Effect of Chronic Use of Proton Pump Inhibitors on Bone Mineral Density

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ABSTRACT:
BACKGROUND:
Proton pump inhibitors (PPIs) are widely used drugs for the treatment of many diseases. Prolonged use was believed to have an effect on bone mineral metabolism.
OBJECTIVE:
To investigate the effect of PPIs on bone mineral density and to identify risk factors affecting bone mineral density among users of PPIs.
PATIENTS AND METHODS:
A cross sectional study was conducted in Rheumatology Consultancy Clinic of Baghdad Teaching Hospital /Baghdad Medical City during the period from 1st of November, 2017 to 31st of October, 2018 on convenient sample of 100 patients were selected; first group was 50 PPI users and 50 PPI non-users. The bone mineral density of patients was assessed using dual energy x-ray absorptiometry (DXA) scan.
RESULTS:
A significant reduction in serum calcium, vitamin D and serum inorganic phosphorus levels of PPIs users with elevated level of alkaline phosphatase activity. All scores of DXA scan like T-scores L2-L4, Z-scores L2-L4 and total scores were significantly reduced among PPIs users in comparison to PPIs-non users (P<0.05).
CONCLUSION:
The proton pump inhibitors have a profound effect on bone mineral density and long term use of proton pump inhibitors is commonly related with osteoporosis and osteopenia development of lumbar spines.
KEYWORDS: ppi,dexa scan, calcium.vitamine d,alp.phophorous.

INTRODUCTION:

Proton pump inhibitors (PPIs) are the main drugs used for treating diseases such as duodenal ulcers and reflux esophagitis. Because these drugs present few adverse effects when administered correctly, they have come to be used not only for acute symptoms in clinical practice, but also for long-term purposes, even though such indications are highly debatable. [1]

The exact mechanism by which PPI use results in a decline in Bone mineral density and resultant increase in fracture risk is still unclear. There are a number of proposed mechanisms by which PPIs may increase risk of fractures.

It has been hypothesized that an acidic environment in the gastric lumen is necessary for effective absorption of calcium. Dietary calcium is often found in an insoluble form at a neutral pH, as it is often found bound to food proteins. However, in the setting of an acidic pH, ionized calcium becomes released from these proteins, and becomes soluble, a form that can be readily absorbed [2]. Therefore, an acidic pH environment in the gastric lumen is necessary for effective calcium absorption. It has been hypothesized that the lack of acidic environment in the setting of PPI use can lead to a decrease in serum calcium, with resultant secondary hyperparathyroidism and an increase in bone resorption. Another hypothesis is the role of increased gastrin levels on fracture risk [3]. Recent epidemiological studies have shown that long-term therapy with proton pump inhibitors (PPIs) significantly increases the risk of osteoporosis and pathological hip fracture in patients with gastroesophageal reflux disease [4]. It is thought that PPIs reduce the production and secretion of hydrochloric acid in stomach,

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increase the pH in the stomach and inhibit absorption of insoluble calcium in the small intestine, thus leading to malabsorption of calcium phosphate and bone metabolism disorder [5]. PPIs also reportedly inhibit bone resorption by osteoclasts [6].

PATIENTS AND METHODS:
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, 2017 to 31st of October, 2018.

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. Reflex 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.
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 erythematous (SLE), Ankylosing spondylitis (AS), Malabsorption, Chronic kidney disease, Chronic Liver disease, Chemotherapy & Menopause.

Sampling of patients
A convenient sample of 100 patients was selected; first group were 50 proton pump inhibitor (PPI) users and 50 PPI non-users.

Data Collection
The data was collected from each patient by the researcher and filled in a prepared questionnaire, which was designed by the researcher and two supervisors.
The questionnaire included the followings:
1. Demographic characteristics of patients: age and gender.
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

Statistical Package for Social Sciences (SPSS) version 20 was used for the analysis of data, which was done by the community medicine specialist. Descriptive statistics presented as [(mean ± standard deviation (SD)] and frequencies as percentages (%). Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables (Fishers exact test was used when expected variables were less than 5). Linear logistic regression analysis was conducted to assess the predictors affecting T-score. In all statistical analysis, level of significance (P value) set at < 0.05 and the result presented as tables and/or graphs.

RESULTS:

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

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

Variable	No. of patients	%
Age mean±SD (42.9±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±SD (27.5±5.3 Kg/m^2)		
Normal	29	29.0
Overweight	38	38.0
Obese	33	33.0
Total	100	100.0

BMI=body mass index

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±0.6 mg/dl and 9.1±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±36 U/L and 74.4±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±26.3 ng/ml and 48.1±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±0.7 mg/dl and 3.5±0.56 mg/dl, respectively.

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±SD	Mean±SD	
Serum calcium (mg/dl)	7.5±0.6	9.1±0.5	<0.001*[S]
Total ALP activity (U/L)	127.9±36	74.4±19.4	<0.001*[S]
Vitamin D(ng/ml)	35.7±26.3	48.1±33.9	0.04*[S]
Inorganic phosph. (mg/dl)	2.7±0.7	3.5±0.56	<0.001*[S]

*Independent sample t-test,P=Probability,S=Significant,PPI= Proton pump inhibitor, Inorganic phosph.=Inorganic phosphorus

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±0.89 and -0.15±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±1.17 and 0.44±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.

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±SD	Mean±SD	
T-score L2-L4	-2.4±0.89	-0.15±0.75	<0.001*[S]
Z-score L2-L4	-2.22±1.17	0.44±1	<0.001*[S]
Total T-score L1-L4	-2.53±0.9	-0.25±0.74	<0.001*[S]
Total Z-score L1-L4	-2.25±1.15	0.34±1	<0.001*[S]

*Independent sample t-test, P=Probability, S=Significant.

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

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

P=Probability. inorg. Phsph.=Inorganic phosphorus, BMI=Body mass index, B=Beta Coefficient, SE=Standard Error, t=t-test.

DISCUSSION:

Currently, there is a wide clues referring to many co-morbidities related with long use of PPI such as high risk of community- acquired pneumonia [8,] infection with clostridium difficile [9], vitamin B12 deficiency [10] and acute interstitial nephritis [11]. Furthermore, many authors revealed that PPIs are negatively affecting the bone mineral metabolism, with a gradual decline in bone mineral density (BMD) which potentiates the risk of fractures [12].

Current study shows that PPI use was significantly associated with low serum calcium (P<0.001) This finding is consistent with results of 59 Yang[13] study in USA which revealed that PPI stimulates the gastric acid suppression that reduce the calcium absorption. However, another American study by Hansen et al [14] 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 CostaRodriguez et al [15] study in Portugal. The means of vitamin D and serum inorganic phosphatase were significantly lower among PPI users (P=0.04, P<0.001respectively). 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 Ozdil et al [17] 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 of Rexhepi et al [18] 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 of Ito et al [19] study in Japan which reported that long term duration use of PPI lead to low T and Z scores. Al-Zahrani et al [20] study in Saudi Arabia found that longer duration use of PPIs aggravating the osteoporotic effect.

Current study showed that the increased frequency of PPI use was significantly deceasing the T score of PPI users (P=0.01). Similarly, Panday et al (100) 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.

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

CONCLUSION:

- The proton pump inhibitors have a profound effect on bone marrow density.
- Long term use of proton pump inhibitors is commonly related with osteoporosis and osteopenia development of lumbar spines.
- 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.

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.

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