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Safety of Anti-Diabetic Therapies on Bone

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Abstract

Osteoporosis and diabetic disease have reached epidemic proportion and create significant public health concerns. The prevalence of these diseases is alarming, and indicates that in the US, 50% of elderly individuals are osteoporotic and almost 20% of population has either diabetic or prediabetic conditions (Centers for Disease Control and Prevention; <http://www.cdc.gov>).

Osteoporosis and diabetes share many features including genetic predispositions and molecular mechanisms. The linkage between these two chronic diseases, which stems from overlapping molecular controls involved in bone homeostasis and energy metabolism, creates a possibility that certain anti-diabetic therapies may affect bone. This concurs with recent findings indicating that bone status is closely linked to regulation of energy metabolism and insulin sensitivity. Indeed, bone and energy homeostasis are under the control of the same regulatory factors, including insulin, peroxisome proliferator activated receptor gamma (PPAR γ), gastrointestinal hormones such as glucose inhibitory protein (GIP) and glucagon inhibitory peptide (GLP), and bone derived hormone osteocalcin. These factors and related mechanisms control glucose homeostasis and fatty acids metabolism in fat tissue, pancreas and intestine, which are pharmacological targets for anti-diabetic therapies. The same factors contribute to the bone quality by their effect on bone cell differentiation and bone remodeling process. This implies that bone should be considered as a vital target for therapies which modulate energy metabolism. This review is summarizing available data on the skeletal effects of clinically approved anti-diabetic therapies.

Keywords

bone; BMD; fractures; anti-diabetic therapy; TZDs; metformin; insulin; glyburide; incretins; DPP-4 inhibitors; PPAR

Bone remodeling

Maintenance of bone homeostasis throughout life relies on the bone remodeling process, which continually replaces old and damaged bone with new bone in order to maintain strength and elasticity (1). In a healthy state, bone resorption is balanced with bone formation. Changes in the milieu of local and systemic factors may alter this balance leading to changes in the bone mass and/or bone biomechanical properties. Aging, estrogen deficiency, and metabolic diseases negatively affect bone mass and/or bone quality leading to the development of osteoporosis and increased fracture rate.

Two types of cells are involved in bone remodeling: osteoclasts resorb damaged bone, and osteoblasts form new bone at the site of the resorpted cavity. Osteoclasts and osteoblasts

develop from two distinct populations of stem cells residing in the bone marrow, hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC), respectively. Osteoclast differentiation is determined by both, factors produced by cells of osteoclast lineage and factors produced by other bone marrow cells including cells of osteoblast lineage (2). Osteoclast recruitment from the HSC pool and their maturation is controlled by osteoblast-derived cytokines: M-CSF, IL-6 and RANKL. Osteoblasts originate in a marrow MSC compartment which also produces adipocytes (3; 4). The commitment of MSC toward either the osteoblast or adipocyte lineage occurs by a stochastic mechanism (5); lineage-specific transcription factors, such as Runx2, Dlx5 and Osterix for osteoblasts and PPAR γ 2 and C/EBPs for adipocytes are activated (6-11). Activation of osteoblast-specific transcription factors is determined by a milieu of extracellular factors, which regulate the cellular activity of Wnt, TGF β /BMP and IGF-1 signaling pathways (12).

Bone as an integral part of energy metabolism system

Integration of bone metabolism with energy metabolism has been presented recently as a model which links anabolic effect of insulin signaling in osteoblasts with bone turnover and regulation of insulin sensitivity in peripheral organs (13; 14). Thus, in osteoblasts insulin signaling regulates an expression of Runx2 and osteocalcin production. In addition, insulin increases support for osteoclastogenesis by decreasing an expression of OPG, a decoy receptor for RANKL. As a result, insulin increases bone turnover and production of undercarboxylated osteocalcin, which in endocrine fashion regulates insulin release from β -cells in pancreas and production of adiponectin in fat tissue (13-16). Although it is not clear whether this regulatory circuit is affected in diabetes, several studies suggest that patients with T2DM have decreased bone turnover (17-19). If so, it would result in the decrease in osteocalcin production, especially its undercarboxylated form, which would lead to the attenuation of signaling responsible for increasing of insulin release from the pancreas and increasing fat sensitivity to insulin.

Skeletal status and fracture risk in T2DM

Diabetes mellitus (DM) and osteoporotic fractures are two of the most important causes of mortality and morbidity in older subjects. Recent data report a close association between fragility fracture risk and DM of both type 1 (T1DM) and type 2 (T2DM). While T1DM is associated with reduced bone mineral density (BMD), which may explain increased fracture risk, patients with T2DM generally have normal or increased BMD (reviewed in (20)). Systematic analysis of 16 different well-controlled studies conducted in the US and in Europe showed that T2DM was associated with a two-fold increase in risk of hip fractures in men (relative risk [RR], 2.8) and women (RR, 2.1) (21). Studies performed on a Japanese population indicated that T2DM patients, both women (odds ratio [OR], 1.83; $P < 0.01$) and men (OR, 4.73; $P < 0.001$), have increased rate of vertebral fractures (22). Increased fracture risk is additionally elevated by diabetic complications including macrovascular complications, diabetic eye and kidney diseases, and neuropathy (23), which may lead to increased risk of trauma due to more frequent incidence of falls (RR, 1.64) (24). In addition, factors such as duration of diabetic disease, aging, prior fracture, and corticosteroid use contribute to the greater fracture risk (25).

A lack of association between BMD and fracture risk suggests that bone in T2DM has altered biomechanical quality. Human histomorphometric studies indicate that bone turnover in older T2DM patients is compromised, which may result in higher BMD but decreased bone quality (17). Recent animal studies showed that high levels of insulin lead to high bone mass by decreasing both osteoclast number and bone resorption, and osteoblast number and bone formation (26). Recent human cross-sectional studies suggest that indeed bone

turnover is attenuated in T2DM. Serum levels of sclerostin, an inhibitor of bone formation, is increased in T2DM independently of gender and age, and is associated with higher BMD (19). Moreover, higher levels of sclerostin correlate positively with duration of T2DM and levels of glycated hemoglobin, while negatively with levels of bone turnover markers. Another study from the same group reported decreased levels of both serum bone resorption markers (CTX and TRAPc) and intact PTH in patients with T2DM as compared to non-diabetic control (18). Decrease in levels of bone resorption markers and PTH correlated with increased BMD and duration of disease. These findings suggest that bone turnover in diabetes is attenuated, which may contribute to the decreased bone quality. Bone quality in T2DM can be also decreased by highly reactive glucose metabolites (advanced glycation end products [AGEs]), which circulating levels are increased in diabetes, and which are implicated in forming additional cross-links between collagen fibers in bone (27). This process affects bone biomechanical properties by increasing its stiffness and fragility (28). In support of this, recent studies showed a positive association between levels of circulating AGE pentosidine and increased incidence of fractures in diabetic patients (27)].

Oral anti-hyperglycemic therapies and their effects on bone

The most common form is insulin-independent T2DM, which is characterized by insulin and glucose intolerance, and is associated with development of hyperglycemia and hyperinsulinemia. Therapies, either approved by FDA or in Phase III clinical trial, include insulin sensitizers, insulin secretagogues, and drugs which prevent digestion of carbohydrates (Alpha-glucosidase inhibitors), regulate glucose absorption in intestine (amylin analog), and increase glucose excretion in the urine (SGLT2 inhibitors) (Table 1).

Thiazolidinediones (rosiglitazone, pioglitazone)

TZDs increase insulin sensitivity *via* activation of peroxisome proliferator-activated receptor (PPAR γ). Two TZDs, rosiglitazone and pioglitazone, have been used clinically since 1999. A number of studies showed superior efficacy of TZDs over other available antidiabetic therapies in the control of diabetic hyperglycemia (29). However, their prolonged use is associated with several adverse effects. Strong clinical evidence points to the connection between rosiglitazone use and a significant increase in risk of myocardial infarction and death from cardiovascular causes (30). This association resulted in a recent review of rosiglitazone safety by the FDA and recommendation for its restricted use in the US. Interestingly, pioglitazone use is associated with a significantly lower risk of death and lower number of myocardial infarction and stroke incidence (31), indicating that cardiovascular effects of TZDs are not a drug class effect, but rather specifically associated with the TZD type. However, increased risk of bladder cancer in long time pioglitazone users resulted in recent restriction of its use by FDA. Both TZDs exhibit drug class properties of fluid retention and weight gain (32). Although the use of both rosiglitazone and pioglitazone is currently restricted, the new TZDs with better safety profile are in development. Therefore, understanding TZDs mechanism of action on bone is needed in respect to improvement of safety for bone of new line of TZDs.

Although they possess beneficial anti-hyperglycemic profiles, rosiglitazone and pioglitazone use is associated with adverse effects on bone (33). Extensive clinical evidence indicate that these drugs cause bone loss and increase fracture risk (29; 34-36). Observational studies using data from the Health, Aging, and Body Composition cohort reported that older postmenopausal TZD users experience bone loss at the rate of -0.61% annually as compared to non-TZD users (34). In Japanese patients with T2DM, treatment for 1 year with pioglitazone decreased serum osteocalcin, femoral and radial BMD, but not BMD in lumbar vertebra (37). Bone loss was also observed with a short treatment with TZDs. A randomized, placebo-controlled study of the effect of pioglitazone on bone in polycystic ovary syndrome

patients in Denmark demonstrated that 16 weeks of treatment resulted in a significant decline in BMD of the lumbar spine (−1.1%) and femoral neck (−1.4%) (38). Similarly, a randomized controlled trial of rosiglitazone effects on bone of postmenopausal nondiabetic women in New Zealand showed that 14 weeks of rosiglitazone administration resulted in a decrease in hip BMD by −1.9% compared with the BMD at the beginning of treatment (35). Changes in BMD were accompanied by a decrease in serum markers of bone formation, such as alkaline phosphatase and aminoterminal propeptide of type I collagen (P1NP). Bone resorption markers lacked change, leading to the conclusion that short-term therapy with rosiglitazone exerts detrimental skeletal effects by inhibiting bone formation (35). In contrast, 16 weeks of treatment with rosiglitazone of T2DM women with a prior diagnosis of cardiovascular disease resulted in significantly increased levels of the circulating bone resorption marker C-terminal collagen crosslinked peptide (CTX), whereas levels of P1NP were not changed (39). The same studies showed that rosiglitazone did not affect markers of bone turnover in men (39). The contrasting results of studies by Grey et al. (35) and Gruntmanis et al. (39) suggest that bone response to TZDs may be determined by hormonal and metabolic status.

The causal connection between TZD therapy and increased fracture risk was determined in a number of studies, the majority of which were retrospective. The analysis of these studies allows for defining of risk factors to increased fractures in TZD users such as gender, age, pre-existing conditions, and duration of treatment. The first demonstration of increased fracture risk was noticed during an analysis of results from ADOPT (A Diabetes Outcome Progression Trial), which was designed to compare an efficacy of different antidiabetic therapy on maintenance of normal glucose levels in prediabetic individuals (29). Post-trial data from the 1840 women and 2511 men randomly assigned in ADOPT to rosiglitazone, metformin, or glyburide for a median of 4.0 years were examined with respect to time to first fracture, rates of occurrence, and sites of fractures (29; 36). Fracture rate in men did not differ between treatment groups and did not demonstrate significant difference in an overall risk. The cumulative incidence of fractures in women was 15.1% (11.2–19.1) with rosiglitazone, 7.3% (4.4–10.1) with metformin, and 7.7% (3.7–11.7) with glyburide, representing hazard ratios of 1.81 and 2.13 for rosiglitazone compared with metformin and glyburide, respectively. Fractures were seen predominantly in the lower and upper limbs, and vertebral fractures were not assessed in this study. An analysis of serum levels of bone turnover markers showed significant increase in levels of resorption marker C-terminal telopeptide (CTX) in women on rosiglitazone therapy but not in men, whereas both genders have decreased levels of marker of bone formation P1NP (40). Increase in bone resorption marker exclusively in women may explain at least in part an increased fracture rate in this gender on TZD therapy (40).

There was no correlation between rosiglitazone use and estrogen status since both pre- and postmenopausal women demonstrated increase in fractures (29; 36). These observations were subsequently corroborated by a number of other studies. A meta-analysis of data from 10 different randomized controlled trials involving 13,715 participants and two observational studies involving 31,679 participants confirmed that long-term TZD use doubles the risk of fractures exclusively in women but not in men with T2DM (41). Recently, the cross-sectional study based on use of medical and pharmacy claims for TZD prescriptions and involving the southeastern region of the United States showed that TZD use, regardless of type, doubled the incidence of distal upper and lower limb fracture, and the proportion was significantly higher in women and increased 2% for every year increase in age (42). Similarly, retrospective studies involving 19,070 individuals of both genders in southeast Michigan showed that women more than 65 years of age appeared to be at greatest risk for fractures (43).

In contrast, retrospective studies on 84,339 diabetic patients in British Columbia (Canada) concluded that both women and men receiving TZDs have increased fracture risk. The risk further increased with duration of treatment, and pioglitazone was more strongly associated with fractures than rosiglitazone, especially in men (44). Observational studies based on the UK General Practice Research Database (GPRD), which included a large population of older individuals, showed that TZD therapy and its duration are associated with significant increase in nonvertebral fractures independent of patient sex and age. The adjusted OR of fracture occurrence for hip/femur was 4.54, for humerus was 2.12, and for wrist/forearm was 2.90 (45). Studies conducted on a cohort of Medicare beneficiaries with diabetes over 65 years of age and older showed that compared with sulfonylureas and metformin monotherapies, TZD monotherapy is associated with increased risk of peripheral fractures regardless of sex and type of TZD (46). Another self-controlled case-series study on the GPRD population suggested that prior fracture(s) increases the risk of the next fracture occurrence. These studies compared rates of fractures within the person with prior fracture during TZD exposed and unexposed periods and showed that exposure to TZD, either rosiglitazone or pioglitazone, increased fracture rate by 43% similarly in men and women and the duration of exposure increased this risk even further (47). Fractures occurred in a range of sites including hip, spine, arm, foot, wrist, and hand.

Taken together, results of available studies indicate the following: 1) TZD effect on bone is a drug class effect; 2) women and elderly are at increased risk of bone loss and increased risk of fractures; however, some studies point to the equal risk in both genders; 3) the risk is increased in individuals who have a history of prior TZD-unrelated fractures; and 4) duration of treatment correlates positively with increased fracture risk.

Mechanism of TZD-induced bone loss

PPAR γ , an essential regulator of lipid, glucose, and insulin metabolism (10), is a target for insulin sensitizing drugs, TZDs. The PPAR protein is expressed in mice and humans in two isoforms, PPAR γ 1 and PPAR γ 2. PPAR γ 1 is expressed in a variety of cell types, including osteoclasts (48), whereas PPAR γ 2 expression is restricted to cells of adipocytic lineage (49). In bone, PPAR γ 2 plays an important role in regulation of MSC differentiation toward osteoblasts and adipocytes, and the maintenance of bone mass. As previously demonstrated, in a model of marrow mesenchymal cell differentiation, activation of the PPAR γ 2 isoform with rosiglitazone converted cells of osteoblast lineage to terminally differentiated adipocytes. Furthermore, rosiglitazone treatment irreversibly suppressed both the osteoblast phenotype and osteoblast-specific gene expression. These *in vitro* results suggest a role for PPAR γ 2 as a positive regulator of adipocyte differentiation and a dominant-negative regulator of osteoblast differentiation (11; 50). In contrast, PPAR 1 expressed in HSC promotes osteoclast differentiation and bone resorption (48). It controls an expression of c-fos protein, an important determinant of osteoclast lineage commitment and development.

An essential role of PPAR γ in maintenance of bone homeostasis was demonstrated in several animal models of either bone accrual or bone loss depending on the status of PPAR γ activity (51-56). In models of bone accrual, a decrease in PPAR γ activity in either heterozygous PPAR γ -deficient mice or mice carrying a hypomorphic mutation in the PPAR γ gene locus led to increased bone mass due to increased quantity of osteoblasts (54; 56). Interestingly, mice deficient in PPAR expression in cells of hematopoietic lineage develop osteopetrosis and are less sensitive to the TZD-induced bone loss than control mice (48). In contrast, in rodent models of bone loss due to PPAR γ activation, administration of rosiglitazone resulted in significant decreases in BMD, bone volume and changes in bone microarchitecture (51; 55; 57). Observed bone loss was associated with expected changes in the structure and function of bone marrow, which included decreased number of osteoblasts, increased number of adipocytes, and increased support for osteoclastogenesis. The degree of

bone loss in response to rosiglitazone correlated with the animal age and the level of PPAR γ expression. In younger animals with less PPAR γ , bone loss was less extensive than in older animals (57). Moreover, age determined the mechanism by which bone loss occurred. In younger animals it occurred due to decreased bone formation, whereas in older animals due to increased bone resorption (57). In addition, studies of rosiglitazone effects in estrogen deficient rats showed that bone loss occurred mainly due to increased bone resorption (52). In conclusion, animal studies suggest that aging and estrogen deficiency confound TZD-induced bone loss and determine its mechanism.

An analysis of gene expression in MSC following rosiglitazone treatment showed reduced expression of genes essential for activity of signaling pathways controlling bone homeostasis and MSC commitment to the osteoblast lineage, among them Wnt, TGF- β BMP and IGF-1 (58; 59). The effect of TZDs on the expression of genes essential for osteoblast development was strikingly similar to changes observed during aging. Due to the type of bone loss and similarities to aging, some speculate that TZDs may accelerate the aging of bone (57; 60). The complexity of PPAR effects on bone cell differentiation and bone remodeling are summarized in Figure 1.

Selective PPAR- γ modulators: Ligand-dependent separation of pro-adipocytic and anti-osteoblastic activities of PPAR- γ

The PPAR γ ligand-binding domain contains a large binding pocket capable of encompassing a variety of ligands. This provides a wide array of potential contact points that can result in various PPAR γ conformations and differential recruitment of coactivators, which determine specificity of this nuclear receptor (61). Although TZDs possess a beneficial anti-diabetic profile, their adverse effects prompt pharmaceutical efforts to develop selective PPAR γ modulators that will retain high potency to treat diabetic disease with minimal adverse effects (62).

The molecular studies provide evidence for distinct regulatory pathways that regulate proadipocytic and antiosteoblastic activities of PPAR- γ . These studies demonstrated that PPAR- γ proadipocytic activity is transcriptional in nature and involves binding to PPAR response elements (PPRE) in gene regulatory regions, whereas its anti-osteoblastic activity is PPRE-independent (58). PPAR- γ anti-inflammatory and anti-atherogenic activities are also regulated in a PPRE-independent manner (63).

With respect to bone, it has been demonstrated that PPAR γ proadipocytic and antiosteoblastic activities can be separated by using ligands of different chemical structures (50). In an in vitro model of marrow mesenchymal cell differentiation under control of PPAR- γ , ligands consisting of several structurally related oxidized derivatives of linoleic acid were able to activate all three combinations of PPAR- γ activity: proadipocytic, antiosteoblastic, or both. In addition, we have shown that the TZD netoglitazone, which has antihyperglycemic properties comparable with rosiglitazone, does not suppress osteoblastogenesis. Mice receiving netoglitazone at the dose that decreased glucose levels similarly to rosiglitazone did not lose bone (64).

Dual PPAR γ /PPAR α agonists (aleglitazar)

T2DM is a complex disease in which hyperglycemia and insulin resistance are often combined with microvascular and cardiovascular diseases. Therefore, a reasonable approach in the treatment of T2DM is a strategy that simultaneously treats insulin resistance and atherogenic dyslipidemia. Research to develop dual agonists that activate insulin-sensitizing properties of PPAR γ and lipid-lowering abilities of PPAR α is ongoing and several agonists have been developed, including muraglitazar and tesaglitazar. However, the development of

both these agents has been discontinued because of safety concerns, with muraglitazar linked to cardiovascular side effects and tesaglitazar to renal impairment. Aleglitazar represents dual PPAR α / γ agonist, which was developed using a structure-based design of indole propionic acid (65).

In preclinical and clinical studies, aleglitazar demonstrated beneficial antidiabetic activities and had a higher antihyperglycemic efficacy than pioglitazone (reviewed in (66)). In T2DM patients, aleglitazar improved the lipid profile and decreased levels of cardiovascular markers of inflammation and clotting (67; 68). The observed adverse events were characteristic of either PPAR γ or PPAR α agonists; however, when compared to pioglitazone-PPAR γ -mediated effects, such as edema and weight gain, these were less severe. The PPAR α -mediated adverse effects on renal function are of concern and are a primary endpoint of ongoing phase II clinical trials in patients with T2DM. A phase III clinical trial is also ongoing in patients with T2DM who had recently experienced a cardiac event. Aleglitazar effect on bone, especially PPAR γ -mediated adverse events, has not been assessed in ongoing trials.

Biguanides (metformin)

Metformin is the most commonly used to increase insulin sensitivity in diabetic patients. Biguanides class of drugs decreases hepatic glucose production and increases glucose uptake in muscle. Metformin is considered by the World Health Organization an essential medicine satisfying the criteria of the public health relevance, evidence on efficacy and safety, and comparative cost effectiveness (www.who.int/medicines). Metformin mechanism of insulin sensitization includes activation of hepatic and muscle AMP-activated protein kinase (AMPK), which results in suppression of fatty acid synthesis and stimulation of fatty acid oxidation in liver and increase in muscle glucose uptake (69). AMPK also decreases expression of sterol-regulatory element-binding-protein 1 (SREBP-1), a transcription factor involved in adipocyte differentiation and pathogenesis of insulin resistance, dislipidemia and diabetes. Animal studies indicate that metformin has a positive effect on osteoblast differentiation due to increased activity of osteoblast-specific Runx2 transcription factor *via* AMPK/USF-1/SHP regulatory cascade (70) and it has a negative effect on osteoclast differentiation and bone loss after ovariectomy by decreasing RANKL and increasing osteoprotegerin levels (71). Interestingly, metformin can prevent the adverse effects of TZDs on bone by either inducing reossification of bone after rosiglitazone treatment or preventing rosiglitazone effects when applied in combination with rosiglitazone (72).

Human studies of the Rochester cohort suggest that metformin decreases fracture risk in T2DM patients (hazard ratio 0.7) (25). Although the ADOPT studies did not demonstrate beneficial effects of metformin on fracture risk (36), however they showed decreased levels of bone resorption marker CTX and, contrary to animal studies, decreased levels of bone formation marker P1NP (40). Recent studies comparing efficacy and safety of rosiglitazone/metformin combination with metformin on long-term glycemic control and BMD in T2DM patients showed that although rosiglitazone/metformin combination is superior over monotherapy with metformin in respect to glycemic control, however 80 weeks treatment with combined therapy was associated with significantly reduced BMD in lumbar spine and hip, while metformin monotherapy therapy did not have an effect on bone (73).

Insulin

According to the Studies of Osteoporotic Fractures, insulin-treated older diabetic women had more than double the risk of foot fractures (multivariate adjusted RR = 2.66) compared with non-diabetics and non-insulin user diabetics (74). Similarly, studies among the Rochester cohort showed that insulin slightly but significantly increases fracture rate (25).

Interestingly, insulin-treated diabetic women have almost a doubled fall incidence (odds ratio 2.78 vs 1.68), which in part explains the increased fracture rate in the lower extremities (24).

Sulfonylureas (glyburide)

Sulfonylureas function as insulin secretagogues. This class of drugs activates sulfonylurea receptors on the surface of pancreatic β cells and stimulates exocytosis of insulin from vesicles. Evidence from both the ADOPT studies and the Rochester studies indicate that glyburide therapy does not have an effect on bone mass and fracture risk (25; 29), however glyburide therapy decreased serum levels of bone formation marker PINP in the ADOPT studies (40).

Incretin analogs and DPP4 protease inhibitors (exenatide, sitagliptin)

This newest class of anti-diabetic drugs enhances the mechanism by which enteric hormones stimulate insulin release from β -cells and inhibit glucagon production in the liver (75). Glucose-dependent insulinotropic peptide (GIP), and glucagon-like peptides (GLP-1 and GLP-2), are released by gut endocrine cells in response to nutrient intake. Bioactivity of incretin hormones is limited by their rapid degradation and inactivation by dipeptidyl peptidase-4 (DPP-4), a serine protease that is present in a soluble form in plasma and is expressed in most tissues (76). Recently, DPP-4 inhibitors have emerged as a new class of pharmacological agents to enhance incretins action and improve glycemic control in patients with T2DM. Incretins and DPP-4 inhibitors have a major advantage over other diabetic medications in that glucose control remains stable with little or no rise in HbA1c levels after long periods of use. The side effects common for incretin-based therapies, including incretin receptors agonists and DPP-4 inhibitors, consist of gastrointestinal, immune system and pancreatic reactions. Since DPP-4 enzyme is known to be involved in the suppression of certain malignancies, particularly in limiting the tissue invasion of tumors, there is a concern that DPP-4 inhibitors may allow some cancers to progress, however clinical data are not as yet available (77-79).

Nutritional hormones are known to be important in bone turnover; as soon as a meal is ingested, bone breakdown is suppressed (80; 81). Osteoblasts and osteoclasts express receptors for both GIP and GLP incretins. A number of studies indicate that GLP-2 acts mainly as an antiresorptive hormone (82), while GIP can act both as an antiresorptive and anabolic hormone (83; 84). Mice deficient in GLP-1 receptor develop cortical osteopenia and have more fragile bone as well as increased quantity of osteoclasts and increased bone resorption (85). GLP-1 receptor signaling may play an essential role in the control of bone resorption indirectly, through a calcitonin-dependent pathway. Calcitonin treatment effectively suppressed bone resorption markers in *Glp-1r(-/-)* mice, and the GLP-1 receptor agonist exendin-4 increased calcitonin gene expression in the thyroid of wild-type mice (85). In summary, a number of animal studies indicate that incretins have beneficial effects on bone mass and protective effects on bone quality. Therefore, anti-diabetic therapies which increase GIP and GLP hormone levels and their bioactivity might exert beneficial effects on human bone.

Since incretin therapy is relatively new the clinical data of its safety for bone is just emerging. The forty-four-week treatment of T2DM patients with incretin mimetic exenatide did not decrease BMD and did not have an effect on levels of serum bone turnover markers, although it decreased body weight by 6% (86). A meta-analysis of 28 clinical trials enrolling it total 20,000 patients showed that treatment with DPP-4 inhibitors were associated with a reduced risk of fractures (odd ratio 0.60) compared to placebo and other treatments (87). Interestingly, although animal studies showed that DPP-4 inhibitor sitagliptin did not affect

bone density, however the absence of DPP-4 in Dpp-4(−/−) mice lead to the greater bone loss after ovariectomy as compared to animals with unaltered DPP-4 expression (88). More clinical studies on incretins and DPP-4 inhibitors effects on BMD and fracture risk with stratification according to gender, postmenopausal status, and age are needed.

Conclusions

In conclusion, the available evidence indicates that anti-diabetic therapies may either increase fracture risk (TZDs and insulin), may not affect this risk (sulfonylurea) or may even decrease the risk (metformin). From a bone perspective, metformin and sulphonylureas are safer than TZDs; randomised trials have shown that TZDS decrease BMD and increase fracture risk. The mechanism of TZD-induced bone loss includes unbalanced bone remodeling processes resulting from decreased bone formation and increased bone resorption. Human and animal studies suggest that aging and estrogen deficiency confound TZD-induced bone loss and determine its mechanism. The emerging potential of incretin-based therapies as sparing or perhaps even beneficial for bones requires systematic clinical assessment in the future.

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Fig. 1.
The complexity of PPAR γ effects on bone. PPAR γ activities: Anti-OB – anti-osteoblastic; Pro-AD – pro-adipocytic; Pro-OC – pro-osteoclastic.

Table 1

Available anti-diabetic drugs and their effects on skeleton

Target	Mode of action	Class of Drugs	Drugs	Skeletal effect
Insulin	Sensitizers	Biguanides	Metformin [*]	Decreased fractures
		TZDs (PPAR γ agonists)	Pioglitazone [†] , Rosiglitazone [†]	Bone loss; increased fractures
		Dual PPAR α /PPAR γ agonists	Aleglitazar [§]	Unknown
	Secretagogues	K ⁺ ATP	Sulfonylureas (e.g. Glyburide [*])	No effect
			Meglitinides (e.g. Nateglinide)	Unknown
		GLP-1 analogs	Exenatide, Liraglutide, Taspoglutide [§] , Albiglutide [§] , Lixisenatide [§]	No effect
		DPP-4 inhibitors	Alogliptin [§] , Saxagliptin, Sitagliptin, Vildagliptin, Linagliptin	Decreased fractures
Other	Analogues/other insulins [*]		Insulin lispro, Insulin aspart, Insulin glargine	Increased fractures
	Alpha-glucosidase inhibitors		Acarbose, Miglitol, Voglibose	Unknown
	Amylin analog		Pramlintide	Unknown
	SGLT2 inhibitors		Canagliflozin [§] , Dapagliflozin [§]	Unknown

^{*} World Health Organization Essential Medicine (WHO-EM);

[†] restricted use in USA and Europe;

[§] Phase III clinical trial