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Risk of Osteoporosis and Osteopenia in Patients with Prolonged Use of Proton Pump Inhibitors

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ABSTRACT

Background and aim of the work: several studies suggest that proton pump inhibitors (PPIs) use may be involved in development and acceleration of osteoporosis. The aim of this study is to investigate the relationships between prolonged uses of PPIs in patients with gastro-esophageal reflux disease (GERD) and to reveal their possible role in development of osteopenia or osteoporosis with evaluation of different diagnostic tools which help in follow up of those patients.

Patient and methods: This prospective controlled study which was conducted at King Abdul Aziz Specialist Hospital in Taif, Saudi Arabia, from January 2013 to June 2016. We compared the prevalence of osteoporosis or osteopenia in 2 groups of individuals, the first group; of 30 patients using PPIs as treatment of GERD for more than 2 years. The second group included thirty healthy control subjects .In both groups we measured the bone mineral density using the dual energy X-ray absorptiometry (DEXA), calcium (Ca), inorganic phosphorus (P), serum alkaline phosphatase, and deoxypyridinoline (DPD) in urine. **Results:** there were no significant differences between the 2 groups as regards, age, gender, and their clinical history ($P > 0.05$), however, the history of fragility fracture was significantly higher in PPIs group of patients ($P< 0.05$). The means of antroposterior spine and left femur BMD-T scores were lower than normal in both groups; however, it was significantly lower in PPIs group than in control group ($P< 0.05$). Serum calcium was slightly lower than the reference range with normal phosphorus level without significant difference between both groups ($P> 0.05$). The serum alkaline phosphatase and urinary DPD were higher than normal reference levels, but, significantly higher in patients receiving PPIs ($P< 0.05$). The number of osteopenic/osteoporotic patients was significantly higher in PPIs group than in control group ($P< 0.05$). Osteopenia and osteoporosis were significantly correlated in PPIs group with male gender, younger age group of patients ($P< 0.05$), and the correlation was highly significant with the duration of use of the drug ($P<0.001$). In control group the decrease in bone density was significantly correlated with the female gender and to older group of patients ($P< 0.05$).

Conclusion: in GERD patient using PPIs, the osteopenic/osteoporotic effect with increased possibility of fragility fractures must be discussed with the patient if prolonged use of these drugs is expected, taking in consideration the potential safety and reliability of laparoscopic or thoracoscopic surgical options as alternative therapy.

Keywords: GERD, PPIs, Osteopenia, Osteoporosis, Fragility fractures

INTRODUCTION

GERD is one of the most common diseases in the world and the incidence to experience the disease at some time reached up to 40% in some studies.[1]The actual incidence is expected to be higher as most of patients control their symptoms with over the counter medications without medical consultation.[2]The disease affects any age with higher incidence above forty years with equal male to female incidence; however, males are more liable to complications as esophagitis, Barrett's esophagus and esophageal adenocarcinoma.[3] PPIs are the gold standards for treatment of gastro-esophageal reflux disease, however, controversial data about the rule of these drugs in calcium metabolism and increase the process of osteopenia/osteoporosis must be validated with multiple prospective studies in different populations not only in western society.[4-8]The aim of this study is to investigate the relationships between prolonged uses of PPIs in patients with gastro-esophageal reflux disease (GERD) and to reveal their possible role in development of osteopenia or osteoporosis with evaluation of different diagnostic tools which help in follow up of those patients.

PATIENT AND METHODS

This prospective controlled study was conducted at King Abdul Aziz Specialist Hospital in Taif, Saudi Arabia, from January 2013 to June 2016. The study was approved by the Hospital Ethics Board and all patients gave informed consent. We compared the prevalence of osteoporosis in 2 groups of patients, the first

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group; of 30 patients selected from the clinic of esophageal surgery, they were listed as possible surgical candidates due to failure of control of GERD in spite of prolonged use (> 2 years)of PPIs. Another healthy group of thirty individuals were selected with matched age, gender, and socioeconomic status (group 2). Both groups were subjected to full clinical evaluation stressing on bone ache, recent decrease in patient height, any kyphotic changes especially in thorax, and any history of fragility fractures with minimal trauma (spine, femoral neck, and radius). Exclusion criteria included; I) if the candidate had hepatic, renal, endocrinal, or degenerative bone disease. II) If the candidate took drugs affecting bone and calcium metabolism. III) If the candidate had fractures within 6 months before the time of study. IV) Immobilized candidates. In both groups we measured the bone mineral density using the dual energy X-ray absorptiometry (DEXA), calcium (Ca), inorganic phosphorus (P), serum alkaline phosphatase, and deoxypyridinoline (DPD) in urine. **Statistical analysis:** SPSS program, version 20.0(SPSS Inc., Chicago, IL, USA) was used. The data were expressed in number and percentage (qualitative) whereas, the quantitative data were expressed as means ±SD. The significance between 2 means was tested by Student's t test. The chi-square test (X^2) and Fisher exact (FE) tests were used to differentiate between two groups. P<0.05 was considered as statistically significant. Pearson and Spearman's correlation tests were used to correlate between each parameter and different variants in the same group to find significant differences.

RESULTS

Table 1 shows that there were no significant differences between both groups as regards, age, gender, and their clinical history, however, the history of fragility fracture was significantly higher in PPIs group of patients than in control group. Table 2 reveals that the means of antroposterior spine and left femur BMD T score are lower than normal in both groups; however, it is significantly lower in PPIs group than in control group. Table 2 shows also that serum calcium is slightly lower than the reference range with normal phosphorus level without significant difference in between both groups, in addition, Table 2 shows that the serum alkaline phosphatase and urinary DPD are higher than normal reference levels, but, significantly higher in patients receiving PPIs. Table 3 shows that, in the PPIs group the number of patients which can be categorized as osteopenic or osteoporotic patients are significantly higher than in control group. Table 4 shows that osteopenia and osteoporosis are significantly correlated in PPIs group with male gender and younger age group of patients (P< 0.05), and the correlation was highly significant with the duration of use of the drug (P<0.001). Table 5 shows that in control group the decrease in bone density was significantly correlated to the female gender and to patients above median age (P< 0.05).

DISCUSSION

Treatment of gastro-esophageal reflux disease (GERD is based on modification of life style, control of gastric acid secretions by medications, of which the PPIs represent the most efficient therapy, however, surgery may be indicated in several situation, as progressive form of the disease, prolonged use of the drug with possible side effects in addition to the financial factors where the drug can be used for life.[1-3] Recent studies found that prolonged use of PPIs (> 2 years) would lead to bone resorption and this effect may increase if higher doses are used.[7, 8]The mechanism by which this effect is produced may be illustrated by the acid suppressant effect of PPIs which can decrease calcium absorption and decrease bone density, as, acidic environment in the stomach facilitates the release of ionized calcium from insoluble calcium salts, and the calcium solubility is thought to be important for calcium absorption.[9, 10]Gastrectomy, pernicious anemia and atrophic gastritis are associated with increased occurrence of osteoporosis and fragility fractures, which is suggested by most of the authors to be secondary to the effect of low gastric acid levels on calcium absorption.[11-13]

In this study there was no significant difference between both groups as regards age and sex and in both groups the mean age was above 50 years which is considered as risk factor for bone resorption especially in postmenopausal females. Ito and Jensen in their study, reported that the majority of the studies evaluated individuals of 50 years or older and the increased risk of fracture was primarily observed in this age group.[14]

In the present study we used different methods to detect the osteopenic and osteoporotic processes in both studied groups and the dual energy *x* ray absorptiometry (DEXA) was the

first tool. DEXA scan is important in measuring bone mineral density (BMD) at the spine and hip and to evaluate the individuals at risk of osteoporosis. Interpretation of these bone mineral density results using the World Health Organization T score definition of osteoporosis would help to predict fracture risk.[15] Our study revealed that the means of antroposterior spine and left femur BMD T score are lower than normal in both groups; however, it is significantly lower in PPIs group than in control group. In adherence to our results, Arj *et al*. in their study verified that PPIs use in patients without risk factors of increased bone resorption had increased risk of developing osteoporosis and osteopenia if compared with the control group.[16]

The results of our study showed also that, the number of patients which can be categorized as osteopenic or osteoporotic patients was significantly higher in the PPIs group than in control group. Similar results were obtained in the studies of Yang *et al.*, Yu *et al.*, and Targownik*et al.*[8, 17, 18]

Biochemical markers are simple tools to follow up patients at risk for bone resorption, Atalay *et al*. revealed in his study that serum ALP level (bone formation marker), may be useful to monitor and follow-up osteoporotic changes that currently cannot be assessed with BMD[19].The present study revealed that mean level of serum ALP was elevated in both groups but it is significantly higher in patients receiving PPIs than control patients with a significant correlation between the ALP level and the decrease in BMD. Mizunashi *et al*. in their study on effect of the inhibitor of H+,K(+)-ATPase (omeprazole), on bone resorption in humans, found that there was a significant increase in the serum alkaline phosphatase in the studied patient.[20]

Costa *et al*. in their study found that the PPIs increases the serum ALP, however, they also observed that on the tissue level, the PPIs have an inhibitory effect on activity of ALP which opens up the possibility of decreased bone mineralization. [21]

Most of the studies reported that biochemical markers of bone turnover allow physicians to detect the risk of bone loss and evaluate response to therapy.[22-26]The pyridinium compound, DPD is formed during the extracellular maturation of fibrillar collagens and is released upon the degradation of mature collagens. [22]Yilmaz *et al.* clarified in their study that DPD was significantly higher in osteoporotic patients and its concentration increased with the severity of the disease.[23] Cho, reported in his study that bone resorption markers were more efficient than bone formation markers and they added that urinary DPD level was more than 50% higher in osteoporotic subjects than that in normal individuals. In our study the urinary DPD was high in urine in both groups; however it was significantly higher in patients receiving PPIs.[22]

Several studies found that markers of bone turnover; especially DPD, are elevated during PPIs treatment in humans suggesting that PPIs alter bone resorption.

Previous studies, reported that serum phosphorus and calcium are insignificantly affected in osteoporotic patients mainly due to mobilization of these minerals from bones.[6, 27]The results of the current study revealed insignificant changes in calcium and phosphorus levels in both groups, even though, both groups showed a decrease in the mean BMD T –score.

Previous studies verified that fragility fractures are commoner in patients with prolonged use of PPIs than in normal population which meets the findings in our study.[4-8, 17]Yang *et al*. reported in their study that the risk of decrease in BMD and in turn fragility fractures progressively increased with the duration of PPI treatment and these findings were stronger in men than in women.[8] Wu *et al.*, in their study on peptic ulcer patients receiving PPIs reported that the osteoporotic effect was more in young males.[17] Our findings were in accordance with that, where osteopenia and osteoporosis were significantly correlated in patients receiving PPIs with male gender, decrease in patient age, and the correlation was highly significant with the duration of use of the drug.

In control group of our study, there was a significant decrease in bone density but significantly less than those receiving PPIs and this decrease was significantly correlated with the female gender and increase in age. These findings was in adherence with that reported in Ito and Jensen study.[14]

Some studies found that the effect of PPIs on bone resorption is modest which can be related to difference in sample characteristics including ethnic variation; however, there is a limited experimental evidence showing that PPIs have inhibitory effect on the osteoclastic proton transport system which may ameliorate its osteoporotic effect.[12, 13] To conclude**,** In GERD patient using PPIs, the osteopenic/osteoporotic

effect with increased possibility of fragility fractures must be discussed with the patient if prolonged use of these drugs is expected, taking in consideration the potential safety and reliability of laparoscopic or thoracoscopic surgical options as alternative therapy.

REFERENCES

1. **DeVault KR, Castell DO (2005).** Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol.,100:190-200.
2. **Kahrilas PJ, Shaheen NJ, Vaezi MF (2008).** American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology, 135:1392–413.
3. **Fass R (2009).** Proton pump inhibitor failure--what are the therapeutic options?. Am J Gastroenterol., 104:S33-8.
4. **Heidelbaugh JJ, Goldberg KL, Inadomi JM (2009).** Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk. Am J Gastroenterol.,104:S27–S32.
5. **Raghunath AS, O'Morain C, McLoughlin RC (2005).** Review article: the long-term use of proton-pump inhibitors. Aliment Pharmacol Ther.,22:55–63.
6. **Wright MJ, Proctor DD, Insogna KL, Kerstetter JE (2008).** Proton pump-inhibiting drugs, calcium homeostasis, and bone health. Nutr Rev., 66:103–108.
7. **Tuukkanen J, Vaananen HK (1986).** Omeprazole, a specific inhibitor of H+-K+-ATPase, inhibits bone resorption in vitro. Calcif Tissue Int., 38:123–125.
8. **Yang YX, Lewis JD, Epstein S, Metz DC (2006).** Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA.,296:2947–53.
9. **Insogna KL (2009).** The effect of proton pump-inhibiting drugs on mineral metabolism. Am J Gastroenterol.,104:S2–S4.
10. **Fournier MR, Targownik LE, Leslie WD (2009).** Proton pump inhibitors, osteoporosis, and osteoporosis-related fractures. Maturitas.,64:9–13.
11. **Nilas, L., Christiansen, C., & Christiansen, J. (1985).** Regulation of vitamin D and calcium metabolism after gastrectomy. Gut, 26: 252–7.
12. **Wright MJ, Proctor DD, Insogna KL, Kerstetter JE (2008).** Proton pump-inhibiting drugs, calcium homeostasis, and bone health. Nutr Rev., 66:103–108.
13. **Sheraly AR, Lickorish D, Sarraf F, Davies JE (2009).** Use of gastrointestinal proton pump inhibitors to regulate osteoclast-mediated resorption of calcium phosphate cements in vivo. Curr Drug Deliv.,6:192–8.
14. **Ito T, & Jensen R T (2010).** Association of Long-term Proton Pump Inhibitor Therapy with Bone Fractures and effects on Absorption of Calcium, Vitamin B12, Iron, and Magnesium. Current Gastroenterology Reports, 12:448–57.
15. **Unnanuntana A, Gladnick B P, Donnelly E, Lane J M, (2010).** The Assessment of Fracture Risk. **The Journal of Bone and Joint Surgery,** *92*: 743–53.
16. **Arj A, Razavizade M, Yavari M, Akbari H, Zamani B, Asemi Z (2016).** Proton pump inhibitors use and change in bone mineral density. Int J Rheum Dis., 19:864-8.
17. **Wu CH, Tung YC, Chai CY, Lu YY, Su YF, *et al.* (2016).** Increased Risk of Osteoporosis in Patients with Peptic Ulcer Disease: A Nationwide Population-Based Study. Medicine (Baltimore), 95: e3309.
18. **Targownik LE, Lix LM, Leung S *et al*(2010).** Proton-pump inhibitor use is not associated with osteoporosis or accelerated bone mineral density loss. Gastroenterology, 138:896–904.
19. **Atalay S, Elci A, Kayadibi, H, Onder C B, Aka N. (2012).** Diagnostic Utility of Osteocalcin, Undercarboxylated Osteocalcin, and Alkaline Phosphatase for Osteoporosis in Premenopausal and Postmenopausal Women. Annals of Laboratory Medicine, *32*:23–30.
20. **Mizunashi K, Furukawa Y, Katano K, *et al*. (1993).** Effect of omeprazole, an inhibitor of H+,K(+)-ATPase, on bone resorption in humans. Calcif Tissue Int., 53:21–25.
21. **Costa-Rodrigues S, Reis S, Teixeira S, Lopes M,Fernandes H, (2013).** "Dose-dependent inhibitory effects of proton pump inhibitors on human osteoclastic and osteoblastic cell activity". FEBS Journal., 280: 5052–64.
22. **Cho SW (2016).** New Biological Markers of Bone Metabolism in Osteoporosis Treatment. Endocrinol Metab (Seoul)., 31: 400-1.
23. **Yilmaz N, Bayram M, Erbagci A (1999):** Diagnostic value of biochemical markers of bone turnover and post-mmenopausal osteoporosis. Clin Chem Lab Med., 37:569-71.
24. **Hart SM and Eastell R (1999):** Biochemical markers in bone turn over. Curr Opin Nephrol Hypertens., 8:421-5.
25. **Cantatore FP and Pipitone V (1999):** Markers of bone turnover: consideration on their clinical application in osteoporosis. Panminerva Med., 41: 247-51.
26. **Chailukit LO, Ongphiphadankul B, Piaseu, P and Saetung S (2001):**Biochemical markers of bone turnover and response of bone mineral density to intervention. J ClinEndocrinolMetab., 86: 136- 43.
27. Hoover PA, Webber CE, Beaumount LF, Black JM (1996): Postmenopausal bone mineral density. Relationship to calcium intake, calcium absorption, residual estrogen, body composition and physical activity. Can PhysiolPharmacol., 47:911-6.

Table 1: Comparison between group 1 (PPIs group) and group 2 (control group) in demographics and clinical data

	Group 1n=30	Group 2 n=30	P-value
Age **Mean age±SD** **Median age**	**53.6±13.4 years** **51.4 years**	**51.8±12.8 years** **51.1 years**	**>0.05 S**
Male to female	**20/10**	**18/12**	**>0.05 NS**
Mean duration of PPIs intake **Median duration of PPIs intake**	**4.2±0.9 years** **3,8 years**	**----------** **----------**	**----------** **----------**
History of fragility fracture(s)	**4/30**	**2/30**	**<0.05 S**
Shortening or kyphotic changes	**0/30**	**0/30**	**---------**
Diabetes	**7/30**	**8/30**	**>0.05 NS**
Smoking	**12/30**	**14/30**	**>0.05 NS**

S; significant, NS; non significant

Table 2:Comparison between control group and PPIs regardingsome investigated parameters

SUB-GROUP VARIABLE	Control group (n= 30)		PPIs group (n= 30)		
	Mean	Range	Mean	Range	*P value*
AP Spine BD T score	-1.5±0.23	-3.2 TO 0.67	-2.1±0.1	-3.1 TO 0.58	***<0.05***
Lt Femur BD T score	-1.2±0.22	-1.9 to 1.2	-1.89±**0.22**	-2.2 to 0.7	***<0.05***
ALP (U/L)	239.5±**6.1**	212 – 255	275±5.8	257 – 331	***<0.05***
Calcium (mg/dl)	8.49±**0.34**	6.9 – 11.3	8.33±0.33	6.9 – 11.1	>0.05
Phosphorus (mg/dl)	3.45±0.19	2.2 – 4.9	3.3±0.81	2.3 – 3.5	>0.05
DPD	6.77±0.17	6.5 – 8.6	7.9±0.19	7.1- 9.4	***<0.05***

Non significant = P > 0.05 Significant = P < 0.05

AP; anteroposterior, Lt; left, ALP; Alkaline phosphatase, DPD; deoxypyridinoline

Table 3: Comparison between PPIs group and control group as regard the osteoporotic, osteopenic patients

	PPIs group	Control group	P value
Total number of patients with T score <– 1	**19/30 (63.4%)**	**14/30 (46.6%)**	**< 0.05**
Osteopenic (T score <–1 to – 2.5)	**11/30 (36.7%)**	**7/30 (23.3%)**	**<0.05**
Osteoporotic (T score <– 2.5)	**8/30 (26.7%)**	**7/30 (23.3%)**	**>0.05**

Table 4: Correlating age, gender, and duration of use of PPI with osteopenic osteoporotic changes in PPI group

Gender	**Males** **11/19 (57.9%)**	**Females** **8/19 (42.1%)**	**P value** **< 0.05**
Age	**Below median age** **12/19 (63.2%)**	**Above median age** **7/19 (36.8%)**	**P value** **< 0.05**
Correlation with duration of use of PPIs	**Below the median duration** **4/19 (21%)**	**Above the median durati** **15/19 (79%)**	**P value** **<0.001**

Non significant = P > 0.05 Significant = P < 0.05 highly significant= P, 0.001

Table 5: Correlating age and gender with osteopenic osteoporotic changes in control group

Gender	**Males** **3/14 (21.4%)**	**Females** **11/14 (78.6%)**	**P Value** **< 0.001**
Age	**Below median age** **4/14 (28.6%)**	**Above median age** **10/14 (71.4%)**	**P value** **< 0.001**

Non significant = P > 0.05 Significant = P < 0.05 highly significant= P, 0.001