm$ 26.3 ng/ml and 48.1 $\pm$ 33.9 ng/ml. Besides, the results of table 2 showed that, a high significant reduction in mean serum inorganic phosphorus in PPI patients users($P<0.001$) compared to the corresponding serum levels in non-PPI users. Mean serum inorganic phosphorus being 2.7 $\pm$ 0.7 mg/dl and 3.5 $\pm$ 0.56 mg/dl, respectively.

Table 3 showed that there was a highly significant difference ($P<0.001$) between the mean T-score L2-L4 of PPI users compared to the corresponding T-score value of PPI non-users; the values being respectively, -2.4 $\pm$ 0.89 and -0.15 $\pm$ 0.75; furthermore, the mean total T-score of L1-L4 was significantly lower among patients on PPI($P<0.001$) compared to the deliberated score of PPI non-user. Besides, table 3 showed that there was a highly significant difference($P<0.001$) between the mean Z-score L2-L4 of PPI users compared to the corresponding Z-score value of PPI non-users; the values being respectively, -2.22 $\pm$ 1.17 and 0.44 $\pm$ 1; furthermore, the mean total Z-score of L1-L4 was significantly lower among patients on PPI($P<0.001$) compared to the deliberated score of PPI non-users.

Linear regression analysis revealed that BMI of PPI users was significantly predicted negatively T-score ($P<0.001$), increase in BMI was predicting lower T-scores. Duration of treatment and frequency of dose for PPI among users were negatively predicting the T-score ($P=0.03$, $P=0.01$, respectively), any increase in duration and frequency was predicting lower T-scores. All these findings were shown in table 4

Currently, there is a wide clues referring to many co-morbidities related with long use of PPI such as high risk of community- acquired pneumonia¹⁷, infection with clostridium difficile¹⁸, vitamin B12 deficiency¹⁹ and acute interstitial nephritis²⁰. Furthermore, many authors revealed that PPIs are negatively affecting the bone mineral metabolism, with a gradual decline in bone mineral density (BMD) which potentiate the risk of fractures²¹.

Current study shows that PPI use was significantly associated with low serum calcium ($P<0.001$) this finding is consistent with results of 59 Yang²² study in USA which revealed that PPI stimulates the gastric acid suppression that reduce the calcium absorption. However, another American study²³ found that after 30 days of continuous PPI therapy, the fractional calcium absorption was not altered. This inconsistency might be attributed short duration effect of American study (30 days). This study shows a significantly higher mean of total ALP activity related with PPI use ($P<0.001$). This is similar to results of study in Portugal²⁴. The means of vitamin D and serum inorganic phosphatase were significantly lower among PPI users ($P=0.04$, $P<0.001$ respectively). These findings are in agreement with results of Jo et al (16) study in South Korea which revealed that long PPI use was related with low levels of vitamin D and serum inorganic phosphatase.

Present study that means of T and Z scores of L2-L4 for PPI users measured by DEXA scan were significantly lower than PPI non-users

($P < 0.001$). This finding is consistent with results of study²⁵ follow up study in Turkey which included 114 GERD patients on PPI therapy and 110 healthy controls and found that treatment with PPI resulted in significant reduction of T and Z scores for lumbar vertebrae after 6 months treatment with PPI.

Linear regression analysis regarding factors affecting T-score of PPI users showed that BMI of PPI users was positively related with BMD ($P < 0.001$).

This finding coincides with results of²⁶ study in Kosovo which reported that BMI of women and men is significantly associated positively with bone marrow density of lumbar spines.

Present study showed that long duration of PPI use was significantly decreasing the T score of users ($P = 0.03$). This finding is similar to results of²⁷ study in Japan which reported that long term duration use of PPI lead to low T and Z scores study in Saudi Arabia found that longer duration use of PPIs aggravating the osteoporotic effect²⁸.

Current study showed that the increased frequency of PPI use was significantly decreasing the T score of PPI users ($P = 0.01$). Similarly, another study in USA documented that increased frequency of PPI doses are significantly affecting both T and Z scores and reducing the BMD of PPI users^{29,30}.

Limitations of the study

1. As other cross sectional studies, the temporal relationship cannot be assessed.
2. Single center study.
3. Selection bias.
4. Small sample size.
5. Duration of study

Recommendation

- » Strict use of proton pump inhibitors specifically for persons at risk of osteoporosis.
- » Continuous seminars and workshops for clinicians regarding disadvantages of proton pump inhibitors with cautions in prescribing these drugs.
- » Further longitudinal controlled clinical trials on effect of proton pump inhibitors use must be supported.

CONCLUSION

- Proton pump inhibitors significantly affect bone mineral density.
- Prolonged use of proton pump inhibitors is often associated with the development of osteoporosis and osteopenia in the lumbar spine.
- Long term use of proton pump inhibitors is accompanied by low levels of serum calcium, vitamin D, serum inorganic phosphorus and high total ALP activity.
- The proton pump inhibitors use more likely to be prevalent among young age, males, rural residents with low body mass index.
- Risk factors related to low T scores and reduction of bone density among proton pump inhibitor users were high body mass index, long duration and high frequency of proton pump inhibitor use.

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Competing Interest: None

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