Research & Reviews: Journal of Medical and Health Sciences ISSN: 2319-9865

The Effect of Pioglitazone Versus Metformin on Bone Minerals Density (BMD) in Patients with Type 2 Diabetic Mellitus

Fadwa Ghassan*, Zainab Mohammed Abdulwahab

Department of Endocrinology, University of Tehran, Tehran, Iran

Review Article

Received: 29-Aug-2023, Manuscript No. JMAHS-23-111648; **Editor assigned:** 01-Sept-2023, Pre QC No. JMAHS-23-111648 (PQ); **Reviewed:** 15-Sept-2023, QC No. JMAHS-23-111648; **Revised:** 13-January-2025, Manuscript No. JMAHS-23-111648 (R); **Published:** 20-January-2025, DOI: 10.4172/2319-9865.14.1.002

***For Correspondence:** Fadwa Ghassan, Department of Endocrinology, University of Tehran, Tehran, Iran;
Email: fadwa.g.hameed@uoalkitab.edu.iq

Citation: Ghassan F, et al. The Effect of Pioglitazone Versus Metformin on Bone Minerals Density (BMD) in Patients with Type 2 Diabetic Mellitus. RRJ Med Health Sci. 2025;14:002.

ABSTRACT

Background: More than 9 million osteoporotic fractures are recorded annually worldwide. Osteoporosis is a significant contributor to morbidity and lost life years globally. A substantial number of studies examined the association between type 2 DM and fracture risk. The prevention of fractures is an important goal for studies concerning older adults.

Aim: To assess the effect of pioglitazone and metformin on bone minerals density among the patients with diabetic mellitus type 2.

Methodology: A comparative study was carried out from 06 December 2021 to 01 June 2022. A probability sample (50) was selected. The data were collected through the application of a validated questionnaire, in the parts, the first part was related to social and demographic data, and the second part was about medication and bone scan.

Results: Most of patients were in age group (51-65) and constitute (48%) most of them were females (88%). The results show that (60%) of patients have severe obesity. This finding shows that the effect of pioglitazone on bone minerals density in patients with DM were high. Metformin shows moderate impact on bones minerals in DM patients and constitutes (38%) of total samples.

Conclusion: The study concluded that the age group (51-65 years) is more prone to bone fractures and resorption of its density. BMI has an effect on bone, especially for patients with type 2 diabetes. Most of the samples were women, and their diagnosis of diabetes was known in less than 5 years.

Keywords: Obesity; Diabetes mellitus; Piglitazone; BMI; Osteoporosis

INTRODUCTION

Osteoporosis is a prevalent, chronic metabolic condition that affects over 200 million people around the world. Diabetes Mellitus (DM) patients have a 4-5 times increased risk of osteoporosis than non-diabetic patients. Genetic predisposition, age >50 years, a sedentary lifestyle, smoking, chronic alcohol consumption, and the use of drugs such as corticosteroids and proton pump inhibitors are all risk factors for diabetes-induced osteoporosis diabetes is a widespread disease that affects the majority of the world's populations [1]. Diabetes is characterized by excessive levels of circulating glucose and leads to most microvascular and macrovascular complications such as retinopathy, nephropathy, neuropathy, stroke, and myocardial infarction [2]. Patients with Type 2 Diabetic Mellitus (T2DM) have a higher risk of fragility fractures. Increased oxidative stress, inflammation, and medicines given to diabetic patients are all factors that increase the risk of fracture in diabetic individuals [3]. Pioglitazone is a commonly used and effective medicine for treatment of hyperglycemia in people with Type 2 diabetes and it may also have metabolic benefits [4]. Increased bone marrow obesity, decreased osteoblast activity, or reduced aromatase activity, all of which lead to altered estrogen production and increased bone resorption are possible effects of pioglitazone. Metformin is an effective hypoglycemic, can modulate different Points of Cancer, Polycystic Ovarian Syndrome (PCOS), cardiovascular disease, TB, and nerve regeneration. Metformin's impact on bone metabolism has been studied [5]. Metformin's intracellular absorption and effect on complex I of the respiratory chain of mitochondria is facilitated by Organic Cation Transporters (OCT1), a polyspecific cell membrane of the Solute Carrier 22A (*SLC22A*) gene family [6]. The insulin sensitizer metformin has been demonstrated to increase osteoblast proliferation and differentiation. Clinical data suggest that treating patients who have type 2 diabetes with pioglitazone has detrimental effects on bone health, as seen by lower bone mineral density and higher fracture rates [7]. Data from human studies support the idea that pioglitazone-induced bone alterations are caused by decreased osteoblast function [8].
Regional Dual Energy X-ray Absorptiometry (DXA) scans of the hip and spine are more commonly utilized in clinical practice to screen for bone loss than total body BMD scans [9].

Aim of the study

Bone is an important target organ subject to diabetic complications, and there is increasing evidence of a link between diabetes and osteoporosis [10]. Type 1 diabetes is an important secondary cause of osteoporosis and is characterized by lower bone mass and higher fracture than those observed in the healthy population [11]. In patients with Type 2 Diabetes Mellitus (T2DM), the Bone Mineral Density (BMD) of the lumbar spine and hip was found to be normal or even higher than that of healthy subjects, and the results were consistent even after adjusting for age, sex, ethnicity, and body mass index [12]. However, the risk of fragility fractures is higher in patients with T2DM [13]. An increased risk of fracture in patients with T2DM is associated with the duration of diabetes, the presence of diabetes complications, the type of antidiabetic medication, or frequent falls. In the women's health initiative observational study, women with T2DM were at increased risk for fractures despite BMD being increased; this result remained consistent even after adjustment for multiple risk factors for fracture. Pioglitazone/metformin Fixed-Dose Combination (FDC) therapy demonstrated additive efficacy in glucose-lowering, with no additive adverse event rate compared with the placebo or between single drugs; however, in practice, it is more common to combine multiple antidiabetic agents with different mechanisms to lower blood glucose than to administer a single agent [14]. Moreover, data on the effects of gemigliptin and empagliflozin on bone metabolism in real practice are limited [15]. The use of pioglitazone is reported to be associated with an increased frequency of fractures [16]. In this observational study, we compared the effects of pioglitazone and metformin on bone metabolism in patients with type 2 diabetes mellitus [17].

Statement of the problem

The effects of pioglitazone versus metformin on Bone Mineral Density (BMD) in patients with type 2 diabetes mellitus [18].

Questions of the study

- Did the pioglitazone more effective on bone in diabetic patients?
- Did the metformin have low effect on bones in diabetic patients?
- Did Type 2 Diabetes Mellitus (T2DM) have an increased risk of fractures?

Objectives of the study

- To find out the effect of metformin/pioglitazone on the bone mineral density of patients with type 2 diabetes.
- To assess the extent, the severity between metformin and pioglitazone medications.

LITERATURE REVIEW

Type 2 Diabetes Mellitus (DM) is a common metabolic disease with an increasing worldwide prevalence rate of 8.3%. Considering that more than 9 million osteoporotic fractures are recorded annually worldwide [19], osteoporosis is a significant contributor to morbidity and lost life years globally. Osteoporosis and type 2 DM share many common characteristics in that they are both chronic diseases with an increasingly global medical burden [20]. Bone fragility results from decreased bone mineral mass and alterations in bone microstructure. Multiple mechanisms can contribute to increased fractures in type 2 DM patients. Glucose toxicity, lack of insulin and other factors affects bone metabolism. A substantial number of studies examined the association between type 2 DM and fracture risk. Longer type 2 DM duration increases diabetic complications, insulin usage, and fracture risk and results in inadequate glucose control. Clinically, assessing the bone microstructure of type 2 DM patients is difficult because CT or MRI should be used. Therefore, determining the BMD is the best approach for now. The prevention of fractures is an important goal for studies concerning older adults. Many studies focus on osteoporosis in women. However, as many as one in four men aged >50 years will develop at least one osteoporosis-related fracture in his lifetime, highlighting the need for more studies on osteoporosis in men. It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. It is estimated that 439 million people would have type 2 DM by the year 2030. The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors. Type 2 Diabetes Mellitus (T2DM) accounts for around 90% of all cases of diabetes. In T2DM, the response to insulin is diminished, and this is defined as insulin resistance. During this state, insulin is ineffective and is initially countered by an increase in insulin production to maintain glucose homeostasis, but over time, insulin production decreases, resulting in T2DM. T2DM is most commonly seen in persons older than 45 years. Still, it is increasingly seen in children, adolescents, and younger adults due to rising levels of obesity, physical inactivity, and energy dense diets. T2DM is an insulin-resistance condition with associated beta-cell dysfunction. Initially, there is a compensatory increase in insulin secretion, which maintains glucose levels in the normal range. As the disease progresses, beta cells change, and insulin secretion is unable to maintain glucose homeostasis, producing hyperglycemia.

Most of the patients with T2DM are obese or have a higher body fat percentage, distributed predominantly in the abdominal region. This adipose tissue itself promotes insulin resistance through various inflammatory mechanisms, including increased Free Fatty Acid (FFA) release and adipocyte dysregulation. Lack of physical activity, prior Gestational Diabetic Mellitus (GDM) in those with hypertension or dyslipidemia also increases the risk of developing T2DM. Evolving data suggest a role for adipocyte dysregulation, inflammation, abnormal incretin biology with decreased incretins such as Glucagon-Like Peptide-1 (GLP-I) or incretin resistance, hyperglucagonemia, increased renal glucose reabsorption, and abnormalities in gut microbiota. Factors that may increase your risk of type 2 diabetes include: Weight, fat distribution, inactivity, family history, race and ethnicity, blood lipid levels, age, prediabetes, pregnancy-related risks, polycystic ovary syndrom, areas of darkened skin, usually in the armpits and neck. Pioglitazone also called thiazolidinedione's" it can be managing type 2 diabetes can help with glycemic control and insulin resistance. There are two thiazolidinedione's, rosiglitazone, and pioglitazone, currently approved by the FDA as monotherapy or combined with metformin or sulfonylureas to manage type 2 diabetes mellitus. These medications should be in conjunction with lifestyle modifications such as diet, exercise, and weight reduction. Thiazolidinedione's may also be used to treat polycystic ovarian syndrome, as these may lead to improved endothelial function, improved ovulation, and reduction of insulin resistance. Pioglitazone specifically reduces hepatic fat and may improve liver fibrosis in patients with Nonalcoholic Steatohepatitis (NASH); however, additional variables and risks require assessment in NASH patients. Thiazolidinediones (TZDs) are insulin sensitizers that act on intracellular metabolic pathways to enhance insulin action and increase insulin sensitivity in critical tissues (Yamanouchi. 2010). TZDs also increase adiponectin levels, decrease hepatic gluconeogenesis, and increase insulin-dependent glucose uptake in muscle and fat. TZDs function by regulating gene expression through binding to peroxisome Proliferator-Activated Receptor-gamma (PPAR-gamma), a nuclear transcription regulator. Peroxisome Proliferator-Activated Receptors (PPARs) are a family of ligand-activated transcription factors of nuclear hormone receptors that regulate energy homeostasis. In addition to their function

in glycemic control and improvement of insulin resistance, TZDs potentially have anti-inflammatory and anti-cancer properties. Metformin, FDA-approved in 1994, is an antidiabetic agent used in type 2 diabetes mellitus. Metformin comes in both immediate-release and extendedrelease and is available in several combination products with other antidiabetic agents. Metformin is often used as monotherapy or in combination when diet and exercise are not effective at lowering hyperglycemia. If the A1c is greater than 9%, then metformin is recommended in combination therapy. Metformin is a biguanide drug that reduces blood glucose levels by decreasing glucose production in the liver, decreasing intestinal absorption, and increasing insulin sensitivity. Metformin decreases both basal and postprandial blood glucose levels. In PCOS, Metformin decreases insulin levels, which then decreases luteinizing hormone and androgen levels.

Thus acting to normalize the menstruation cycle. In gestational diabetes, metformin is recommended as an alternative to insulin. Hyperglycaemia is associated with congenital malformations. Therefore, metformin works to decrease blood glucose during pregnancy. Metformin is considered weight neutral with the potential for modest weight loss. It is also unlikely to cause hypoglycaemia and may be potentially cardio protective. The onset of metformin is about 3 hours after taking the medication with a half-life of 20 hours. Metformin is not metabolized in the liver, nor does it have substantial protein binding. Metformin is renally eliminated, mostly unchanged. Multiple studies have noted that patients with T2DM are at increased risk of bone fractures. The reasons remain incompletely understood and are the result of a complex interaction between insulin resistance, diabetes and multiple factors leading to bone fragility. Patients with T2DM are often obese which further complicates the matter as it leads to increased Bone Mineral Density (BMD) but an underestimation about their true fracture risk reported from their reported greater bone fragility. Treatment of T2DM with pioglitazone is associated with broad effects not only on glucose and lipid metabolism, but also on bone formation (as well as resorption) altering the biology of mesenchymal stem cell differentiation into osteoblasts, adipocytes and chondrocytes. However, there is still significant controversy surrounding the effect of pioglitazone on bone turnover and fracture risk. Early studies with pioglitazone in patients with T2DM reported an increase in fracture risk restricted to women. Metformin, a wide spectrum of efficacy, safety hypoglycemic agents, was introduced as a medication for Type 2 Diabetes (T2D) in 1957. The effect of metformin on bone metabolism in humans has been studied. A multicenter study showed metformin treatment may decrease fasting bone turnover markers representing bone resorption, suggesting that metformin may have beneficial effects on bones in diabetic patients. Metformin also decreased the fracture rate in patients *in vivo* and promoted the osteogenesis of osteoblasts in culture. Moreover, a lot of data showed a long-term protective effect of metformin in bone metabolism of diabetic or prediabetic patients. Diabetes mellitus is manifested with abnormal Bone Mineral Density (BMD), hyperglycemia, secondary calcium imbalance, disturbances in vitamin D, microvascular disease, and an increased risk of fall. With a high morbidity and mortality, it also adversely affects bone metabolism and increases the fracture risk. Hyperglycemia also disrupts the production of Reaction Oxygen Spices (ROS) and Advance Glycation End-products (AGE), which affects cell death processes. Several studies have reported that metformin has a potential osteogenic effect by promoting the differentiation of preosteoblasts and MSCs.

METHODOLOGY

Design of the study

A comparative design of the studies effect of pioglitazone and metformin on bone minerals density in diabetic patient with type 2 at Kirkuk city from 06 December 2021 to 01 June 2022. Setting of the study. The study was conducted to evaluate the effect of pioglitazone and metformin on bone minerals density in diabetic patient with type 2 at Azadi teaching hospital (diabetic clinic ward). The sample is selected is an unambiguous sample consisting of (50) all samples collected from Azadi teaching hospital. The data collection educators shall be submitted by distributing a questionnaire on patients in English for the purpose of the study. The questionnaire is made up of 2 parts covered with social and demographic data to identify the patients with medication demographic social data demographic data containing this part (age, gender, date of diagnose, family history etc.). Effect of medication on patients diabetic mellitus type 2 and contain (2 items). Data have been collected throughout the face-to-face interview for the present study. The data was collected during the period of (03 January 2022 to 03 March 2022).

Descriptive statistical data analysis

Analysis of statistical data through application of descriptive statistical data analysis approaches have been prepared in the computer file and apply this policy in the following:
1_ frequencies% x 100 sample size Frequencies 2_ percentage.

RESULTS

This chapter presents the statistical analysis for the data collected during the study period (Table 1).

Table 1. Distribution of the socio-demographic characteristic of the study sample (No=50).

Socio-demographic data	Variables	Frequency	Percentage
Age groups	20-35	3	6.0
	36-50	10	20.0
	51-65	24	48.0
	66-80	11	22.0
	81 and above	2	4.0
Gender	Male	6	12.0
	Female	44	88.0
Date of diagnosis with diabetic	1-5 y	21	42.0
	6-10 y	11	22.0
	11-15 y	13	26.0
	16-20 y	5	10.0
Family history	No	39	78.0
	Yes	11	22.0
Sedentary lifestyle	Irregular	30	60.0
	Regular	20	40.0
Obesity	Yes	32	64.0
	No	18	36.0
Height of patient	Less than 150 cm	6	12.0
	150-170 cm	40	80.0
	171-190 cm	4	8.0
Weight of patient	Less than 50 kg	3	6.0
	50-60 kg	3	6.0
	61-70 kg	13	26.0
	71-80 kg	13	26.0
	81-90 kg	15	30.0
	91-100 kg	3	6.0
BMI	18.5 and lower	0	0.0
	18.6 - <25	6	12.0
	25.0 - <30	14	28.0
	30 and higher	30	60.0

Table 1 shows that most of patients were in age group (51-65) years and constitute (48%) most of them were females (88%), regarding the period of diagnosis with diabetic, the results indicate (42%) of patients discover their disease between

(1-5) years (78%) of them won't have a family history with diabetic, in sedentary life style (60%) of them have irregular lifestyle, (64%) complaining from being obesity, (80%) of them were ranged (150-170) cm, and (30%) have 81-90 kg of weight. In body mass indexes the results show (60%) of patients have severe obesity (Tables 2 and 3).

Table 2. Demonstrate of medication use in diabetic patients (N=50).

Character	Type of medication	Frequency f	Percentage %
Medication	Metformin	30	60.0
	Pioglitazone	20	40.0
	Total	50	100%

Table 2 shows that (60%) pf patients uses metformin and (20%) of them uses pioglitazone.

Table 3: Demonstrate of DXA scan in diabetic patients with bone minerals density (N=50).

Character	Type of DXA scan	Frequency f	Percentage %
Bone minerals density	Osteoporosis	24	48.0
	Osteopenia	19	38.0
	Normal	7	14.0
	Total	50	100%

The Table 3 shows that most of cases have osteoporosis and constitute (48%).

The Table 4 shows that the effect of pioglitazone on bone minerals density in patients with diabetic mellitus were high and most of them have osteoporosis constitute (40%), while metformin shows moderate impact on bones minerals in diabetic mellitus patients and constitute (38%) of total samples.

Table 4: Comparison of DXA scan between metformin and pioglitazone in diabetic patients with bone minerals density (N=50).

Medication	DXA scan regarding bone minerals density				
	Test type	Not effect (1 to -1)	Moderate effect (-1.1 to -2.4)	High effect (-2.5 and below)	Total
		F (%)	F (%)	F (%)	F (%)
Pioglitazone	Normal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Osteopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Osteoporosis	0 (0.0)	0 (0.0)	20 (40.0)	20 (40.0)
Metformin	Normal	7 (14.0)	0 (0.0)	0 (0.0)	7 (14.0)
	Osteopenia	0 (0.0)	19 (38.0)	0 (0.0)	19 (32.0)
	Osteoporosis	0 (0.0)	0 (0.0)	4 (8.0)	4 (8.0)
	Total	7 (14.0)	19 (38.0)	24 (48.0)	50 (100.0)

DISCUSSION

Regarding socio-demographic data, The results of current study indicate that (48%) of patients were in age group (51-65) years, the study in line with Kim who indicate that most of patients were ranged between (50-65) years and constitute of (50%), regarding to gender 88% of patients were female, our finding agree with Ljunggren who indicate that most of bone problems comes early in women's and constitute (82%), in the period of diagnosis with diabetic the results indicate that (42%) discover their disease within (1-5) years , our finding agree with Matthews who indicate that most of patients early

discover their disease with the first five years and constitute (40%). During the family history (78%) of patients have no family history with DM-T2, our finding disagrees with Benvenuti who indicate that (66%) of patients have a family history with the disease, regarding the sedentary lifestyle (30%) have Irregular lifestyle, our finding agrees with Global burden of diabetes. It indicates bone pain and diabetic mellitus can lower the quality of life and make irregular lifestyle. Regarding obesity (64%) of patients suffering from obesity, the results of our finding agree with Lyznicki they indicate that (62%) of patients complaining from obesity. The study indicated that most patients have a height between (150-170) cm, the current study agrees with Krawczynski where they indicated that most patients have an average height of 150 cm. The study indicated that 1/3 of the patients had a weight ranging between 81-90 kg. The current study agrees with Angotti where it indicated that 34% of patients suffer from bone and joint pain due to excess weight. The current study indicated that 60% of patients have a very high body mass index compared to the lower age groups. The current study does not agree with as it indicated that 66% of patients follow the keto diet and intermittent fasting to reduce excess weight gain and maintain a healthy health system. The results indicate that most of patients were Non-smokers and constitute (95%), Our finding agree with Fiore who indicate that (98%) of patients avoid smoking because the damage of it cause in the future.

The results of current study indicate that (60%) prefer metformin and (40%) use pioglitazone drug to treat DM-T2. Most of the evidence for skeletal harm of TZDs comes from studies of rosiglitazone. Although both clinically available TZDs improve insulin sensitivity and glycemic control, there may be differences between the drugs in their effects on other tissues, results suggest that pioglitazone, administered at a dose frequently used in clinical practice, has small effects on bone turnover and BMD. Risk of osteoporosis is increased with the development of type 2 diabetes. Osteoporosis may occur in patients with type 2 diabetes for a variety of reasons. First, type 2 diabetes makes blood glucose higher than normal for a long time, which means a large amount of glucose is excreted in the urine, and islet function is influenced gradually. Furthermore, a large amount of calcium and phosphate ions in serum is excreted out of the body by osmotic diuretics. In that, the decreased blood calcium and phosphate concentrations may lead to osteocyte dysfunction. Second, the poor blood glucose control may cause accumulation of glycosyl compound that may further promote oxidative stress and then lead to osteopenia and myelosuppression. All of this may have adverse effects on osteoblast and bone formation. In another way, physical activity is not low in elderly male patients. Microstructure impairment at subchondral bone is more likely to occur resulting from bone disorders where the bone remodeling process occurs too frequently. This increases the possibility of fracture. The results of current finding indicate that (48%) of total samples were infected with osteoporosis and less common of patients were have osteopenia and constitute (38%) while the study indicate that (14%) of samples were have normal effect of medication on the bone. Patients with T2DM already have an increased risk for fractures. Paradoxically, risk fracture assessment in T2DM is difficult as diabetes is associated with a higher bone density (possibly due to obesity) which often may mislead standard bone density risk fracture prediction models. In this context, TZDs have been at center stage as agents with potential to increase fracture rate in patients with T2DM factors often at play also in patients with NASH. The ADOPT trial triggered such debate when rosiglitazone was reported to increase the risk of fractures in women, but not in men. Controlled studies carried out after ADOPT with rosiglitazone, either small trials exclusively in female populations or larger RCTs appeared to confirm the association of bone loss only in females. Takeda Pharmaceuticals Inc. (manufacturer of pioglitazone) reported from its database of prospective RCTs that pioglitazone also increased only in females the risk of fracture in upper and distal lower limbs. Among several relatively small RCTs that have attempted to follow-up and address this issue, results have beensomewhat more discordant with pioglitazone than with rosiglitazone. In a RCT of 16-week duration in women with polycystic ovary syndrome, Glintborg et al., observed a decrease in lumbar and total hip BMD with pioglitazone. In contrast, Bone et al., reported no significant changes in bone density or bone turnover in 156 postmenopausal women treated with pioglitazone 45 mg per day for 12 months. Metformin as the first-line treatment for type 2 diabetes shows good efficacy in lowering blood glucose. Meanwhile, it greatly improves BMD in patients with type 2 diabetes. In other hand Metformin can promote the osteogenic differentiation and mineralization of induced mesenchymal stem cells, which are derived from pluripotent stem cell and can differentiate into many cell types such as adipocytes, osteoblasts and chondrocytes. Its effect on differentiation can be regulated by cellular transcription factors. Several animal experiments reported that metformin may enhance and induce osteogenic differentiation of mesenchymal stem cells. *In vitro* studies revealed that metformin may increase type I collagen synthesis, alkaline phosphatase activity, extracellular calcium deposition and osteocalcin synthesis and may repair bone lesions with diabetes.

The results of current finding indicate that (40%) of patients have osteoporosis during take the pioglitazone medication and (14%) of patients shown a normal score of dxa scan during take metformin, (38%) of patients suffering from osteopenia

during take the drug and only (8%) have osteoporosis during take metformin drug. Previously, a lot of clinical and preclinical researches have revealed that pioglitazone decreases trabecular bone volume, Bone Mineral Density (BMD), and Bone Marrow Cells (BMC). Therefore, it seems that this antidiabetic medicine (and the other insulin-sensitizing TZDs) can increase bone resorption and decrease bone formation by inhibiting osteoblast differentiation specifically in post-menopausal women. Consistent with previous significant works, this *in vivo* animal study indicated that pioglitazone had such an effect on the BMD and trabecular bone volume, which is associated with elevation of bone resorption and reduction of bone formation. In other findings metformin can inhibit osteoclast differentiation and reduce the activity of C-terminal properties of type I collagen. Metformin's effect on bone metabolism is realized through several ways in patients with diabetes mellitus including activating the extracellular signal-regulated kinase and AMP-activated protein kinase signaling pathway, changing the expression of bone morphogenetic proteins and nitric oxide and influencing osteoblasts). When used at high doses, metformin can reduce blood glucose, inhibit advanced glycation end product deposition, relieve injuries to the thigh and induce the osteogenic differentiation. Similarly, the present study revealed that the relationship between osteoporosis and blood glucose levels should be taken into consideration in addition to usage of osteogenic promoting agents in the treatment of type 2 diabetes complicated with osteoporosis in elderly patients. In this way, the treatment efficacy will be improved greatly in these population.

CONCLUSION

The current study concluded that the age group (51-65)
years are more prone to bone fractures and resorption of its density. Most of the samples were women, and their knowledge of diabetes was diagnosed within less than 5 years. The study concluded that BMI has an effect on the bones, especially for patients with type 2 diabetes, most of whom have an irregular lifestyle. The current study concluded that the drug Pioglitazone affects the bones and the structure of bone tissue formation, in contrast to metformin, which improves the regulation of glucose levels and increases the density of bone tissue in the body.

RECOMMENDATIONS

In my opinion is that glycemic control remains the objective of treatment. Obesity may be managed as one of the major steps to early atherosclerosis and the assessment of fat tissue should be one of the outcomes for clinicians. Diabetic patients are often treated with multiple drugs, and may require a more practical and convenient therapeutic regimen, which can be provided by a fixed-dose combination. Side effects do not appear to be increased when a fixed dose is compared with monotherapy or other combination therapy, when drugs are administered according to manufacturers' advice.

Diabetic patients may require a more practical and convenient therapeutic regimen, which can be provided by a fixed-dose combination. Side effects may not appear to be increased when a fixed dose is compared with mono therapy or other combination therapy. Obesity may be managed as one of the major steps to early atherosclerosis and the assessment of fat tissue should be part of the outcome for clinicians.

REFERENCES

1. Cortizo M, et al. Osteogenic actions of the anti-diabetic drug metformin on osteoblasts in culture, Eur J Pharmacol. 2006;536:38–46. [Crossref] [Google Scholar] [PubMed]
2. American Diabetes Association. 8. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41:S73-S85. [Crossref] [Google Scholar] [PubMed]
3. Amin NB, et al. Dose-ranging efficacy and safety study of ertugliflozin, a sodium-glucose cotransporter 2 inhibitor, in patients with type 2 diabetes on a background of metformin. Diabetes Obes Metab. 2015;17:591–598. [Crossref] [Google Scholar] [PubMed]
4. Angotti CM, et al. Combined dietary and exercise intervention for control of serum cholesterol in the workplace. Am J Health Promot. 2011;15:9–16. [Crossref] [Google Scholar] [PubMed]
5. Benvenuti S, et al. Rosiglitazone stimulates adipogenesis and decreases osteoblastogenesis in human mesenchymal stem cells. J Endocrinol Invest. 2017;30:26-30. [Crossref] [Google Scholar] [PubMed]

6. Billington EO, et al. The effect of thiazolidinediones on bone mineral density and bone turnover: Systematic review and meta-analysis. Diabetologia 2015;58:2238-2246. [Crossref] [Google Scholar] [PubMed]
7. Blonde L, Dipp S, Cadena D. Combination Glucose-Lowering Therapy Plans in T2DM: Case-Based Considerations. Adv Ther. 2018;35(7):939-965. [Crossref] [Google Scholar] [PubMed]
8. Bonds DE, et al. Risk of fracture in women with type 2 diabetes: The women's health initiative observational study. J Clin Endocrinol Metab. 2006;91:3404-3410. [Crossref] [Google Scholar] [PubMed]
9. Bone HG, et al. Effects of pioglitazone on bone in postmenopausal women with impaired fasting glucose or impaired glucose tolerance: A randomized, double-blind, placebo-controlled study. J Clin Endocrinol Metab. 2013;98:4691-4701. [Crossref] [Google Scholar] [PubMed]
10. Bannister C, et al. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. Diabetes Obes Metab. 2014;16:1165–1173. [Crossref] [Google Scholar] [PubMed]
11. Chamnan P, et al. Incidence of type 2 diabetes using proposed HbA1c diagnostic criteria in the EPIC-Norflok cohort: Implication for preventive strategies. Diabetes Care. 2011;34:950-956. [Crossref] [Google Scholar] [PubMed]
12. Cusi K. Role of obesity and lipotoxicity in the development of nonalcoholic steatohepatitis: pathophysiology and clinical implications. Gastroenterology. 2012;142:711-725. [Crossref] [Google Scholar] [PubMed]
13. Daniels SR, et al. The utility of body mass index as a measure of body fatness in children and adolescents: differences by race and gender. Pediatrics. 2012;99:804–807. [Crossref] [Google Scholar] [PubMed]
14. DeFronzo RA, et al. The effect of insulin on renal sodium metabolism. A review with clinical implications. Diabetologia. 2011;21:165-171. [Crossref] [Google Scholar] [PubMed]
15. Dormandy J, et al. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: An overview of data from PROactive. Drug Saf. 2009;32:187-202. [Crossref] [Google Scholar] [PubMed]
16. Dormuth CR, et al. Thiazolidinediones and fractures in men and women. Arch Intern Med. 2009;169:1395-1402. [Crossref] [Google Scholar] [PubMed]
17. Du Q, et al. Comparative effects of sitagliptin and metformin in patients with type 2 diabetes mellitus: a meta-analysis. Curr Med Res Opin. 2013;29:1487-1494. [Crossref] [Google Scholar] [PubMed]
18. Losada E, et al. Real-world antidiabetic drug use and fracture risk in 12,277 patients with type 2 diabetes mellitus: A nested case-control study. Osteoporos Int. 2018;29:2079–2086. [Crossref] [Google Scholar] [PubMed]
19. Feng WH, et al. Effects of liraglutide, metformin and gliclazide on bodycomposition in patients with both type 2 diabetes and non-alcoholic fatty liver disease: A randomized trial. J Diabetes Investig. 2019;10:399-407. [Crossref] [Google Scholar] [PubMed]
20. Floyd JS, et al. Case series of liver failure associated with rosiglitazone and pioglitazone. Pharmacoepidemiol Drug Saf. 2009;18:1238-1243. [Crossref] [Google Scholar] [PubMed]