ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Proton Pump Inhibitors Adversely Induce Selective Changes in the Bone Mineral Density Detected by Dual-Energy X-ray Absorptiometry in Postmenopausal Women

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Article History:

Received on: 16 Jul 2020
Revised on: 17 Aug 2020
Accepted on: 24 Aug 2020

Keywords:

Proton pump inhibitors,
Osteoporosis,
T-score,
postmenopausal women

ABSTRACT

Dual-energy X-ray absorptiometry (DEXA) is a universal tool that can detect bone loss and diagnose osteoporosis. Long term of using certain drugs contributed to the etiopathology of bone loss. Proton pump inhibitors (PPIs) users are at risk of developing osteoporosis. This study aimed to prove the selectivity of PPIs in inducing bone loss in postmenopausal women by determining the T-score of the axial spine and femur bone. A total number of 215 menopausal women were recruited from a Teaching hospital and private clinics from August 2018 to November 2019. The participants were grouped into Group I, n=150 (had no PPIs treatment) and Group II, n=65 (had treatment with PPIs). All the participants were subjected to DEXA investigation. Group II patients showed significantly lower T-score of the femur bone, while Group I patients showed a significantly lower T-score of lumbar vertebrae. The percentage of Group II patients had a T-score – 2.5 in femur ward bone is 35.4%, while the percentage of Group I patients had a T score -2.5 in the lumbar-3 vertebrae is 35.3%. Moreover, PPIs users showed an acceleration of bone loss despite the age, duration of menopause, body mass index, and waist-to-height ratio. We conclude that PPIs users are at risk of developing bone mass loss in the femur more than in the lumbar vertebrae.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i4.3175

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INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterized by a reduction of the bone mass which complicated with the fragile fractures of the bones in the spine, hip and forearm (Hu *et al.*, 2020). The hallmark of a radiological feature of osteoporosis that detected by dual-energy X-ray absorptiometry (DEXA) is a reduction of mineral bone density with a T-score $\leq$ -2.5 (WHO, 2004). Risk factors of osteoporosis were age $\geq$65 years, female sex, postmenopausal period, genetic factor, family history, smoking, and drug intake. Body mass index inversely correlated with fractures due to the osteoporosis (WHO, 2004). Drugs that reduce the bone mineral density (BMD) included glucocorticosteroids (Whittier and Saag, 2016; Adami and Saag, 2019), antiepileptic drugs (Shen *et al.*, 2014), medroxyprogesterone acetate (Cromer *et al.*, 2008; Lanza *et al.*, 2013), Aromatase inhibitors (Hadji *et al.*, 2011), selective serotonin receptor inhibitors (Rabenda *et al.*, 2013), insulin sensitizers, e.g. thiazolidinediones (Yang *et al.*,

Table 1: Characteristics of the participants

Variables	Group I (n=150)	Group II (n=65)	p-value
Age (Year)	60.3±6.1 (56.0-65.75)	56.0±5.3 (52.0-60.0)	<0.001
Smoking			
Current smoker	12 (8.0)	13 (20.0)	0.012
Ex-smoker	10 (6.7)	0 (0.0)	0.033
Duration of menopause (year)	10.38±6.13 (5-15)	9.02±6.52 (5-15)	0.144
Concomitant illnesses			
Diabetes mellitus	28 (18.7)	3 (5.6)	0.007
Hypertension	53 (35.3)	6 (9.2)	<0.001
Ischemic heart disease	15 (10.0)	3 (4.6)	0.190
Rheumatic illnesses	38 (25.3)	26 (40.0)	0.031
Peptic ulcer	3 (2.0)	57 (87.7)	<0.001
Body mass index (kg/m^2)	31.5±5.8 (26.66-35.67)	32.4±6.1 (28.30-36.52)	0.305
Waist-to-height ratio	0.634±0.087 (0.580-0.696)	0.632±0.091 (0.571-0.708	0.879

The results are expressed as number (percentage) and mean ± S.D. (IQR). P-value was calculated by using a Chi-square test for categorized data and independent two-sample Student- t-test for continuous data. Group I: patients had not treated with proton-pump inhibitors, Group II Patients had treated with proton pump inhibitors.

2017), Calcinurine inhibitors, e.g. cyclosporine and tacrolimus (Zawawi *et al.*, 2012), anticoagulants, e.g., heparin (Rajgopal *et al.*, 2008), and proton pump inhibitors (PPIs) (Yang *et al.*, 2006). Targowink et al. showed a non-significant association between bone fracture and PPIs (Targownik *et al.*, 2010).

Moreover, the effect of PPIs on the BMD is usually reversible (Corley *et al.*, 2010). Current studies claimed that hypochlorite due to PPI is the cause of bone fractures as hypohydrochloria and high gastrin levels reduced the mineral absorption and thereby producing a defect in the bone remodelling (Thong *et al.*, 2019). Some authors claimed that PPIs directly altered bone regeneration and osseointegration (Mester *et al.*, 2019). Brozek et al. studied the link between subsequent fractures with the PPIs doses and found low defined daily dose of PPIs (<90 mg cumulative doses) is not linked with increased risk of later fracture (Brozek *et al.*, 2019).

The effect of PPIs on the BMD in postmenopausal women without earlier or current evidence of bone fracture was not investigated in the previous studies. Moreover, there is no study investigated the direct effect of PPIs on the specific bones. Therefore, this cross-sectional study was carried on postmenopausal women using PPIs, and they had no clinical history of bone fracture looking for changes in the BMD which detected by DEXA investigation.

MATERIALS AND METHODS

The present study is an observational cross-sectional study carried on patients treated regularly with a proton pump inhibitors for different medical conditions. This study carried on at the University of Anbar, College of Medicine/ Department of Pharmacology in collaboration with the private clinics and the Teaching Hospital in Anbar city-Iraq from August 2018 till February 2020.

The Ethical and Scientific Committees of the College of Medicine reviewed the interventions, investigations, and approved the study, according to the guidelines of investigations of osteoporosis patients. The patients are free to refuse participation or withdraw from the study at any time of the study.

The criteria of inclusion were postmenopausal women aged $\geq$ 50 years subjected to DEXA investigation. Their profile was assessed to get information about age, duration of menopause, smoking, concomitant diseases, and anthropometric measurements, and using PPIs. Patients with a history of earlier or current fractures, use of medicines (such as glucocorticosteroids, insulin sensitizers, anticoagulants, selective serotonin reuptake inhibitors), and terminal illnesses were excluded.

The patients were grouped into patients had no treatment with PPIs (Group I), and patients had treated with PPIs (Group II). Group II patients had a history of regular treatment with PPIs, including

Table 2: T-score of the vertebrae and femur bones

Site	Group I (n=150)	Group II (n=65)	p-value
Lumbar-1	45 (30) -2.5(-3.1 — -1.2)	25 (38.5) -2.2(-2.7 5— -1.45)	0.224
Lumbar-2	53 (35.3) -2.2(-2.9 — -0.9)	13 (20) -1.4(-2.4 — -0.6)	0.025
Lumbar-3	34 (22.7) -1.6(-2.4 — -0.2)	0 (0) -0.9 (-1.75 — -0.2)	<0.001
Lumbar-4	27 (18.0) -1.35(-2.3 — 0.2)	10 (15.4) -0.8(-2.0 — -0.1)	0.641
Lumbar-1-Lumbar-2	61 (40.7) -2.2(-3.2— -1.1)	22 (33.8) -1.8(-2.6 — -1.0)	0.345
Lumbar-1-Lumbar-3	61 (40.7) -2.2(-2.8 — -1.0)	7 (10.8) -1.5(-2.3 — -1.0)	<0.001
Lumbar-1-Lumbar-4	50 (33.3) -2.1(-2.8 — -0.5)	14 (21.5) -1.2(-2.2 — -0.8)	0.082
Lumbar-2-Lumbar-3	47 (31.3) -2.1(-2.58 — -0.7)	0 (0) -1.1(-2.1 — -0.65)	<0.001
Lumbar-2-Lumbar-4	33 (22.0) -1.8(2.38 — -0.3)	10 (15.4) -0.9(-1.7 — -0.45)	0.265
Lumbar-3-Lumbar-4	24 (16.0) -1.6(-2.3 — -0.1)	6 (9.2) -0.7(-2.1 — -0.3)	0.188
Femur neck	10 (6.7) -0.5(-1.5 — 1.4)	15 (23.1) -0.9(-1.6 — -0.6)	<0.001
Femur wards	32 (21.3) -1.6(-2.4 — -0.45)	23 (35.4) -2.1(-3.3 — -0.8)	0.030
Femur trochanter	9 (6%) -0.2 (-0.9 — 1.0)	15 (23.1) -0.05 (-2 — 0.4)	<0.001

The results are expressed as number (percentage) of T-score at a threshold of -2.5 and as median (interquartile range) of T-score. P-value was calculated by using a Chi-square test for categorized data. GroupI: patients had not treated with proton-pump inhibitors, Group II Patients had treated with proton pump inhibitors.

omeprazole, lansoprazole, and esomeprazole with different therapeutic regimen. A cutoff value of T-score -2.5 indicated evidence of osteoporosis.

The anthropometric measurements included body weight (kg), height (m), and waist circumference (cm). Body mass index (BMI) and waist-to-height ratio (WHeR) were calculated using the following formula

BMI (kg/m^2) = body weight (kg)/ [height (m)]^2

WHeR = waist (cm)/ height(cm)

Statistical Analysis

The results are expressed as a number, percentage, interquartile range and mean $\pm$ S.D. Difference between means of two groups of continuous data was analyzed using a two-tailed independent two-sample t-test. The Chi-square test analyzed categorized data, and Pearson's correlation test did the correlations between age, duration of menopause, and anthropometric measurements with DEXA data. The P-value of ≤ 0.05 is the cutoff level of significance. Excel software (2010) program was used for data analyses.

RESULTS

Characteristics of the participants

Table 1 showed that there are significant differences between Group I and II in the characteristics of the patients. The mean of Group II patients was lower than the corresponding mean of the Group I. There is no significant difference in the duration of the menopause, BMI, and WHeR between Groups I and II. Significantly higher percentages of smokers and patients presented with rheumatic illnesses and peptic ulcers were observed in Group II compared with the corresponding values of the Group I. The percentages of concomitant illnesses, including diabetes mellitus and hypertension, were significantly

Table 3: Correlation between the T-score of vertebrae and femur bones with the age, body mass index, and waist-to-height ratio

T-score of bone	Group I (n=150)				Group II (n=65)			
	Age	BMI	WHeR	Duration of menopause	Age	BMI	WHeR	Duration of menopause
Lumbar-1	-0.120 0.144	0.690 <0.001	0.674 <0.001	-0.213 0.009	0.175 0.163	0.359 0.003	0.263 0.034	0.295 0.017
Lumbar-2	-0.224 0.006	0.669 <0.001	0.523 <0.001	-0.238 0.003	0.68 0.498	0.617 <0.001	0.425 <0.001	0.245 0.049
Lumbar-3	-0.055 0.504	0.438 <0.001	0.350 <0.001	-0.080 0.331	-0.056 0.657	0.224 0.073	0.257 0.039	0.089 0.479
Lumbar-4	-0.199 0.015	0.579 <0.001	0.443 <0.001	-0.220 0.007	-0.256 0.040	0.720 <0.001	0.536 <0.001	-0.041 0.747
Lumbar-1-Lumbar-2	-0.177 0.030	0.716 <0.001	0.620 <0.001	-0.233 0.004	0.140 0.266	0.518 <0.001	0.373 0.002	0.286 0.021
Lumbar-1-Lumbar-3	-0.145 0.077	0.674 <0.001	0.570 <0.001	-0.187 0.022	0.040 0.753	0.535 <0.001	0.357 0.004	0.224 0.073
Lumbar-1-Lumbar-4	-0.175 0.032	0.650 <0.001	0.530 <0.001	-0.212 0.009	-0.092 0.465	0.677 <0.001	0.476 <0.001	0.130 0.303
Lumbar-2-Lumbar-3	-0.135 0.100	0.584 <0.001	0.459 <0.001	-0.146 0.076	-0.025 0.844	0.586 <0.001	0.383 0.002	0.182 0.164
Lumbar-2-Lumbar-4	-0.174 0.033	0.586 <0.001	0.451 <0.001	-0.188 0.021	-0.132 0.293	0.704 <0.001	0.500 <0.001	0.088 0.487
Lumbar-3-Lumbar-4	-0.150 0.067	0.524 <0.001	0.404 <0.001	-0.170 0.037	-0.207 0.099	0.684 <0.001	0.479 <0.001	0.025 0.841
Femur neck	-0.266 0.001	0.048 0.560	0.137 0.095	-0.252 0.002	-0.110 0.383	0.001 0.991	-0.194 0.122	0.033 0.793
Femur wards	-0.313 <0.001	0.026 0.752	-0.032 0.700	-0.204 0.012	-0.189 0.131	-0.194 0.122	-0.098 0.437	-0.2013 0.104
Femur trochanter	-0.228 0.005	-0.030 0.716	-0.036 0.662	-0.241 0.003	-0.222 0.076	-0.259 0.037	-0.310 0.012	-0.271 0.029

The results are expressed as a correlation factor (above value) and the p-value(below the value) in each cell. Group I: patients had not treated with proton-pump inhibitors, Group II Patients had treated with proton pump inhibitors.

higher in Group I compared with the corresponding Group II.

Assessment of T score

Table 2 shows significant differences between Groups I and II in the T-scores of the BMD. The percentages of Group I patients with T-score -2.5 were higher in the lumbar region (L2, L3, L1-L3, L2-L3) compared with the corresponding values of the Group II patients. The significantly higher percentages of patients who have T- score -2.5 in the femur were observed in Group II.

Relationship between T score and risk factors

In the Group I patients, T-scores of BMD of lumbar and femur regions were correlated significantly and inversely with the age and the duration of the menopause as significant positive correlations with the anthropometric measurements (BMI and WHeR) were observed (Table 3).

In Group II, the correlations between the T-scores of the BMD at lumbar and femur regions were non-significant. As with Group I, the T-scores of the BMD at lumbar and femur regions were significantly and positively correlated with the anthropometric measurements in the Group II patients.

Significant positive correlations between the T-scores and the BMD at L1, L2 and L1-L2 regions were observed in Group II. At the same time, there is a significant inverse correlation between T-score of BMD at a trochanter region of the femur with the duration of the menopause.

DISCUSSION

The present study shows that PPIs users have a significantly lower T score of femur bone compared with non-PPIs users who had a significant T score of lumbar spines. The percentage of patients who have T-scores that indicated osteoporosis is higher in femur bone (Group II) and lumbar vertebrae (Group I). Baseline data showed that the age Group II patients were less than the corresponding value of Group I, indicating that the osteoporotic process is accelerated in Group II. Ageing is a significant risk factor for the decline in the BMD of the total hip (Westbury *et al.*, 2020). The percentage of current smokers among Group II is significantly higher than the corresponding percentage of the Group I patients, indicating that smoking is a confounding risk factor of osteoporosis among Group II patients. In the cohort study carried in the male population, smokers showed a significantly high percentage of hips and vertebrae bone fractures (Cho *et al.*, 2020). Chronic concomitant diseases, e.g. diabetes, hypertension, and ischemic heart disease are not confounding risk factors of osteoporosis in the Group II patients as the percentages of these illnesses are less than the corresponding values of Group I.

Hypertension Per se is not a risk factor of bone mass loss, but using thiazides or beta-blockers can significantly decrease the BMD (Hijazi and Alourfi, 2020). Significantly higher percentages of peptic ulcer and rheumatic illnesses in the Group II patients link to the prescription of PPIs as therapeutic and prophylactic remedies. Anthropometric measurements of our patients indicated that the patients are overweight in both groups. This finding does not agree with earlier studies, which showed that there is an inverse relationship between BMI and BMD (Hijazi and Alourfi, 2020). Moreover, our observation of higher WHeR (>0.5) in both groups is in agreement with other studies that showed a significant inverse correlation between WHeR and BMD (Jafari-Adli *et al.*, 2019).Table 2 shows that Group II patients have significantly lower T scores of femur bones compared with corresponding values of Group I, and vice versa with the lumbar vertebrae. This observation indicates that PPIs induced selective adverse effects against bone minerals in the femur, and this finding agreed other earlier studies (Fattahi *et al.*, 2019). Moreover, people had used PPIs more frequently are at risk of atypical femur fractures (Buitendijk *et al.*, 2019). The correlations between the T-scores with age, duration of menopause, and body mass index in both groups do no show specific differences between Group I and II. Moreover, the positive correlation between WHeR with the T-score of the spine, indicating that WHeR is a significant risk factor of losing body mass in the spine. The T-score of the femur trochanter is significantly correlated with WHeR in Group II patients, indicating that PPIs accelerate bone loss in the femur bone. Previous studies showed that not all PPIs induced bone loss as (Bahtiri *et al.*, 2016) reported that esomeprazole is independently reduced the bone mass of lumbar spine and femur, while omeprazole does not show a significant effect.

Study limitations

Risk factors of lower T score that reported in this study do no impact our findings, while the results of each PPIs user and the duration of using PPI may limit our findings which are far away from goals of this study. Different generic names of PPIs that used by patients may limit the results because not all PPIs induced bone loss to the same level.

CONCLUSION

We conclude that PPIs users are at risk of bone loss in the femur and osteoporosis rather than the axial bones in postmenopausal women.

ACKNOWLEDGEMENT

The authors express their gratitude and thank the staff of the Department of DEXA at the Teaching Hospital, and the patients for their cooperation.

Conflicts of interest

The authors declare that they have no conflict of interest for this study.

Funding support

The authors declare that they have no funding support for this study.

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