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Bone mineral changes in young adult females on short-term proton pump inhibitor: A retrospective cohort study

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Ethics Committee Approval
The study was approved by the Istanbul Gaziosmanpasa Taksim Health Research Hospital Ethics Committee in 2015, approval numer: 2015/6.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Proton pump inhibitors (PPIs), despite being the most prescribed medications today, have generated controversy due to their potential impact on bone metabolism. Numerous studies have emphasized the potential of prolonged PPI use to reduce bone mineral density, thereby increasing the risk of bone fractures among elderly and young individuals. However, the precise impact of PPI usage for 1 year or less on bone mineral density in young adults remains incompletely understood.
Method: In this retrospective cohort study, we conducted a comprehensive review of all dual x-ray bone densitometric examinations conducted on females under 40 years old at our tertiary care center between 2010 and 2014. Among the initial 685 patients assessed, 117 samples met the predefined inclusion criteria and were consequently enrolled in the study. Subsequently, the enrolled cases were categorized into three distinct groups: Group 1 (n=46), which received PPI treatment for less than six months; Group 2 (n=31), which received PPIs for a duration ranging from 6 to 12 months; and Group 3 (n=40), comprising individuals with no history of PPI use, thus serving as the control group. Comprehensive baseline descriptive data, encompassing bone mineral density, t-scores, and z-scores, were meticulously compared among the three groups mentioned above.
Results: The overall mean age of the study population was 32.84 (5.27) years, with an age range spanning from 20 to 40 years. No statistically significant differences in age were discerned among the three groups. Similarly, the groups exhibited no significant body mass index (BMI) variations. Noteworthy findings emerged after examining the effects of PPI usage on bone mineral density, z-scores, and t-scores across the three groups. Specifically, the data suggested that PPIs might influence t-scores (Group 1: -0.48 (0.77); Group 2: -1.25 (0.86); Group 3: -0.33 (0.78)), yielding an *F*-value of 13.28 for (2.116), signifying statistical significance at $P<0.001$. Moreover, the observed mean square error (MSE) was 64, while the effect size (eta²) was 0.19. Subsequent post-hoc Tukey tests indicated a significant distinction in the T-score of Group 2 compared to the other two groups. Furthermore, the analysis of z-scores (Group 1: 0.46 (0.79); Group 2: -1.27 (0.76); Group 3: -0.35 (0.86)) revealed a similar trend, with an *F*-value of 13.21 for (2.116) and a *P*-value below 0.001. The corresponding MSE was 0.65, and the eta² stood at 0.19. Additional post-hoc Tukey tests indicated that the Z-score of Group 2 significantly diverged from the other groups. However, it is noteworthy that both t and z-scores for Group 1 and Group 3 did not exhibit statistically significant differences.
Conclusion: Prolonged use of PPIs for durations surpassing 6 months may potentially reduce bone mineral density among young adults. Nevertheless, this observed impact does not attain clinically significant levels of osteopenia. Conversely, using PPIs for periods under 6 months did not significantly affect bone mineral density.

Keywords: proton pump inhibitor, bone mineral density, T-score, Z-score, osteopenia, osteoporosis

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Introduction

Proton pump inhibitors (PPIs) are the primary drugs for addressing conditions such as duodenal ulcers and esophageal reflux. Overall, PPIs are widely regarded as an exceedingly safe class of medications. However, variations in their metabolism can lead to specific drug interactions [1,2]. Prolonged utilization of PPIs may exert noteworthy effects on bone metabolism. Theoretically, hypochlorhydria could diminish calcium absorption and impede osteoclastic activity, potentially culminating in reduced bone density [3-5].

Measurements of bone density are conducted alongside assessments of fracture risk in osteoporosis screening. Diminished bone mineral density (BMD) correlates with heightened fracture susceptibility, irrespective of the measurement technique employed [6]. Dual-energy x-ray absorptiometry (DXA) of the spine, hip, and forearm is the singular diagnostic method for osteoporosis without a fragility fracture. It is the premier approach for monitoring BMD changes over time [7,8].

PPIs fall within a category of medications suspected to exert negative effects on the skeletal system, potentially elevating the risk of osteoporosis and fractures [9]. Epidemiological investigations have illuminated a potential link between extended PPI use and bone metabolism; however, this correlation remains controversial. Several articles propose that short-term PPI use might not impact BMD, yet the matter remains ambiguous [10-13].

Within the medical literature, multiple studies have identified baseline disparities in BMD between PPI users and non-users. Nevertheless, consistent associations have predominantly eluded longitudinal analyses across various anatomical sites. Moreover, these studies contend with notable methodological limitations that may complicate the interpretation of their findings [14]. Most publications encompass individuals aged ≥ 50 years who exhibit an escalated risk of fractures. Data concerning young adults undergoing brief or on-demand PPI treatment is lacking.

The present study assesses alterations in BMD, indicated by t and z-scores, in young female adults subjected to short-term (< 6 months or between 6–12 months) PPI treatment using DXA.

Materials and methods

This retrospective cohort study was conducted within the Internal Medicine Department of our tertiary care center, namely the University of Health Sciences, Taksim Training and Research Hospital. We collected data from female patients who had undergone DXA screening and were under 40 years of age between 2010 and 2014. Ethical approval was granted by the Ethics Committee of the same hospital, as evidenced by decision number 2015/6.

Our study aimed to encompass young adults 18 to 40 years old who had undergone BMD measurements for nonspecific reasons like trauma or bone pain. Furthermore, our scope encompassed individuals who had either used or refrained from using PPIs within the past year, excluding those with comorbidities. Hence, we meticulously reviewed the files of the 685 patients from whom we had collected data, adhering to the subsequent exclusion criteria.

All patient records underwent scrutiny in alignment with the subsequent exclusion criteria:

i) Systemic diseases: Patients diagnosed with or suspected of having endocrine disorders (such as amenorrhea, eating disorders, Cushing's syndrome, hyperthyroidism, hyperparathyroidism, hypogonadism, type 1 diabetes mellitus, deficiencies in vitamin D and calcium, hypercalciuria), gastrointestinal ailments (including Celiac disease, inflammatory bowel disease, malabsorption syndrome, severe liver disease), bone marrow disorders (such as amyloidosis, leukemia, lymphoma, multiple myeloma, hemochromatosis, sickle cell anemia, thalassemia), connective tissue disorders (e.g., osteogenesis imperfecta, Marfan Syndrome, Ehlers-Danlos Syndrome, hypophosphatasia, recipients of organ transplants), and inflammatory conditions (rheumatoid arthritis, ankylosing spondylitis, and Systemic Lupus Erythematosus [SLE]) were subject to exclusion.

ii) Individuals using medications recognized for inducing osteoporosis (such as glucocorticoids, immunosuppressive agents, anti-epileptic drugs, and chemotherapeutics), those with a history of smoking (equivalent to more than five pack-years), and excessive alcohol consumers were not considered eligible for participation in this current study.

iii) Samples displaying a body mass index (BMI) below 20 kg/m^2 or surpassing 35 kg/m^2 were omitted from the study due to their potential influence on BMD.

iv) Due to the study's design, cases involving prolonged PPI usage beyond one year were also precluded from participation.

Following the application of the exclusion criteria, a total of 409 patients were deemed ineligible for inclusion in the study. The remaining patient cohort included individuals who had employed PPIs for differing durations over the past year, from 0 to 12 months and those who had refrained from PPI use entirely. Initially, a cohort of 276 women was categorized into three distinct groups: Group 1 encompassed patients with PPI usage for less than six months; Group 2 consisted of patients who had been undergoing PPI treatment for a duration of 6 to 12 months; and Group 3 comprised cases characterized by a lack of PPI utilization.

From the initial pool of 199 cases within Group 3, a subset of 40 individuals was randomly chosen and incorporated into the study to equalize participant numbers across all groups. Consequently, data analysis encompassed 46 cases in Group 1, 31 in Group 2, and 40 in Group 3, respectively.

Dual-energy X-ray absorptiometry (DXA)

Central DXA for quantifying BMD remains the foremost standard in diagnosing osteoporosis and monitoring patient advancement, heralded as the definitive approach in this domain. This specialized x-ray technique furnishes precise evaluations of bone density at critical skeletal sites – such as the spine, hip, and forearm – while concurrently minimizing radiation exposure [15].

Bone density test results are typically presented in "T" or "Z" scores. T-scores provide a measure of the comparison

between your bone health and that of a typical young individual with healthy bones. Conversely, z-scores evaluate how your bone condition compares to your peers. Ordinarily, the T-score takes precedence in interpreting these two indicators. T-scores generally fall within the negative spectrum. A lower T-score indicates an elevated fracture risk attributed to reduced bone density.

Bone density is categorized through t-scores, which stratify various conditions. Individuals with normal bone density exhibit t-scores ranging from +1 to -1. Those with osteopenia, a precursor to osteoporosis, exhibit t-scores between -1.1 and -2.4, signifying a heightened risk of progression to osteoporosis. T-scores of -2.5 or lower characterize osteoporosis. Notably, as bone density decreases, the susceptibility to fractures escalates [16,17].

Within our study, our objective encompassed a statistical comparison of the femoral neck t and z-scores across all three groups. Furthermore, we explored whether each group's t and z-scores met the diagnostic thresholds for osteopenia or osteoporosis.

Statistical analysis

All analyses were performed utilizing IBM SPSS version 26. A one-way analysis of variance (ANOVA) was employed to assess the main effects, and for subsequent post-hoc comparisons, Tukey's HSD (honestly significant difference) test was applied. All analyses were conducted as one-tailed tests, with a significance level set at a *P*-value of 0.05.

Results

The mean age of our entire study population was 32.84 (5.27) years, ranging from 20 to 40 years. A one-way ANOVA was conducted to assess any age differences among the three groups. The means for Group 1, Group 2, and Group 3 were 32.9 (5.23), 34.26 (5.46), and 31.35 (4.93) years, respectively. The ANOVA results indicated no significant age differences among the groups ($F(2.116)=2.278$, $P=0.066$, $MSE=75.04$, $\eta_p^2=0.047$).

Similarly, a one-way ANOVA was performed to analyze potential differences in BMI among the three groups. The mean BMI for Group 1, Group 2, and Group 3 were 27.67 (7.02), 26.21 (6.47), and 25.74 (6.37), respectively. The ANOVA results showed no significant differences in BMI among the groups ($F(2.116)=0.973$, $P=0.381$, $MSE=44.35$, $\eta_p^2=0.017$). Consequently, BMI was not considered in subsequent analyses. The distribution of age and BMI can be found in Table 1.

Table 1: Baseline descriptive data in three groups under investigation

	Group 1 (n=46)	Group 2 (n=31)	Group 3 (n=40)	*P*-value
Age	32.91	34.26	31.35	0.066
BMI	**27.66**	**26.21**	**25.74**	**0.381**

BMI: body mass index, Group 1: patients had less than 6 months of PPI treatment, Group 2: patients on PPI treatment for 6-12 months, Group 3: no PPI treatment.

A comparison was made among the three groups to assess the impact of PPI use on BMD, z-scores, and t-scores. The mean t-scores for Group 1, Group 2, and Group 3 were -0.48 (0.77), -1.25 (0.86), and -0.33 (0.78), respectively. The ANOVA results indicated a significant effect of PPI on t-scores ($F(2,116)=13.28$, $P<0.001$, $MSE=64$, $\eta_p^2=0.19$). Subsequent post-hoc Tukey testing revealed that the t-score of Group 2 significantly differed from the other two groups. However, there were no significant differences in t-scores between Group 1 and Group 3 (Table 2).

Table 2: T and z-score changes in patients between Groups 1, 2, and 3

	T-score	Z-score
Group 1	-0.48	-0.46
Group 2	-1.25	-1.27
Group 3	**-0.33**	**-0.35**

Our data analysis revealed that PPI use exerted an influence on z-scores, with the mean z-scores for Group 1, Group 2, and Group 3 being 0.46 (0.79), -1.27 (0.76), and -0.35 (0.86), respectively. The ANOVA findings demonstrated a statistically significant effect of PPI use on z-scores ($F(2.116)=13.21$, $P<0.001$, $MSE=0.65$, $\eta_p^2=0.19$). Further post-hoc Tukey analysis indicated a significant disparity in z-scores between Group 2 and the other groups. Conversely, the z-scores of Group 1 and Group 3 exhibited similarity (Table 2).

Contrarily, our results did not reveal a significant impact of PPI use on BMD scores, despite observing mean BMD scores of 1.08 (0.10) for Group 1, 0.96 (0.25) for Group 2, and 1.05 (0.32) for Group 3. Notably, this result approached marginal significance ($P=0.080$). In the post-hoc Tukey test, it was suggested that this marginal *P*-value could be attributed to Group 2 ($P=0.070$).

Correlation analyses were conducted between the descriptive parameters and BMD indicators using Pearson correlation coefficients (Table 3). Additionally, it was observed that t-scores and z-scores exhibited a positive correlation with each other.

Table 3: Results of correlation analysis between descriptive parameters and bone mineral density indicators (n=31)

		Age	BMI	t-score	z-score	BMD
Age	Pearson Correlation	1	-0.177	0.014	-0.025	-0.079
	P		0.342	0.941	0.895	0.674
BMI	Pearson Correlation	0.177	1	-0.148	-0.067	0.317
	P	0.342		0.427	0.72	0.082
t-score	Pearson Correlation	0.014	-0.148	1	0.975**	0.179
	P	0.941	0.427		0	0.337
z-score	Pearson Correlation	-0.025	-0.067	0.975**	1	0.341
	P	0.895	0.72	0		0.06
	Pearson Correlation	-0.079	0.317	0.179	0.341	1
BMD	*P*	0.674	0.082	0.337	0.06	

** Correlation is significant at the 0.01 level (2-tailed), BMD: bone mineral densitometry, BMI: body mass index

Discussion

PPIs rank among the most frequently prescribed medications today, boasting an excellent short-term safety profile. These drugs find common application in acid-pepsin-associated diseases such as peptic ulcers, gastroesophageal reflux disease, Barrett's esophagus, laryngopharyngeal reflux, Zollinger-Ellison Syndrome, and functional dyspepsia [18,19]. Notably, they are recognized as highly effective and dependable medications. Despite their high reliability, it's important to acknowledge the potential side effects associated with PPIs. These encompass inducing cell differentiation to neoplasia, heightening susceptibility to infectious diseases, giving rise to gastrointestinal absorption issues, and causing a range of electrolyte imbalances and nutrient absorption deficits. Furthermore, they have been implicated in acute interstitial nephritis and may adversely affect BMD [20].

Drawing from existing literature studies and comprehensive meta-analyses, a connection has been suggested between prolonged PPI usage and an increased risk of hip fractures. However, the relationship between PPI use and

changes in BMD remains elusive, with inconsistent and conflicting outcomes [21,22].

Multiple studies have indicated that prolonged PPI use may diminish BMD and elevate the susceptibility to bone fractures across various age groups, encompassing both older and younger individuals [22]. Despite these noteworthy observations, the exact implications of PPI utilization lasting one year or less on BMD in young adults continue to elude complete understanding.

Hence, we classified the 117 patients who had used PPIs for less than one year into three distinct groups, subsequently evaluating their femoral neck t and z-scores. The connection between BMD or bone mass and specific variables such as body weight, BMI, advancing age, and female gender has been firmly established in the literature [23]. To attenuate the influence of gender and advanced age and to enhance the diversity of our study population, we exclusively included females below 40 years ols (with an average age of 32.84 [5.27]). Notably, there existed no significant variance in BMI across the three groups, with all participants maintaining a normal weight status (average BMI of 26.1 kg/m^2).

Prolonged utilization of PPI therapy has been associated with a noteworthy reduction in BMD, although it falls short of constituting a diagnostic marker for osteoporosis. Furthermore, prevailing evidence indicates that chronic PPI usage does not heighten the risk of osteoporosis [24]. In this context, Targownik et al. [25] reported that patients undergoing chronic PPI therapy displayed lower BMD than non-PPI users. Nevertheless, a follow-up spanning 5 to 10 years revealed that the decline in BMD did not progress to osteoporosis. Additionally, it has been theorized that the risk of hip fractures in patients on chronic PPI therapy stems from mechanisms independent of osteoporosis [20].

Curiously, the impact of acid inhibition on calcium absorption and BMD lacks consistent effects [26]. This observation suggests that PPIs might elevate fracture risk irrespective of calcium balance and BMD, or the established connection could be erroneous. The operation of vacuolar proton pumps employed by bone osteoclasts for bone resorption can be impeded in vitro by PPIs, potentially reducing bone resorption [4]. However, as bone resorption is crucial for developing a normal bone microstructure, speculation arises that the PPI-induced hindrance of the osteoclast-associated vacuolar proton pump might elevate the risk of fractures [27].

In our investigation, the t and z-scores across the three groups proved inadequate for definitive diagnoses of osteoporosis or osteopenia (femur neck DXA scores not falling below -1.1). Concurrently, due to the unavailability of patients' x-ray records, an assessment of the relationship between fractures and PPI usage within our sample remained unattainable.

Over the past decade, numerous prospective cohorts have provided substantial evidence of declining t and z-scores in bone mineral densitometry, particularly after prolonged PPI usage spanning over 12 months [28-32]. Within our study, discernible alterations in femoral neck t and z-scores were absent among both the group abstaining from PPI usage within the last year and the group utilizing PPIs for durations less than six months. However, among participants in Group 2, who employed PPIs for periods ranging from 6 to 12 months, a reduction in both t and z-scores was noted, indicating a decline in bone density.

Parallel to our research, a prospective cohort study by Özdil et al. [29] 2013 explored bone densitometry measurements of 114 GERD patients undergoing PPI treatment. Although the subjects of their investigation were not exclusively young adults, the average age, at 37.7 (8.8) years, closely resembled our sample. This study similarly unveiled noteworthy declines in densitometric t-scores, assessed through bone densitometry of the vertebrae and femur, among patients employing PPIs for at least 6 months.

Limitations

By deliberately excluding males in our study, aimed at mitigating gender-related effects and including only a restricted male population for statistical analysis, we acknowledge that this approach could potentially curtail the broad applicability and generalizability of our findings. Given the retrospective nature of our study, we refrained from delving into the assessment of hip or other types of fractures.

Distinct from many studies that categorize PPIs based on their specific types, our study encountered a limitation. The unavailability of patients' generic medication details hindered our ability to perform such a classification. This absence of differentiation among different PPI types, including noteworthy variants like esomeprazole, which could potentially exert diverse effects on BMD compared to other PPIs, impedes a comprehensive exploration of this aspect.

Given the relatively modest sample size and the confined nature of the data sourced from a single institution's experience, we must exercise caution when extending the implications of our outcomes to the broader population.

Conclusion

Our findings propose that short-term PPI usage (less than 6 months) among females might not significantly impact BMD, whereas prolonged usage for over six months could contribute to a decline in bone mineral densitometry. This observation should be duly considered when formulating treatment plans involving PPIs. However, it's worth noting that this effect doesn't reach the diagnostic thresholds for osteopenia or osteoporosis.

It is essential to acknowledge that this retrospective cohort study is accompanied by several limitations that inevitably influence the broader applicability of our results. Further research is warranted to arrive at more precise and definitive conclusions, necessitating larger-scale, multicentric, randomized, and prospective trials.

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