Effect of Diabetes Mellitus and Anti-Diabetic Drugs on Bone Health-A Review

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EFFECT OF DIABETES MELLITUS AND ANTI-DIABETIC DRUGS ON BONE HEALTH-A REVIEW

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ABSTRACT

Osteoporosis and diabetes mellitus (DM) are widespread diseases and have a significant health burden. Type-1 diabetes mellitus (T1DM) and Type-2 diabetes mellitus (T2DM) are associated with an increased bone fracture. In T1DM, the increased risk of bone fracture is associated with low bone mass. In patients with T2DM, the risk of fracture of the bone is increased due to low quality of bone, despite increased bone mineral density (BMD). In type 2 diabetic patients, bone fragility depends on the quality of bone instead of a reduction in bone mass. Thiazolidinediones (TZD) cause differentiation of adipocytes and inhibit differentiation of osteoblast and bone marrow stromal stem cells (BMSC). In this review, we have described the effect of anti-diabetic drugs and diabetes mellitus on bone health and our finding shows that sulfonylureas and metformin have no negative effect on bone health and protect bones against fractures.

Keywords: Osteoporosis, diabetes mellitus, adipocytes, sulfonylurea, metformin.

INTRODUCTION

Damage bone quality and expanded bone fracture chance have emerged as a diagnosed complication of diabetes mellitus (Zamarioli et al., 2020). The improved fracture threat in individuals dwelling with DM is compounded by using impaired fracture recovery. Specifically, alteration in bone metabolism and the improvement of the micro-vascular disorder can prolong recovery time (Hansen-Algenstaedt et al., 2006; Loder, 1988). Patients with T2DM have an elevated chance of osteoporotic fractures (Filardi et al., 2019; Kurra & Siris, 2011). Osteoporosis is a skeletal syndrome described by mutual bone power prompting a high threat fracture (Janghorbani et al., 2007). Many of these fractures are associated with vast morbidity and mortality. Currently, diabetes is also another disorder increasing at an alarming rate in an association of Covid-19, with good-sized related morbidity and mortality (Azar et al., 2020; Janghorbani et al., 2007).

Diabetes mellitus is a chronic disease characterized by a high level of glucose. But osteoporosis is a condition in which the density and quality of bone are deteriorating (Yamamoto et al., 2009). Both types of diabetes, T1DM, and T2DM are associated with fracture risk and osteoporosis (Botushanov & Orbetzova, 2009). According to IDF (International Diabetes Federation), it is estimated that DM affects 415 million people globally and this amount will increase to 642 M by 2040 year. Osteoporosis causes greater than 8.9M fractures annually, resulted that every 3 second, has osteoporotic fractures globally (Bommer et al., 2018).

Diabetic patients have different skeletal diseases, including osteoporosis or osteopenia, diabetic foot syndrome, and Charcot’s arthropathy (Schwartz, 2003). Mineral and bone abnormalities in diabetic patients are caused by the direct effect of deficiency or resistance of
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Insulin and hyperglycemia on bone marrow and bone microenvironment (Inzerillo et al., 2004). It may be caused by abnormal adipokine and cytokine production and their harmful effects on cells of bone and impaired skeletal or neuromuscular interactions (Leidig-Bruckner et al., 2001).

The disease treatment itself is difficult, because of both micro-vascular and macro-vascular complications like a coronary artery, stroke, peripheral vascular disease, and neuropathy. Interestingly, DM seems to affect the health of bone (Botolin & McCabe, 2007). There are many changes in T1DM and T2DM bones of diabetic patients regarding bone turnover, differentiation of stem cells, and bone strength that result in changed bone structure and bone mineral density. One outcome that is common to both diabetes types is that stem cells of mesenchyme in marrow show differentiation on the way of adipocytes compared with osteoblast (Botolin & McCabe, 2006).

This review presents an overview of factors involved in the risk of osteoporosis and fracture in diabetic patients. It also describes the effects of the antidiabetic drug on bone health. TIDM and T2DM show different effects on bone health either bone mass or quality of bone. Some anti-diabetic drugs decrease the fracture risk but some drugs increase the risk of bone fracture and have other kinds of side effects.

![Figure 1: Graphical presentation of review.](image)

**Osteoporosis**

Osteoporosis is characterized as a combination of diminished bone mass and modified bone quality with micro-architectural deformities, resulting in diminished bone quality with an expanded risk of cracks (Klibanski et al., 2001; Tang et al., 2017). Although the disorder generally has been accounted for the most part in white ladies, it can influence people of either sex including every ethnic group (Chau et al., 2003). Osteoporosis is not symptomatic until there is a bone rupture. Females are high at risk than males, developing osteoporosis due to changes in the hormone that occur at menopause and affect directly bone density. Estrogen, a female hormone is important for bone health. After menopause, estrogen levels decrease, and then it leads to a rapid fall in bone density (Keen & Reddivari, 2020).

One out of five ladies is not determined to have osteoporosis despite cracking. Any fracture continued between the ages of 20 and 50 years is related to a 74% expansion later on
the risk of cracks after the age of 50 years (Wu et al., 2002). Thus, the occurrence of osteoporosis is underestimated in those women who have minimum cracks are not assessed for bone fracture (Siris et al., 2001).

i. Frequency level

The most serious fractures in osteoporotic fractures are hip fractures. The mortality rate is high in hip fractures. It may result in mortality either indirectly, directly, mediated through comorbidities that are simply associated with fracture risk (Alegre-López et al., 2005). In certain patients groups, e.g those with a mental issue, the death rate has been accounted for to be greater than 50% (Cooper et al., 1993; Ferrari et al., 2016).

![Figure 2: Predictors of mortality following osteoporotic hip fractures (Tosteson et al., 2007).](image)(image)

The mortality of osteoporotic hip fractures can be predicted by different factors like pre-fracture health like comorbidities, physical function, mental function, age, sex, race, short-term mortality, and long-term mortality.

The prevalence of hip fracture is higher in women, but men have a high risk of death than women after a hip fracture (Teng, 2008). The mortality rate can be reduced by reducing the number of hip fractures and optimize post-fracture medical care. 22 million women and 5.5 million men in the twenty-seven countries of the European Union were estimated to have osteoporosis and 3.5 million new fragility cracks were sustained (Al Anouti et al., 2019; Svedbom et al., 2013) as shown in Figure 3.
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Figure 3: Types of fragility fractures.

There are different types of fragility fractures such as hip fractures, vertebral fractures, forearm fractures, and some others. But hip fractures are most common among these fractures.

ii. Risk Factors

There are many risk factors for cracks and osteoporosis. Some physical features take part in the occurrence of osteoporotic cracks. Bone strength is determined by the quality of bone mass and geometry (Fonseca et al., 2014; Wergedal et al., 2005). Bone mineral thickness (BMD) measured using dual X-ray beam absorptiometers (DXA) is the most widely recognized standard device for bone mass evaluation (Jannot et al., 2017). Despite the fact, DXA is the best indicator and evaluator of osteoporosis, however, it is not a good tool as there are numerous bone characteristics and bone geometries that are not detectable through DXA (Chau et al., 2003). Therefore, a comprehensive hazard assessment for osteoporosis should reach beyond BMD estimation. This is especially true when surveying patients with diabetes.

Diabetes

Diabetes is a set of metabolic disorder characterized by high glucose levels because of the flaw in insulin secretion, insulin activity, or both. The persistent high glucose level of diabetes is associated with long-time period damage, impairment, and failure of different organs (Ceriello et al., 2019).
Table 1: Osteoporosis risk factors.

| Modifiable                                                                 | Non-modifiable                                                                 |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Inadequate physical activity                                              | Dementia                                                                      |
| Estrogen and androgen deficiency                                           | History of cracks in the first-degree relative                               |
| Smoking                                                                    | White race                                                                    |
| Chronic condition (e.g., thyroid, cystic fibrosis, renal disease and diabetes) | Personal history of bone fracture as an adult                                |
| Excessive alcohol intake                                                  | Poor frailty                                                                  |
| Less calcium Intake                                                       | Female gender                                                                 |
| Less body weight                                                          | Advanced age                                                                  |
| Medication (e.g., vitamin A, steroids, hormones and anti-seizure)         |                                                                                |

Table 2: Frequency of diabetes and impaired glucose tolerance patients (Group, 2015).

|                  | Diabetes | Impaired glucose tolerance |
|------------------|----------|----------------------------|
| Recent patients  | 382 million | 316 million               |
| Future risk      | 592 million | 471 million               |

i. **Complication in Diabetes**

The impact of diabetes mellitus type 1 on bone cells and the bone network directly, in addition to diabetic problems happening in other body frameworks are significant in affecting crack risk. Neurologic, Ocular, cardiovascular and renal complications are resulting from DM that is linked with a higher than 10-fold elevated in the overall risk of cracks among both women and men (Ahmed et al., 2006; Beckman et al., 2002; Goldin et al., 2006). While cardiovascular, visual, and neurological confusions, similar to hypoglycemic appearance, increase chances of fractures by increasing the risk of falls, impacts of nephropathy might be interceded by disturbances in vitamin D and subsequently metabolism of parathyroid hormone (Giangregorio et al., 2012). Diabetic complications including nephropathy, neuropathy, cardiomyopathy, and retinopathy also harm the bone.

However, the turnover of bone and as a consequence, the integrity of skeletal may additionally be affected by diabetes, and diabetic bone disorder can constitute an ignored problem of diabetes (Bullon et al., 2014; Hamann et al., 2012).

ii. **High risk of fracture with higher BMD in T2DM**

It has been reported that non-diabetic people with a high level of bone mass density play a protective role against fractures, this relationship appears somewhat different in T2DM because in diabetic patient bone mass density is reduced and then it increases the risk of fracture (van Daele et al., 1995b). Patients with T2DM are at higher risk (69%) of non-vertebral cracks than the non-diabetic patient (De Liefde et al., 2005). The risk of hip fracture for Type 1 is 6.9 and that for type 2 is 1.4 than those without diabetes (Vestergaard, 2007). The risk of fracture is higher than T2DM for a given age and bone mineral density than those without diabetic patients (Bullon et al., 2014; Schwartz et al., 2001).

People with T2DM have a greater risk of fracture than those without T2DM (Wang et al., 2016). Bone strength also includes bone quality along with bone density and is often used as a measure of bone disorders associated with fractures. Numerous studies have shown that
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Mineral density (BMD) is not lower in patients with T2DM, and in fact, is higher than in non-T2DM people (Wang et al., 2019).

![Diagram of Late Complications of diabetes]

**Figure 4: Late Complications of diabetes.**

In the current study, diabetes is observed to be at an elevated level commonly found among individuals with the following factors; age, elevated body mass index or weight, decrease insulin level, less bodily exercise, higher alcohol uses, and they generally smoke increasingly more often. Also, the usage of diuretics is more not unusual in diabetes and specifically loop diuretics (for example, furosemide) can be associated with reduced bone mass density and expanded threat of cracks through elevated excretion of calcium in the urine and osteoclastic bone resorption (Ruiter et al., 2013), while less crack risk and elevated bone mass density are associated by thiazides (Aung & Htay, 2011). Further, the higher risk of fracture is due to usage of anti-diabetic (thiazolidinediones) has been reported (Habib et al., 2010; Liao et al., 2019).

Patients with DM fall more often, which may be a result of suffering from sarcopenia, neuropathy, suboptimal physical fitness, and retinopathy. Instead, patients using insulin with decrease level of HbA1C ranges are mentioned to fall more, probably on account of hypoglycemia (Schwartz et al., 2002b). These attributes may impact bone digestion and brake chance; by the by, factual examination with rectification in previously mentioned investigation purpose freedom of the distinction in Bone mass density and crack hazard from these deliberate confounders, e.g threats of falling (Kao et al., 2003; Schwartz et al., 2001).
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### iii. Osteoporosis and T1DM

The connection between osteoporosis and DM1 recognized decades prior has picked up considerably as of late. While various cell components have been hypothesized to intercede this affiliation, it is presently settled that imperfection in osteoblast separation and movement is the principal culprit of bone delicacy in type 1 diabetes mellitus. Other contributing variables incorporate an aggregation of the advanced glycation end product and the advancement of diabetes inconveniences, e.g hypoglycemia, and neuropathy, which bring about an additional decrease in bone mineral thickness, computing geometric properties inside the bone, and expanded fall chance. Subsequently, patients with DM1 have a 6.9-crease expanded frequency of hip crack contrasted with controls (Khan & Fraser, 2015).

Osteoporosis is the most widely recognized bone disorder, influencing an expected 200 million individuals around the world (Botushanov & Orbetzova, 2009). Approximately 30% of every postmenopausal lady is influenced and up to 40% will build up a delicacy crack inside their lifetime (van Daele et al., 1995a). After some time, various hazard factors have been related to osteoporosis and are valuable when utilized in screening instruments and treatment calculation (Janghorbani et al., 2007). Diabetes, although diagnosed more than a half-century in the past as being associated with bone frailty, has come to the forefront best inside the ultimate decades as a crucial osteoporosis chance factor (Schwartz et al., 2002a).

### iii. Bone Fragility with T1DM with the Pathophysiology

Bone renovating is reliant on an exact balance between bone formation, carried out by osteoblast, and bone formation brought about by osteoclasts (Weivoda et al., 2020). This equalization is directed by a bunch of molecular signs. Interruption in any of these molecular pathways can disturb the balance of bone turnover and thereby influence bone quality. Various changes in cell, mini-architectural and humoral elements associated with bone renovating have been recognized in the setting of DM1 (Khan & Fraser, 2015).

**Bone Formation (Osteoblast)**

Impeded osteoblastic action and separation are fundamental deep down delicacy found in a patient with type 1 diabetes. Initial hints highlighting this was recognized in the pediatric investigation which reliably exhibited a decline in bone development marker carboxy-terminal PICP (propeptide of type 1 collagen) among kids with T1DM (Gunczler et al., 1998).

Rat models gave further bits of knowledge into the molecular premise basic this imperfection and proposed that T1DM influences osteoblast work, yet additionally regulates numerous means long the osteoblast separation pathway in the bone marrow. Studies utilizing the streptozotocin actuated rodent model of T1DM demonstrated that this separation imperfection begins at the SC (stem cell) level with a decrease in both the all outnumber of mesenchymal SC just as osteoblast progenitor cells. These progressions were seen as at any rate incompletely, interceded by an expansion in apoptosis of the mesenchymal SC (Stolzing et al., 2010).

Ongoing investigation strengthens these discoveries and shows that ESCs (early-stage stem cell) developing in a high grouping of glucose have diminished potential for self-reestablishment as appeared by an abatement in the number of states of undifferentiated cells contrasted with immature microorganism developed in physiologic glucose concentration (Dienelt & zur Nieden, 2011). This concludes that some portion of the osteoblast shortfall among T1DM is intervened by an inability to keep up pluripotent SC for osteoblast separation (Bredella et al., 2012).
i. **Bone Resorption (Osteoclasts)**

Unlike, DM1 impacts osteoblasts; the role of diabetes mellitus type 1 in mediating osteoclast function has been merged. In vitro, the investigation showed diminished osteoclast action as estimated by TRAP (Tartrate resistant alkaline phosphatase) in ESC developed in high glucose level versus corporal culture media (Dienelt & zur Nieden, 2011). Conversely, osteoclasts from diabetes mellitus type 1 mice, regardless f their little size, exhibited expanded bone resorption in light of the expansion of RANK-L (receptor activator of nuclear factor kappa-B ligand) and M-CSF (macrophage colony-stimulating factor) (Catalfamo et al., 2013).

The osteoprotegerin (OPG) level, a soluble receptor of RANK-L which adversely manages osteoclast separation, were seen as decreased in an animal model of type 1 DM, prompting expanded bone resorption (J. A. F. Silva et al., 2012). Curiously, this expanded osteoclast activity was not found in animal examines where untreated type 1 diabetes mellitus rodents (rats) had a diminished number of osteoclasts at the femoral neck locale contrasted with non-diabetic controls, a discovering corresponded with diminished bone quality at this site in these rodents (Hou et al., 1993). This purposes that bone delicacy in these animal models may either be mainly interceded by diminished osteoblast action or be optional to proceeded with the aggregation of minor bone injury because of decreased osteoclast movement. These outcomes have been imitated in other animals indicating no change or even decrease in bone resorption following stimulation of diabetes (Motyl et al., 2009). Human investigation assessing the impacts of diabetes on the marker of bone resorption have been blended with both an expansion and a reduction revealed in various examination among people with diabetes mellitus 1 (Maggio¹ et al., 2010). Given the reliable information concerning impaired osteoblast separation and its DM1 function, osteoblast plays a major role to determine the phenotype of bone.

ii. **Osteocytes**

Osteocyte strength has the potential for the care and reliability of bone. Osteocytes involve more prominent than 90-95% of every bone cell. They are the standard methenolone sensor, and through a broad system of canaliculi, intently manage bone remodeling (Bonewald & Johnson, 2008). Osteocytes have been found to assume a significant role in adjusting the bone delicacy in diabetes mellitus 1 (DM1). In the early hours, histomorphometric examination recognized a decrease in the marker of osteocytes action remembering a decrease for all-out osteocytes density and lacunar density in a DM1 rodent model (Villarino et al., 2006). These outcomes were imitated in an examination that exhibited are reduction in the number of osteocytes, in any event somewhat because of expanded apoptosis, with DM1 in mice contrasted with non-diabetic control. As the osteocytes only secrete sclerostin, the negative controller of WSP (Wnt signaling pathway) basics for osteoblast separation, it has been proposed that sclerostin may have a key role in forming bone quality in diabetes mellitus. Not like, reports of expanded sclerostin movement repressing the Wnt pathway in diabetes mellitus 1 rodent, a murine report indicated a reduction in its action in mice with DM1 (Portal-Núñez et al., 2010).

In people, information from focus cross-sectional investigation demonstrated that expanded sclerostin levels among people with diabetes mellitus (DM2), with just a pattern towards an expansion among more youthful, yet not more older patients with DM1 contrasted with non-diabetic controls (Gennari et al., 2012). Communally, these discoveries recommend that DM1 may influence the Wnt pathway and consequently osteoblast differentiation at
numerous levels including osteocytes-osteoblast communication, further investigation is expected to explain the role of sclerostin in regulating these impacts.

### iii. Bone Matrix

Besides, affecting the cell associated with remodeling of bone, DM1 additionally influences the matrix of bone, thereby bone quality is modulated (Khan & Fraser, 2015). These impacts are intervened by AGEs (advance glycation ends) products, which are generated because of non-enzymatically glycosylation of lipids or protein and are concerned in the various complication of diabetes, bone fragility is also included (Goldin et al., 2006). Proof for this was furnished by an investigation in rodents with DM1 which indicated an expansion in the non-enzymatic cross-connecting in diabetic rodents contrasted with controls (Silva et al., 2009).

Supplementing these outcomes are those from a medical cross-sectional investigation that exhibited that a higher level of serum of pentosidine (product of AGE) was related to cracks in patients with diabetes mellitus type1 in the wake of modifying for age, smoking, body mass index, the inadequacy of vitamin D, family ancestry of cracks and bone mass density at the femoral neck, lumbar spine and all-out hip (Neumann et al., 2014). Although, enzymatic cross-connecting is useful, at that point on enzymatic AGEs give the lower quality of bone (Saito, 2013).

In the first place, as both non-enzymatic and enzymatic cross-joins occur on lysine buildups, the development of AGEs seriously represses the site(s) left for cross-linking by the enzyme (Monnier et al., 2008). Secondly, AGEs cause apoptosis of osteoblast through the initiation of the receptor for RAGE (receptor for advance glycation end product) (Mercer et al., 2007), proposing that a few impacts of diabetes on apoptosis of osteoblast cell might be interceded by AGEs.

### Fracture Risk and Skeletal Status in T2DM

Commonly, people with T2DM have a typical or expanded bone mass density contrasted with the non-diabetic patients; nonetheless, they have a high frequency of bone fracture (Lecka-Czernik, 2009). A precise investigation of 16 diverse well-controlled examinations led in Europe and the United States indicated that T2DM related with a 2 fold increase in the threat of hip cracks in females (relative risk, 2.1) and males (RR, 2.8) (Janghorbani et al., 2007). Increased crack risk is additionally elevated by diabetic complications including diabetic eye, macro-vascular complications, renal disorders, and neuropathy (Vestergaard et al., 2009), which may lead to an increased threat of trauma due to more frequent incidence of falls (RR, 1.64) (Schwartz et al., 2001), including factors such as life span of diabetic disorder, earlier cracks, maturing and corticosteroids use add to the more prominent crack risk (Melton et al., 2008). An absence of relationship among bone mass density and crack risk recommends that diabetic bone has been modified biomechanical quality (Al Anouti et al., 2019). Studies of human histo-morphometric demonstrate that bone yield in more older T2DM patients is undermined which may bring about higher bone mass density yet diminished bone quality (Krakauer et al., 1995).

### i. Type 2 Diabetes (T2DM), Obesity and Bone

The most significant hazard factor for T2DM is obesity (Okamura et al., 2019), and the worldwide occurrence of type 2 diabetes is to be 629 million by 2045 (Gomes et al., 2019). As the population increases, the weightage of osteoporosis also increases. T2DM and obesity have impacts on crack risk and cracks in T2DM are related to more morbidity than all-
inclusive communities (Walsh & Vilaca, 2017). Crack hazard in obesity is not brought down at all skeletal sites, the hazard of some non-spine cracks including upper leg (RR 1.7), proximal humerus (RR 1.28), and lower leg crack (RR 1.5) is increased (Lecka-Czernik, 2009). A greater number of low injury cracks occur in obese women and men and overweight people and the occurrence of low injury cracks is parallel in non-obese females and obese females (Yamamoto et al., 2009).

Among postmenopausal women, moderate obesity is a protective factor in osteoporosis. But in high-risk groups, BMI was shown to be positively correlated with BMD. As BMI increase, BMD has also increased while the bone loss rate decreases (Siris ES). In obese people, bone mass density is higher by DXA (dual-energy X-ray absorptiometry) (Knapp et al., 2012). It is probable that even if the bone mass density is elevated in reaction to obesity, the capability for the increase is inadequate and ultimately the load-to-strength value increases far sufficient to cause cracks in lower trauma injuries (Sornay-Rendu et al., 2013).

In obesity intramuscular lipid level is increases and it may be related to poorer muscle activity and increased crack hazard (dynamic obesity) (Scott et al., 2015). In falling, poorer muscle activity could elevate falls and damage (Himes & Reynolds, 2012). Accordingly, even though bone mass density is higher in obesity, it may not be expanded adequately to oppose the greater powers acting when obese individuals fall. Non-bone factors, for example, delicate tissue thickness and muscle activity ought to be likewise being considered as defensive and contributory factors.

### ii. Metabolism of Bone in T2DM Patients

Remodeling of bone is a continuing cyclic procedure usually characterized by a fixed combination of the formation of bone through osteoblasts and resorption of bone through osteoclasts (Sims & Martin, 2020). Resorption and bone formation are determined by measurement of the number of biomarkers present in serum and urinary concentration. These markers (enzymes) are involved in components of bone matrix or remodeling of bone secreting in circulation during resorption and formation of bone (Singer & Eyre, 2008). There are pieces of evidence that the turnover of bone in type 2 Diabetes mellitus results from the depletion of bone formation due to decreased number of osteoblast and reduced possible activity (Sassi et al., 2018).

### Effects of Anti-Diabetic Therapy on the Metabolism of Bone

#### i. Glycemic Control

According to ACCORD study, there are no differences between standard or intensive glycemic control on crack incidence, suggested that an intensive administration of glycemia doesn’t improve the metabolism of bone in diabetic patients (A. V. Schwartz et al., 2012). Generally, drugs that improve diabetic control may be estimated to prevent changes in bone with diabetes, but suggested that ACCORD study fixed glycaemic control is not positively influenced status of bone (Monami et al., 2008).

**Metformin**

Metformin has a direct osteogenic effect through stimulating the differentiation and proliferation of osteoblastic cell-lines in rats (Jiating et al., 2019). Additionally, Metformin protects the osteoblastic cells from AGE-induced downbeat effects. The potential of the upbeat effect of Metformin on the bone seems to be confirmed through clinical studies that
show a 20% crack risk decrease in patients who are treated with Metformin (Vestergaard et al., 2005).

**Thiazolidinediones**

Insulin sensitivity is increased through PPARγ (peroxisome-proliferator-activated receptor) (Guerre-Millo et al., 2000). Pioglitazone and rosiglitazone are being used clinically. Various studies showed that thiazolidinediones (TZDs) efficacy is superior to other anti-diabetic therapies in diabetic hyperglycemia, control. Though, it is prolonged use to link with many adverse effects. Precise clinical proof points out the connection between rosiglitazone use and a considerable increase in the hazard of myocardial infarction and due to cardiovascular causes, leads to death (Nissen & Wolski, 2007).

![Figure 5: Summary of the potential effect of TZDs and Metformin on cells.](image)

Thiazolidinediones raise the loss of bone and fracture risk through activation of PPARγ in BMC and hamper the osteoblastogenesis via reducing Runx2. Metformin has a neutral positive effect on the health of bone and decreases fracture risk.

**Alpha-glucosidase Inhibitors**

This group of anti-diabetic drugs, including miglitol, voglibose, and acarbose inhibits the transformation of carbohydrates into monosaccharides by competitive inhibition of alpha-glucosidase enzymes that live in the enteric cells. Thus, reduce hyperglycemia by inhibiting glucose absorption in circulation. Besides, these inhibitors have been shown to promote the release of GLP-1 from L-cells of the intestinal tract (Patel & Research, 2016). In a large, nationwide study involving more than 2.89 million patients taking anti-diabetic drugs, no significant risks were reported in patients taking alpha-glucosidase inhibitors (Dabhi et al., 2013). The negative effects of voglibose on bone health have not been reported.
**Sulphonylureas**

Sulphonylureas is an oral medication that is commonly used for type 2 diabetes. It increases the Hip fractures risk by increasing the risk of hypoglycemia-induced falls among the elders. In a retrospective cohort study comparing people using sulphonylureas with non-users, its use was associated with approximately 30% increased hip fracture risk among elderly women and men (Brodovicz1). Through epidemiological data, sulphonylureas have an indirect effect on cracks of bone in diabetic patients by improving glycaemic control (Vestergaard et al., 2005).

**Dipeptidyl Peptidase 4 (DPP-4)**

A universal enzyme, found in the plasma membrane of osteocytes, osteoblast, and osteoclast has been involved in the synchronization of collagen synthesis (Carbone et al., 2017). Other reports indicate that vildaglitin show no effect on bone formation in osteoporosis after one year of treatment (Bunck et al., 2012). In contrast, a meta-analysis of 28 clinical trials showed that DPP-4 inhibitors improve bone health. As DPP-4 inhibitors improve the pool of incretins, which have an anabolic effect on bone, it is possible that DPP-4 inhibitors, if used properly, in moderation and duration, can elevate bone health in osteoporotic patients. In fact, in a meta-analysis of 28 clinical trials, it was concluded that these inhibitors may be related to a decreased bone rapture risk (Monami et al., 2011). Overall, several reports have been shown that the majority of DPP-4 inhibitors have neutral and/or favorable effects on bone marrow. However, several different effects of sitagliptin and saxagliptin have been reported. For example, saxagliptin has a detrimental effect on bone health (Yang et al., 2017).

**CONCLUSION**

Osteoporosis and DM are frequent conditions and occur simultaneously. Osteoporosis and bone fractures are prevalent in DM. In T1DM, there is increased bone fracture due to decreased bone mass. There are more bone fractures in T2DM despite increased BMD, which is due to hypoglycemia, cerebral ischemia, and impaired eyesight complications. Anti-Diabetic drugs also affect the risk of bone fracture. This review shows the significance of effective clinical management of diabetic patients, to control DM to implicate positive effect on bone health, to reverses impairments of bone. It is necessary to keep in mind that patients which are undertreatment of hypoglycemia have greater susceptibility to attain fractures. Many antidiabetic drugs have a positive or negative effect on bone health like metformin and sulphonylureas etc. Our review provides a direction to the use of anti-diabetic drugs with short-term and long-term bone-related bio-pathological manifestation.

**AUTHOR’S CONTRIBUTION:**

Conceptualization, F. D.; N. Q.; T. M.; N. I.; Writing of the original draft, N. Q.; T. M.; S. Y.; Writing—review and editing, F. D; S. H.; Supervision, F. D. All authors have read and agreed to the published version of the manuscript.

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