

## Diabetes Therapies and Bone

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### Abstract

Both osteoporosis and diabetes are chronic conditions that affect a large proportion of the elderly population. The prevalence of diabetes is increasing. National Diabetes Statistics Report, 2020 indicates that 34.2 million or 10.5% overall US population; 34.1 million adults aged 18 years or older or 13.0% of all US adults have diabetes. Fractures are common in patients with type 1 and type 2 diabetes compared with persons without a diabetes. There is significant evidence to show compromised bone quality in diabetes such as hyperglycemia with increased advanced glycation end products (AGEs), decreased osteocalcin and increased PTH results in compromised mesenchymal stem cell (MSC) differentiation, and decreased osteogenesis and decreased bone turn over. That, in turn, results in reduced bone quality and decreased bone strength and resultant increase in fracture risk. The mechanisms involved include effects of insulin, insulin-like growth factor 1, cytokines, advanced glycation end products, and altered calcium homeostasis. Persons with diabetes have increased risk for falls due to poor vision, neuropathy, and/or hypoglycemia. In addition, drug-induced alterations are reported and related to diabetes therapies. Here we review the risk of fractures related to diabetes therapies.

**Key words:** Diabetes; BMD; thiazolidinediones; Glucagon-like Peptide-1 agonist; Diabetes therapies

**Abbreviations:** BMD: Bone mineral density; GLP-1: glucagon like Peptide; SGLT 2 inhibitor: Sodium-Glucose Cotransporter-2 inhibitors; DPP4 inhibitors: Dipeptidyl Peptidase 4 inhibitors

### Introduction

Data from World Health Organization based on trends in diabetes indicate 422 million people have diabetes and the Center for Disease Control state that 10.5% of US population have diabetes. Fractures are a major cause of morbidity and mortality[1], resulting in substantial health care and social costs[2, 3]. Both men and women with diabetes mellitus (DM) have a higher risk of hip fractures [4-8] as well as fractures at other sites. The diagnosis of osteoporosis is based on areal bone mineral density (BMD) measurement using

dual-energy X-ray absorptiometry (DXA). The World Health Organization (WHO) defines osteoporosis as a BMD > or equal to 2.5 SD below that of a young normal adult (i.e. a T-score of < or equal to -2.5) and osteopenia as a BMD between 1 and 2.5 SD below the BMD of a normal adult (T between -1 and -2.4). Known risk factors for osteoporotic fractures include increasing age >75, female gender, white race, oophorectomy at an early age, low body mass index (BMI) <19kg/m<sup>2</sup>, prolonged immobility and the long-term use

of corticosteroids [9, 10]. The BMD of the hip is lower in persons with diabetes compared with age and BMI-matched non-diabetic men, and its level is similar in age and BMI-matched diabetics and non-diabetic men [11]. The risk of hip fracture in type 2 diabetes is considered secondary to deteriorating trabecular bone microarchitecture [12]. Decreased bone quality that correlates with duration of diabetes and decreased bone remodeling are important factors. Cytokines can decrease the osteoblast activity whereas interleukin (IL)-1, IL-6, IL-11, and tumor necrosis factor (TNF) can stimulate osteoclast development and thereby the process of bone resorption, leading to inflammation related increased bone loss [13, 14].

## Materials and Methods or Experimental Procedures

Review of the literature on the topic of effect of glucose lowering therapies for treatment of diabetes.

## Discussion

### Diabetes therapies and bone health

Some diabetes therapies have negative effect on the bones, whereas some have neutral and some others have positive effect.

### Therapies with neutral or positive effects on bone

**Insulin:** Though observational studies suggest increased risk of fractures in insulin users, [15] insulin is said to be anabolic to the bone [16]. In rodent models, decreased osteoblast activity present from the onset of diabetes is correlated more often with levels of than with insulin levels [17].

Metformin and sulfonylurea are considered to have a neutral effect on bone based on lack of correlation of incidence of fractures related to use of these agents. Insulin-sensitizing treatment with metformin is not associated with a higher incidence of bone fractures [18]. In clinical studies, it did not show any decrease in BMD [19]. The key molecule responsible for antidiabetic mechanism of metformin is AMP-activated protein kinase (AMPK) that improves insulin sensitivity through insulin receptor substrate 1 (IRS1). Similarly, AMPK plays a significant role in osteogenesis and inhibits adipogenesis in bone.

The key molecule in metformin antidiabetic mechanism of action, is also effective in signaling pathways involved in bone physiology, through alterations in receptor activator of nuclear factor-kb ligand (RANKL); the mechanistic target of rapamycin (mTOR) signaling.

Metformin decreases osteoclast development and prevents macrophage proinflammatory responses to AGEs by decreasing receptor for advanced glycation end-products (RAGE) signaling, potentially decreasing bone marrow support for resorption.

**Incretin hormones and Bone:** Important incretin hormones are gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), secreted from enteroendocrine cells of the small intestine. They are secretagogues for insulin and lowers glucose in addition to decreasing appetite. The exact mechanism of the GLP-1 analogues on bone metabolism is not clear. In stem cell studies, the addition of a GLP-1 led to decreased apoptosis and inhibited adipocyte differentiation by decreasing the expression of the peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ );[20] and is said to have stimulated osteoblast differentiation and decreased adipogenicity in a dose-dependent manner [21]. In animal studies, Yang and associates reported that liraglutide improved BMD, bone microstructure, and bone strength and reversed glucocorticoid induced osteoporosis, primarily through the reduction of bone resorption and promotion of bone formation [22]. Though animal studies show benefit by improving osteoblast activity and decreased osteoclast activity, there is very little information in humans. Limited information is available in humans. In a subgroup analysis of the Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD)-3 study, liraglutide monotherapy did not negatively affect total BMD in a 2-year prospective study, suggesting it may not exacerbate the consequences of bone fragility [23]. In a short-term study of liraglutide for 26 weeks, liraglutide did not affect bone resorption and preserved hip BMD despite weight loss in patients with T2D, suggesting that liraglutide has some antiresorptive effect. Hip BMD decreased in placebo treated patients from baseline to end of study, whereas no changes were seen in patients treated with liraglutide ( $p = 0.01$  difference between groups) [24]. At present we have limited clinical data to support beneficial effects of GLP-1 analogues in humans. Both osteoblasts and osteoclasts express GLP-1 receptors. In one animal study, both exenatide and liraglutide increased trabecular bone without significant effect on cortical bone; while serum calcitonin levels increased with decreased sclerostin levels with exenatide but not liraglutide [25]. Similar effect on bone was reported with liraglutide [26]. Animal studies on the effect of dipeptidyl-peptidase (DPP)-4 inhibitors on bone have not shown consistent results.

## Therapies with neutral or negative effects on bone

### Thiazolidinediones (TZDs)

**TZDs and BMD:** The realization that TZDs increase fracture risk has resulted in a new awareness of the potential for glucose-lowering agents to affect skeletal health. Decreased BMD secondary to pioglitazone has been reported even as early as 6 months noted [27]. Rosiglitazone, another TZD decreases the bone mineral density in post-menopausal women with type 2 diabetes [28]. Following the fracture data with TZDs, fracture events are now generally reported as a distinct category of adverse events for new glucose-lowering medications. Consequently, data are available for fractures reported as adverse events in randomized clinical trials of other glucose-lowering agents, such as incretin-based medications and sodium-glucose cotransporter 2 (SGLT2) inhibitors, as discussed below.

**TZDs and fractures:** Results of the ADOPT trial (A Diabetes Outcome and Progression Trial) of 4360 Type 2 diabetic patients treated for a mean of 4 years with rosiglitazone, metformin, or glyburide indicated that rosiglitazone doubled the fracture risk in women, although not in men [29]. In a meta-analysis, long term use of thiazolidinedione use was reported to double the risk of fractures among women with type 2 diabetes, without a significant increase in risk of fractures among men with type 2 diabetes [30]. Another meta-analysis suggested that TZD treatment is associated with an increased risk of fractures in women (OR 1.94 [95% CI 1.60, 2.35]). The effects of rosiglitazone and pioglitazone are similar; fracture risk is independent of age and fracture risk has no clear association with duration of TZD exposure [31]. In a subsequent meta-analysis with median trial duration of 48 weeks, it was reported that modest bone loss with TZD treatment may not be reversed 1 year after cessation of treatment. Bisphosphonates improved BMD in subjects receiving TZDs for diabetes that was similar to those not on TZDs at total hip and lumbar spine but less improvement at femoral neck in TZD users [32]. Limited evidence is available on the persistence of the effect of TZDs on the skeleton after discontinuation of use. Data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial bone ancillary study reported that fracture rate was reduced in women who had discontinued TZD use for 1-2 years (HR = 0.57; 95% CI, 0.35, 0.92) or > 2 years (HR = 0.42; 95% CI, 0.24, 0.74) compared with current users [33].

**TZDs and preclinical studies:** Preclinical studies indicate TZDs increase peroxisome proliferator-activated receptor  $\gamma$ 2 (PPAR $\gamma$ 2) stimulation with excessive adipocyte production and decreased

osteoblastogenesis, altered TGF-beta and BMP2/4 signaling pathways [34]. TZDs cause bone loss in mice and rats by simultaneously decreasing bone formation (osteoblastogenesis) and increasing bone resorption (osteoclastogenesis) [35].

Sodium glucose cotransporter 2 (SGLT2) inhibitors are a class of novel hypoglycemic drugs, also called gliflozins that alters calcium and phosphate homeostasis and acts on the kidneys to promote urinary glucose excretion, thereby decreasing the plasma glucose level. Currently available gliflozins are empagliflozin, dapagliflozin, ertugliflozin and canagliflozin. SGLT2 inhibitors lower cardiovascular mortality and reduce proteinuria. Increased risk of fractures of small bones and lower limb amputations were reported with canagliflozin vs placebo in the CANagliflozin cardiovascular Assessment Study (CANVAS) Program. Subsequently, in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE) trial, it was suggested that the observed association in CANVAS is likely to be a chance finding, although an unidentified fall-related mechanism remains a possibility [36].

SGLT2 inhibitors increase serum phosphate levels via increased tubular reabsorption of phosphate and that in turn stimulate parathyroid hormone and fibroblast growth factor 23 (FGF23) and may affect bone metabolism. Furthermore, as an additional mechanism, a greater frequency of intravascular volume depletion with SGLT2 inhibitor use could increase falls, leading to greater fracture risk. Clinical studies into the effects of SGLT2 inhibitors on bone and fracture risk have produced mixed results. Thus, further studies are required to determine whether there are differences in fracture effects within the SGLT2 inhibitor class of medications.

### Conclusion

Pathology of bone in diabetes is complex with increased fracture risk independent of BMD. TZD are associated with increased risk of fractures and decreased BMD; risk with SGLT-2 inhibitors still need attention to bone health while insulin, metformin and DPP-4 inhibitors have neutral effect and GLP-1 analogs possible have minimal beneficial effect with current knowledge. There is a need for biomarkers for fracture potential in subjects with diabetes.

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**Conflict of interest**

The author declares that there is no conflict of interest with this manuscript.

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