Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1318023

Anatolian Curr Med J. 2023;5(3):261-265

The effect of long-term use of pioglitazone on bone mineral density in patients with diabetes mellitus

Muhammed Bahaddin Durak[1], Alpay Yesilaltay[2]

[1]Department of Gastroenterology, Ankara City Hospital, Ankara, Turkey
[2]Division of Hematology, Department of Internal Medicine, Başkent University İstanbul Hospital, İstanbul, Turkey

Cite this article as: Durak MB, Yesilaltay A. The effect of long-term use of pioglitazone on bone mineral density in patients with diabetes mellitus. *Anatolian Curr Med J.* 2023;5(3):261-265.

Received: 21.06.2023 ◆ **Accepted**: 11.07.2023 ◆ **Published**: 28.07.2023

ABSTRACT

Aims: This study aimed to explore the incidence of osteoporosis in patients with diabetes mellitus (DM) who have been on a long-term pioglitazone regimen, and to ascertain the link between pioglitazone usage and the onset of osteoporosis.

Methods: We enrolled patients prospectively and conducted a comparative analysis between two groups of DM patients: those who had been using pioglitazone for a period exceeding two years, and those with no history of pioglitazone use. Bone Mineral Density (BMD) was assessed using dual energy X-ray absorptiometry (DEXA).

Results: There were no significant differences in age, gender, disease duration, fasting plasma glucose levels, and HbA1c levels between pioglitazone users and non-users. However, a significant variation was found in the BMD measurements. Patients on pioglitazone had an L1-L4 vertebra BMD T-score of -1.3, compared to -0.9 in non-users ($p<0.05$), signifying a substantial divergence in BMD between both cohorts. Furthermore, it was observed that patients with a disease duration of less than 10 years had higher BMD T-scores compared to those with disease durations exceeding 10 years, suggesting a decrease in BMD with increased disease longevity. Moreover, a higher BMD was observed in patients aged less than 50 years in comparison to those aged over 60 years.

Conclusion: Despite the clinical preference for pioglitazone in the management of DM and insulin resistance, our findings suggest that it may affect bone metabolism adversely in the long run. Hence, careful monitoring is advised during extended periods of pioglitazone use. To investigate the incidence of osteoporosis in patients with DM who use pioglitazone for a long time and to determine the relationship between pioglitazone and the cause of this osteoporosis.

Keywords: Pioglitazone, bone mineral density, diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a diverse metabolic disorder that is predominantly prevalent among adults, causing disruptions in carbohydrate, fat, and protein metabolism due to the absolute or relative deficiency of insulin secretion and/or insulin action.[1,2] There is established knowledge that bone and skeletal metabolism are affected in DM patients, hence positioning DM as a potential risk factor for osteoporosis.

In addition to DM itself being a risk factor for osteoporosis, pioglitazone, an oral antidiabetic agent used in treating Type 2 DM, has been associated with potential deleterious effects on bone health. These effects are presumably brought about by pioglitazone's role in decreasing osteoblast differentiation and promoting adipocyte differentiation.[3] Especially in women, pioglitazone has been linked to an increase in bone loss, and it has been associated with an augmented risk of fractures.[3,4] Moreover, the use of pioglitazone has been related to alterations in markers of bone turnover and a reduction in bone mineral density (BMD).[5] There are a number of possible explanations for this association, with some in vitro data suggesting that activation of the peroxisome proliferator-activated receptor (PPAR)-g increases adipogenesis at the cost of osteoblastogenesis, with the potential to prevent bone formation and lead to bone loss.

Pioglitazone functions as a ligand for nuclear receptors, specifically peroxisome proliferator-activated receptors (PPAR). When pioglitazone binds to the PPAR-gamma receptor, it either activates or inhibits numerous gene transcriptions, thereby impacting lipid metabolism, insulin action, and the regulation of adipose tissue differentiation.[6] Pioglitazone's primary pharmacological effects involve the enhancement of insulin-mediated glucose uptake (thereby reducing insulin resistance) and the promotion of adipogenesis in muscle tissue in vivo.

Corresponding Author: Muhammed Bahaddin Durak, doctormbd@gmail.com

It reduces insulin resistance by decreasing proteins such as TNF-alpha, resistin, and leptin in adipose tissue, and concurrently increasing adiponectin, which heightens hepatic insulin sensitivity. Besides improving glycemic control, it also ameliorates several components of insulin resistance syndrome. For instance, pioglitazone reduces the levels of plasminogen activator inhibitor type 1 (PAI-1), thereby minimizing the inhibition of fibrinolysis, a characteristic feature of insulin resistance.[7] It also leads to an increase in subcutaneous adipose tissue and a slight reduction in visceral adipose tissue.[8,9]

Studies have indicated that pioglitazone increases bone marrow adipose tissue, diminishes osteoblastic activity, and is associated with a decrease in BMD in women by reducing the activity of the aromatase enzyme. However, more extensive research is needed for pioglitazone to be firmly classified among the risk factors for osteoporosis.[10,11]

The primary objective of this study is to investigate the incidence of osteoporosis in DM patients with long-term pioglitazone use and to establish the relationship between pioglitazone usage and the development of osteoporosis.

METHODS

Ethics

The study was approved by the Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.12.2012, Decision No: 20149/2012). This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Study Population

We conducted a retrospective analysis of data collected from our cohort of type 2 DM patients. Patients younger than 18 years of age, those with diseases predisposing them to osteoporosis (such as hyperthyroidism, hyperparathyroidism, chronic renal failure, long-term steroid use, etc.), and nondiabetic individuals were excluded from the study.

Data Collection

The study employed data retrospectively obtained from electronic medical records and outpatient clinics. The collected data included demographics, past medical histories, and bone mineral density (BMD). A comparative analysis was performed between patients who had been using pioglitazone for more than two years and those who had never used pioglitazone. Dual Energy X-ray Absorptiometry (DEXA), recognized as the gold standard for BMD measurement, was used on all patients.[12]

Patient management

The age, gender, and disease duration of patients who had been using pioglitazone for over two years, as well as those who had no experience with pioglitazone, were noted. All patients were on a daily dosage of 30mg of pioglitazone. Patients were questioned about their use of steroids and heparin. Blood samples were collected from all patients to test for fasting blood glucose, HbA1c, kidney function, thyroid function, serum parathormone level, and serum fasting cortisol level. DEXA was used to measure BMD in each patient, with BMD calculated based on the L1-L4 vertebral T-score. T-scores ranging between -1 and -2.5 SD were classified as osteopenia, while T-scores lower than -2.5 SD were considered indicative of osteoporosis.

Statistical Analysis

Statistical analysis was performed using the NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). The study data was evaluated using descriptive statistical methods (Mean, Standard Deviation, Minimum, Maximum, Median, Frequency, Ratio). For comparisons of quantitative data, the Mann Whitney U test was used for two-group comparisons when parameters did not conform to normal distribution. The Kruskal Wallis test was employed for the comparison of groups of three or more that did not conform to normal distribution, while the Mann Whitney U test was used to ascertain the group causing the difference. The Yates Continuity Correction Test (Chi-square with Yates correction) was utilized for comparing qualitative data. Finally, Spearman's Correlation Analysis was used to assess the relationships between parameters.

RESULTS

Our study involved a total of 102 patients, out of which 67 (65.7%) were female. The patient cohort was divided into two groups: 52 (51%) were using pioglitazone (pioglitazone group), while the remaining 50 comprised the control group (without pioglitazone experience). There were no statistically significant differences in fasting blood glucose and hemoglobin A1c measurements between the two groups in relation to pioglitazone use ($p>0.05$) (**Table 1**). Similarly, gender distribution was not statistically different with regard to pioglitazone use. The female gender ratio was 61.5% in the pioglitazone group versus 70% in the control group, with no statistically significant difference observed ($p>0.05$) (**Table 2**).

Table 1. Evaluation of related parameters according to study groups

	Pioglitazone (+)		Pioglitazone (-)		p
	Range	Mean±sd	Range	Mean±sd	
Fasting blood glucose	92-302 (150.0)	157.96±47.10	86-423 (151.5)	168.08±61.12	0.529
HbA1c	5.7-11.3 (7.1)	7.38±1.18	5.6-14.9 (7.4)	7.82±1.69	0.161
Disease duration (years)	4-20	9.37±3.72	3-25	9.60±4.80	0.890

Mann-Whitney U Test

Table 2. Relationship between gender distribution and pioglitazone use

		Pioglitazone Use		p
		(+)	(-)	
		N (%)	N (%)	
Gender	Male	20 (38.5%)	15 (30.0%)	0,489
	Female	32 (61.5%)	35 (70.0%)	

Yates Continuity Correction Test

A comparison between the pioglitazone and control groups revealed a statistically significant difference in DEXA measurements (-1.37±1.29 vs -0.82±1.16, p=0.032, respectively). The DEXA measurements of patients who used pioglitazone for more than two years were significantly lower than those who had never used it (**Figure 1**).

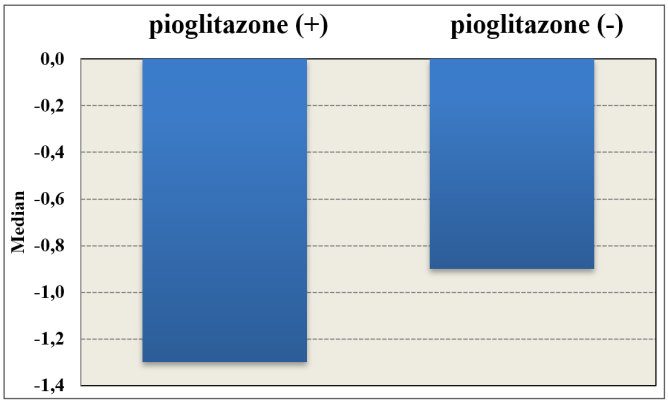

Figure 1: L1-L4 vertebral T-score measurement distribution by pioglitazone usage.

Within the pioglitazone group, a comparison of DEXA measurements between patients with a disease duration of <10 years and >10 years revealed no statistical difference. However, the DEXA values of patients with diabetes for over 10 years were lower (-1.9 vs -1.1, respectively, p=0.054). The DEXA measurements varied significantly according to age (p=0.011). The pairwise comparisons indicated that although DEXA measurements were lower in subjects under 50 years compared to those aged between 50 and 60, the difference was not statistically significant (p=0.054). DEXA measurements were significantly lower in subjects aged <50 years than in those aged over 60 years (p=0.004). No significant difference was observed in DEXA measurements between subjects aged 50-60 years and those aged >60 years (p>0.05) (**Table 3**).

Table 3. Osteoporosis evaluation based on disease duration and age in pioglitazone users.

Pioglitazone (+) (n=52)		DEXA			p
		Mean±sd	Median	Range	
Disease duration	<10 years	1.17±1.21	-1.1	-4.2-1.5	[a]0.054
	>10 years	-1.79±1.39	-1.9	-3.8-1.8	
Age range	<50 years	-0.67±0.99	-0.4	-3.0-0.5	[b]0.011
	50-60 years	-1.33±1.28	-1.2	-4.2-1.5	
	>60 years	-1.83±1.32	-1.9	-3.8-1.8	

[a]Mann-Whitney U Test, [b]Kruskal-Wallis Test

A statistically significant negative correlation was observed between age and DEXA measurements (DEXA level decreases with increasing age) (r=-0.450; p=0.001). Furthermore, a statistically significant negative correlation was observed between disease duration and DEXA measurements (the DEXA level decreases as the duration of diabetes increases) (r=-0.364; p=0.008) (**Table 4**).

Table 4. Evaluation of the relationship between age, diabetes year and osteoporosis in pioglitazone users.

	DEXA	
	r	p
Age	-0.450	0.001
Disease duration	-0.364	0.008

r=Spearman's correlation coefficient

DISCUSSION

In the present study, we did not find any difference in age, gender, disease duration, fasting plasma glucose, and HbA1c levels when comparing patients using pioglitazone for >2 years to patients without pioglitazone experience. However, a statistically significant difference was found in bone mineral density (BMD) between both groups, with a T-score of -1.3 in pioglitazone users versus -0.9 in non-users (p<0.05). This observation suggests that pioglitazone use may be associated with lower BMD. Furthermore, we found that BMD was higher in patients with a disease duration of <10 years compared to those with >10 years, supporting the notion that BMD decreases with the progression of the disease. A statistically significant higher BMD level was found in patients aged <50 years compared to those aged >60 years.

An interesting meta-analysis of 19 pioglitazone-related studies conducted at the University of Ottawa,[13] reviewed 8157 patients retrospectively. This analysis found no

increased fracture risk in men, while an increased risk of forearm fractures was observed in women, increased by 2.6%. Unlike our study, BMD was normal in this meta-analysis. Interestingly, the fractures in these cases were not associated with osteoporosis or trauma. The reason for the increase in forearm fractures in this study is unclear. However, we considered the use of pioglitazone over 2 years in our study. Therefore, the resorptive effects of possible pioglitazones on bone may have become more pronounced during this time. In a study supporting this possibility, it was determined that after 1 year of use of pioglitazone in patients with type 2 DM, serum osteocalcin level decreased in the pioglitazone group, however, while the bone mineral density of the femoral and radial bones decreased, the vertebral bone mineral density did not change.[14]

Our findings align with another study which also showed that pioglitazone use decreased bone mineral density in women.[15] The increased risk of fracture has been attributed to increased adipocyte activity in the bone marrow, decreased osteoblastic activity, and increased bone resorption associated with decreased estrogen levels due to decreased aromatase activity. The reason why pioglitazone has less resorptive effects on bone tissue in men has been attributed to the fact that postmenopausal women have more estrogen than estrogen levels.[16] Similarly, some studies have shown an increased risk of vertebral fractures in both sexes due to the use of pioglitazone.[17,18] However, it was not clear whether the increased risk of fracture was with pioglitazones or due to DM.

Studies have clearly shown that bone turnover is increased in patients with type 2 DM, and it has been determined that the use of high-dose insulin increases osteoblastic activity in the bone and decreases osteoclastic activity.[19,20] Again, in the same study, it was suggested that advanced glycosylated products create a more fragile bone tissue by disrupting the crosslinks between collagen fibrils, and this causes osteoporosis, especially in poorly controlled diabetics. In our study, it is clear that the use of pioglitazone, in parallel with previous studies, reduces bone mineral density and triggers osteoporosis.

The strengths of the study were the clear demonstration of the effect of pioglitazone on bone tissue based on long-term use of pioglitazone, the inclusion of patients using standard dose pioglitazone (30 mg/day), and the design of the study to include both genders. The weaknesses of the study were that it was retrospective design and we could not specify the fracture risk. Based on the L1-L4 vertebral T-score, the effect of pioglitazone on bone tissue was assessed in the current study. As well as with bone mineral density, evaluating the risk of fracture as a clinical outcome may be beneficial.

Pioglitazone, especially together with metformin, are antidiabetic agents that have valuable effects in reducing insulin resistance in the treatment of DM. However, in the decision-making process of pioglitazone use and in the follow-up of pioglitazone use, measurement of bone mineral density may be useful, especially in patients using pioglitazone for >2 years, and may be a clinical laboratory parameter that warns against the risk of fractures that may occur in the future.

CONCLUSION

Although pioglitazone remains a valuable choice for managing DM and insulin resistance, its potential effects on bone metabolism warrant careful monitoring during long-term use. Regular measurement of bone mineral density, particularly in patients using pioglitazone for >2 years, may help to identify increased fracture risks.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ümraniye Training and Research Hospital Clinical Researches Ethics Committee (Date: 27.12.2012, Decision No: 20149/2012).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Green A, Hede SM, Patterson CC, et al. Type 1 diabetes in. 2017: global estimates of incident and prevalent cases in children and adults. *Diabetologia.* 2021;64(12):2741-2750.
2. Xu G, Liu B, Sun Y, et al. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in. 2016 and. 2017: population based study. *BMJ (Clinical research ed).* 2018;362:k1497.
3. Merlotti D, Gennari L, Dotta F, et al. Mechanisms of impaired bone strength in type 1 and 2 diabetes. *Nutr Metab Cardiovasc Dis.* 2010;20(9):683-690.
4. Karjalainen J, Knip M, Hyoty H, et al. Relationship between serum insulin autoantibodies, islet cell antibodies and Coxsackie-B4 and mumps virus-specific antibodies at the clinical manifestation of type 1 (insulin-dependent) diabetes. *Diabetologia.* 1988;31 (3):146-152.

5. Brown SA, Sharpless JL. Osteoporosis: an under-appreciated complication of diabetes. *Clinical Diabetes.* 2004;22 (1):10-20.
6. Collino M, Aragno M, Castiglia S, et al. Pioglitazone improves lipid and insulin levels in overweight rats on a high cholesterol and fructose diet by decreasing hepatic inflammation. *Br J Pharmacol.* 2010;160(8):1892-1902.
7. Igarashi M, Hirata A, Yamaguchi H, et al. Pioglitazone reduces atherogenic outcomes in type 2 diabetic patients. *J Atheroscler Thromb.* 2008;15(1):34-40.
8. Richter B, Bandeira-Echtler E, Bergerhoff K, et al. Pioglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2006;2006(4):CD006060.
9. Stunes AK, Westbroek I, Gustafsson BI, et al. The peroxisome proliferator-activated receptor (PPAR) alpha agonist fenofibrate maintains bone mass, while the PPAR gamma agonist pioglitazone exaggerates bone loss, in ovariectomized rats. *BMC Endocr Disord.* 2011;11:11.
10. Lecka-Czernik B. Bone loss in diabetes:use of antidiabetic thiazolidinediones and secondary osteoporosis. *Curr Osteoporos Rep.* 2010;8(4):178-184.
11. Takano M, Otsuka F, Matsumoto Y, et al. Peroxisome proliferator-activated receptor activity is involved in the osteoblastic differentiation regulated by bone morphogenetic proteins and tumor necrosis factor-alpha. *Mol Cell Endocrinol.* 2012;348(1):224-232.
12. Epstein M, Bakris G. Newer approaches to antihypertensive therapy. Use of fixed-dose combination therapy. *Arch Intern Med.* 1996;156(17):1969-1978.
13. Meymeh RH, Wooltorton E. Diabetes drug pioglitazone (Actos): risk of fracture. *CMAJ.* 2007;177(7):723-724.
14. Kanazawa I, Yamaguchi T, Yano S, et al. Baseline atherosclerosis parameter could assess the risk of bone loss during pioglitazone treatment in type 2 diabetes mellitus. *Osteoporos Int.* 2010;21(12):2013-2018.
15. Schwartz AV, Sellmeyer DE, Vittinghoff E, et al. Thiazolidinedione use and bone loss in older diabetic adults. *J Clin Endocrinol Metab.* 2006;91(9):3349-3354.
16. Sottile V, Seuwen K, Kneissel M. Enhanced marrow adipogenesis and bone resorption in estrogen-deprived rats treated with the PPARgamma agonist BRL49653 (rosiglitazone). *Calcif Tissue Int.* 2004;75(4):329-337.
17. Janghorbani M, Van Dam RM, Willett WC, et al. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol.* 2007;166(5):495-505.
18. Yamamoto M, Yamaguchi T, Yamauchi M, et al. Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications. *J Bone Miner Res.* 2009;24(4):702-709.
19. Huang S, Kaw M, Harris MT, et al. Decreased osteoclastogenesis and high bone mass in mice with impaired insulin clearance due to liver-specific inactivation to CEACAM1. *Bone.* 2010;46(4):1138-1145.
20. Krakauer JC, McKenna MJ, Buderer NF, et al. Bone loss and bone turnover in diabetes. *Diabetes.* 1995;44(7):775-782.