Chapter 7
Safety of Antidiabetic Therapies on Bone

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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 (Fig. 7.1).

Three types of cells are involved in bone remodeling: osteoclasts which resorb an old or damaged bone, osteoblasts which form new bone at the site of the resorbed cavity, and osteocytes which orchestrate the whole process. Osteoclasts and osteoblasts/osteocytes 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

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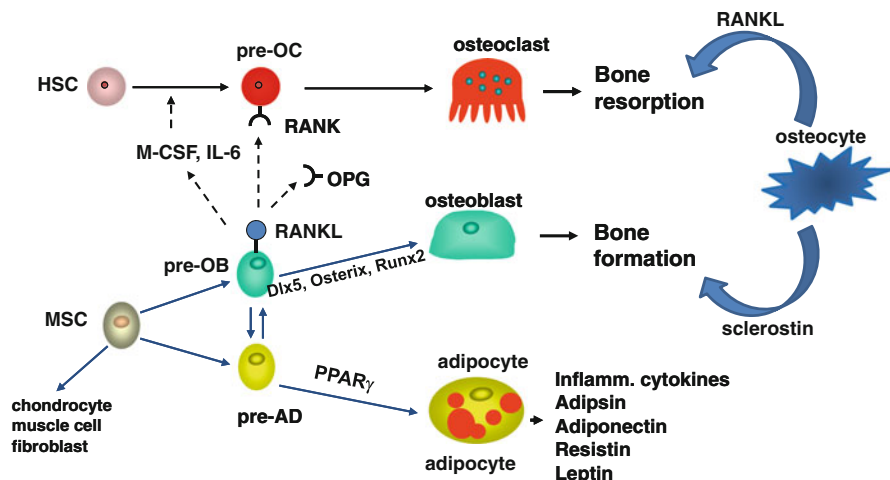
Fig. 7.1 Schematic representation of coupling between osteoblast, osteocyte, and osteoclast development and function. *MSC* mesenchymal stem cells, *HSC* hematopoietic stem cells

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 PPARγ2 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, TGFβ/BMP, and IGF-1 signaling pathways [12]. Process of bone remodeling is controlled by osteocytes, which represent specialized cells of osteoblast lineage [13]. They are located inside of bone mineralized matrix and communicate with other osteocytes and bone marrow environment through the system of dendrite-like processes. Osteocytes control dynamics of bone remodeling process by secreting RANKL to control bone resorption and sclerostin to control bone formation [13].

Bone as an Integral Part of Energy Metabolism System

Bone is closely integrated with the system regulating energy balance. Organs involved in this regulation including brain, fat, gastrointestinal system, and pancreas are secreting hormones which in endocrine manner regulate both energy metabolism and bone mass. Their effect on bone is possible because bone marrow cells, both mesenchymal and hematopoietic lineage, are equipped with necessary receptors to respond to these signaling (Fig. 7.2).

Integration of bone metabolism with energy metabolism has been presented recently as a model which links anabolic effect of insulin signaling in osteoblasts
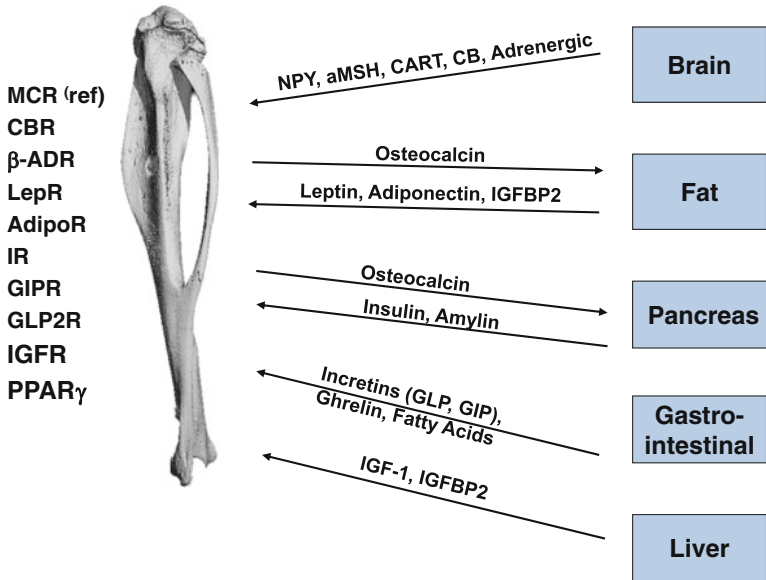
Fig. 7.2 Bone is a part of energy metabolism network. Factors and their receptors which mediate a cross-talk between bone and other organs involved in regulation of energy metabolism. *MCR* melanocortin receptor, *CBR* cannabinoid receptor, *LepR* leptin receptor, *AdipoR* adiponectin receptor, *GIPR* glucose inhibitory protein receptor, *GLP2R* glucagon inhibitory peptide receptor, *β-ADR* beta adrenergic receptor, *IR* insulin receptor, *IGFR* insulin growth factor receptor, *PPARγ* peroxisome proliferator activator receptor γ

with bone turnover and regulation of insulin sensitivity in peripheral organs [14, 15]. Thus, in osteoblasts insulin signaling regulates an expression of Runx2 and osteo-calcin 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 [14–17]. Although it is not clear whether this regulatory circuit is affected in diabetes, several studies suggest that patients with T2DM have decreased bone turnover [18–20]. If so, it would result in the decrease in osteocalcin production, especially its undercarboxylated form, which would lead to the attenu-ation of signaling responsible for increasing of insulin release from the pancreas and increasing fat sensitivity to insulin.

Anti-hyperglycemic Therapies and Their Effects on Bone

The most common form of diabetes is insulin-independent T2DM, which is charac-terized by insulin and glucose intolerance, and is associated with development of hyperglycemia and hyperinsulinemia. Therapies, either approved by FDA or in

Table 7.1 Antidiabetic drugs and their effects on skeleton

Target	Mode of action	Class of drugs	Drugs	Skeletal effect
Insulin	Sensitizers	Biguanides	Metformin[a]	Neutral
		TZDs (PPARγ agonists)	Pioglitazone[b], Rosiglitazone[b]	Bone loss; increased fractures
		Dual PPARα/ PPARγ agonists	Aleglitazar[c]	Unknown
	Secretagogues	K+ ATP	Sulfonylureas (e.g. Glyburide[a])	Neutral
			Meglitinides (e.g. Nateglinide)	Unknown
		GLP-1 analogs	Exenatide, Liraglutide, Taspoglutide[c], Albiglutide[c], Lixisenatide[c]	Unknown
		DPP-4 inhibitors	Alogliptin[c], Saxagliptin, Sitagliptin, Vildagliptin, Linagliptin	Decreased fractures
		Analogs/other insulins[a]	Insulin lispro, Insulin aspart, Insulin glargine	Increased fractures
Other	SGLT2 inhibitors		Canagliflozin, Dapagliflozin	Increased fractures
	Amylin analog		Pramlintide	Unknown
	Alpha-glucosidase inhibitors		Acarbose, Miglitol, Voglibose	Unknown

[a]World Health Organization Essential Medicine (WHO-EM)
[b]Restricted use in USA and Europe
[c]Phase III clinical trial was halted due to unfavorable renal effects

Phase III clinical trial, include insulin sensitizers, insulin secretagogues, and drugs which increase glucose excretion in the urine (SGLT2 inhibitors), regulate glucose absorption in intestine (amylin analog), and prevent digestion of carbohydrates (Alpha-glucosidase inhibitors) (Table 7.1).

In general, there is a lack of rigorous clinical evidence regarding the skeletal effects of these medications. Fracture is the primary outcome of interest but is a relatively rare outcome, requiring large studies. Randomized controlled trials (RCT) of diabetes medications have not included fracture as a primary endpoint, but increasingly studies are reporting the evidence from fractures identified as adverse events in RCTs. This provides the best evidence available to us regarding the clinical effects of these medications on the skeleton. Large observational studies have also considered the effects of diabetes medications on fracture risk. However, medications may be systematically prescribed to patients with different risk profiles for fracture, making it difficult to distinguish effects of the medications themselves on fracture, a problem known as "allocation bias" or "confounding by indication." Changes in bone mineral density are an important marker for skeletal health, but are not always a consistent predictor of the effects of a medication on fracture risk [21]. In addition, diabetic bone is compromised by other deficits, distinct from BMD, that have not been clearly delineated but may include increased cortical porosity and

greater accumulation of advanced glycation endproducts in bone collagen (see Chap. 9). As research clarifies which secondary markers are important predictors of fracture risk in diabetic patients, it will be essential to clarify how they are affected by diabetic medications.

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, stimulation of fatty acid oxidation in liver and increase in muscle glucose uptake [22]. 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 [23] and it has a negative effect on osteoclast differentiation and bone loss after ovariectomy by decreasing RANKL and increasing osteoprotegerin levels [24]. Interestingly, in rodent models 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 [25].

Human studies of the effects of metformin on the skeleton are limited in design and number. The only RCT with a fracture outcome that included metformin is the ADOPT trial, discussed in more detail in the section on "Thiazolidinediones (Rosiglitazone, Pioglitazone)" [26]. Briefly, this trial randomized participants to receive metformin, glyburide (a sulfonylurea), or rosiglitazone; the primary outcome was time to monotherapy failure. Fractures were identified as adverse events. The fracture rates were similar in those randomized to metformin or glyburide. During the first 12 months of ADOPT, changes in the levels of the bone resorption marker CTX were similar in women (difference in 12-months change: +2.0 %) and modestly greater in men (−8.4 %) in those assigned to metformin compared with glyburide [27]. The metformin group had greater decreases in levels of the bone formation marker P1NP (difference in 12-months change: −9.4 % women; −19.5 % men), compared with glyburide.

Several observational studies have reported a lower risk of fracture with metformin use. In a study of the Danish population, metformin use was associated with lower fracture risk, compared with nondiabetic residents [28]. In the Rochester cohort, metformin use was associated with a lower rate of fracture in T2DM patients

(adjusted hazard ratio 0.7; 95% CI 0.6–0.96) [29]. However, other studies have found no difference in fracture risk with metformin use [30–35]. Interestingly, results from a study of hip fracture in Scotland suggest that metformin tends to be prescribed to patients with a lower overall risk of fracture while sulfonylureas are prescribed to those at higher risk [33]. This finding suggests that some of the reduction in fracture risk reported with metformin use in observational studies may be due to the underlying prescribing pattern.

Insulin

There are no randomized trials of insulin therapy with fracture or BMD outcomes. Most observational studies have identified increased fracture risk in those using insulin [29–31, 36–38] although others have not found an increased risk [28, 33]. Insulin treatment is also associated with a higher risk of falls [39, 40], and this is likely a contributing factor to the increased fracture risk. Insulin does not appear to have a negative effect on bone; indeed, preclinical studies suggest an anabolic effect. Increased falls and fractures may be the result of more frequent episodes of hypoglycemia and greater frailty due to diabetic complications.

Thiazolidinediones (Rosiglitazone, Pioglitazone)

TZDs increase insulin sensitivity via activation of peroxisome proliferator-activated receptor (PPARγ). 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 [41]. 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 [42]. This association resulted in a recent review of rosiglitazone safety by the FDA and recommendation for its restricted use in the United States. Interestingly, pioglitazone use is associated with a significantly lower risk of death and lower number of myocardial infarction and stroke incidence [43], 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 [44]. 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 the skeleton [45, 46]. The crucial clinical evidence of a causal connection between TZD therapy and

increased fracture risk was determined from secondary analyses of results from randomized clinical trials of rosiglitazone and pioglitazone. The first demonstration of increased fracture risk was reported from ADOPT (A Diabetes Outcome Progression Trial), designed to compare time to monotherapy failure of rosiglitazone, metformin and glyburide in recently diagnosed T2DM patients [41]. Because of growing concern, based on rodent models and clinical trials, that TZDs might have a negative effect on bone, the investigators undertook a post hoc analysis of fracture rates in the three groups, using adverse event reports to identify fractures. In 1840 women and 2511 men with a median follow-up of 4.0 years and an average age of 56 (SD 10) years, fracture rates in men did not differ across treatment groups [26, 41]. However, in women, the cumulative incidence of fractures at 5 years was 15.1 % (11.2–19.1) with rosiglitazone, 7.3 % (95 % CI 4.4–10.1) with metformin, and 7.7 % (95 % CI 3.7–11.7) with glyburide, representing hazard ratios of 1.81 (95 % CI 1.17–2.80) and 2.13 (95 % CI 1.30–3.51) for rosiglitazone compared with metformin and glyburide, respectively. Increased fracture rates were seen in the lower and upper limbs. The incidence of hip and clinical vertebral fractures did not differ across treatment assignments, but only four hip and three clinical vertebral fractures were reported in women, as expected in the age range of this trial. Rosiglitazone was associated with higher fracture rates in both pre-and postmenopausal women, suggesting that estrogen status does not modify the effect on bone.

Soon after the ADOPT findings were published, Takeda performed a meta-analysis of pioglitazone trials and reported a similar pattern of increased fracture risk in women, but not men [47]. These observations were subsequently corroborated by other randomized trials. An early meta-analysis of data from ten different randomized controlled trials confirmed that TZD use doubles the risk of fractures exclusively in women [48]. More recently, a meta-analysis of 22 randomized controlled trials, including 896 fracture events, reported increased fracture incidence in women (OR = 1.94; 95 % CI 1.60–2.35) but not in men (OR = 1.02; 95 % CI 0.83–1.27) [49]. Effects in women were similar for rosiglitazone (OR = 2.10; 95 % CI 1.61–2.51) and pioglitazone (OR = 1.73; 95 % CI 1.18–2.55).

Because the TZD trials have included few hip or vertebral fractures, it is necessary to rely on observational studies to assess whether TZD use increases fractures at these particular skeletal sites. A study using registry data in Scotland focused exclusively on hip fracture risk and reported increased risk with greater cumulative TZD use among those with any use (OR per year of exposure 1.18; 95 % CI 1.09–1.28) [33]. Results were similar for pioglitazone and rosiglitazone considered separately. In contrast to reports from randomized trials, increased hip fracture risk was found in men (OR per year of exposure 1.20; 95 % CI 1.03, 1.41) as well as women (OR per year of exposure 1.18; 95 % CI 1.07, 1.29). Those with >4 years of TZD use had OR for hip fracture of 1.94 (95 % CI 1.28, 2.94), compared with those who used a TZD for up to 2 years. Finally, results were similar when evaluated in a subset with adjustment for use of other antidiabetic medications (insulin, metformin, or sulfonylurea). A large observational study using the UK General Practice Research Database also concluded that TZD use increased hip fracture incidence (Rate Ratio 2.09; 95 % CI 1.29–3.40) as well as spine fracture incidence (RR 2.72; 95 % CI

1.29–5.73) [50]. This study reported similar increases in risk of any fracture in men (RR 1.44; 95 % CI 1.18–1.77) and women (RR 1.42; 95 % CI 1.20–1.69).

The principal mechanism underlying increased fracture risk with TZD use appears to be bone loss. A recent meta-analysis of ten randomized clinical trials that assessed change in BMD reported greater bone loss at the lumbar spine, total hip and femoral neck in women randomized to TZD treatment compared with placebo or other antidiabetic medication [49]. Only one trial included men.

Clinical studies of changes in bone turnover markers with TZD treatment have not provided consistent results. In the largest study to date, 12-month changes in serum markers were assessed in 1605 participants in ADOPT [27]. This analysis showed modest but statistically significant increases in levels of resorption marker C-terminal telopeptide (CTX) in women on rosiglitazone therapy compared with glyburide (10.7 % difference, $p=0.002$) or metformin (7.3 % difference, $p=0.029$). In men, CTX was elevated in the rosiglitazone group compared with metformin (12.2%, $p<0.001$) but not compared with glyburide. Both genders had modest reductions in levels of the marker of bone formation P1NP (women −4.4 %, men −14.4 %), but those in the metformin arm experienced greater reductions. For women, changes in P1NP did not differ between the rosiglitazone and glyburide groups while in men losses were greater in the rosiglitazone group. Although rodent models suggest an important role for reduced bone formation as a mechanism of bone loss with TZD treatment, the ADOPT results instead indicate that increases in bone resorption may explain at least in part the increased fracture rate in women on TZD therapy [27].

Smaller trials of rosiglitazone treatment have also reported relative increases in markers of bone resorption compared to placebo [51, 52] and to metformin [53]. However, others have reported a relative reduction in bone formation markers with rosiglitazone treatment, compared with placebo [54] or with diet only treatment [55], and others have reported no difference [56]. For pioglitazone, the largest trial included 156 postmenopausal women with prediabetes and found no differences in bone turn-over markers after 12 months compared with placebo [57]. In contrast, a trial in 71 diabetic men reported relative increases in markers of bone resorption (CTX) and formation (P1NP) in the pioglitazone group compared with metformin [58] while a trial in 86 diabetic men and women found a relative increase in a formation but not a resorption marker with pioglitazone treatment compared with placebo [59].

Taken together, results of available clinical studies indicate the following regarding TZD use (1) women are at increased risk of fractures; however, some studies point to elevated risk in men as well; (2) the increased fracture risk appears to be a class effect of currently available TZDs; (3) bone loss is an underlying mechanism; (4) fracture risk is increased in the extremities and most likely at the hip and spine as well.

Mechanism of TZD-Induced Bone Loss

PPARγ, an essential regulator of lipid, glucose, and insulin metabolism [10], is a target for TZDs. The PPARγ protein is expressed in mice and humans in two iso-forms, PPARγ1 and PPARγ2. PPARγ1 is expressed in a variety of cell types,

including cells of hematopoietic lineage macrophages and osteoclasts [60], whereas PPARγ2 expression is restricted to cells of mesenchymal lineage adipocytes [61]. In bone, PPARγ2 plays an important role in regulation of MSC differentiation toward osteoblasts and adipocytes, and the maintenance of bone mass. Activation of the PPARγ2 isoform with rosiglitazone converts cells of osteoblast lineage to terminally differentiated adipocytes and irreversibly suppresses both the osteoblast phenotype and osteoblast-specific gene expression. Thus, in MSCs PPARγ2 acts as a positive regulator of adipocyte differentiation and a dominant-negative regulator of osteoblast differentiation [11, 62]. In contrast, PPARγ1 expressed in HSC promotes osteoclast differentiation and bone resorption [60]. It controls an expression of c-fos protein, an important determinant of osteoclast lineage commitment and development.

An essential role of PPARγ in maintenance of bone homeostasis was demonstrated in several animal models of either bone accrual or bone loss depending on the status of PPARγ activity [63–68]. In models of bone accrual, a decrease in PPARγ activity in either heterozygous PPARγ-deficient mice or mice carrying a hypomorphic mutation in the PPARγ gene locus led to increased bone mass due to increased quantity of osteoblasts [66, 68]. Interestingly, mice deficient in PPARγ expression in cells of hematopoietic lineage develop osteopetrosis and are less sensitive to the TZD-induced bone loss than control mice [60]. In contrast, in rodent models of bone loss due to PPARγ activation, administration of rosiglitazone resulted in significant decreases in BMD, bone volume, and changes in bone microarchitecture [63, 67, 69]. 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 PPARγ expression. In younger animals with less PPARγ, bone loss was less extensive than in older animals [69]. 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 [69]. In addition, studies of rosiglitazone effects in estrogen deficient rats showed that bone loss occurred mainly due to increased bone resorption [64]. In conclusion, animal studies suggest that aging and estrogen deficiency confound TZD-induced bone loss and determine its mechanism.

The negative effect of TZDs on osteoblastogenesis includes decreased activity of Runx2, Dlx5, and Osterix, which are osteoblast-specific transcription factors, and decreased activity of osteoblast-specific signaling pathways controlling bone homeostasis, among them Wnt, TGF-β/BMP, and IGF-1 [70, 71]. The effect of TZDs on the expression of genes essential for osteoblast development is 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 [69, 72]. The complexity of TZDs effects on bone remodeling resulting from changes on osteoblast and osteoclast differentiation and alterations in bone marrow milieu supporting remodeling are summarized in Fig. 7.3.
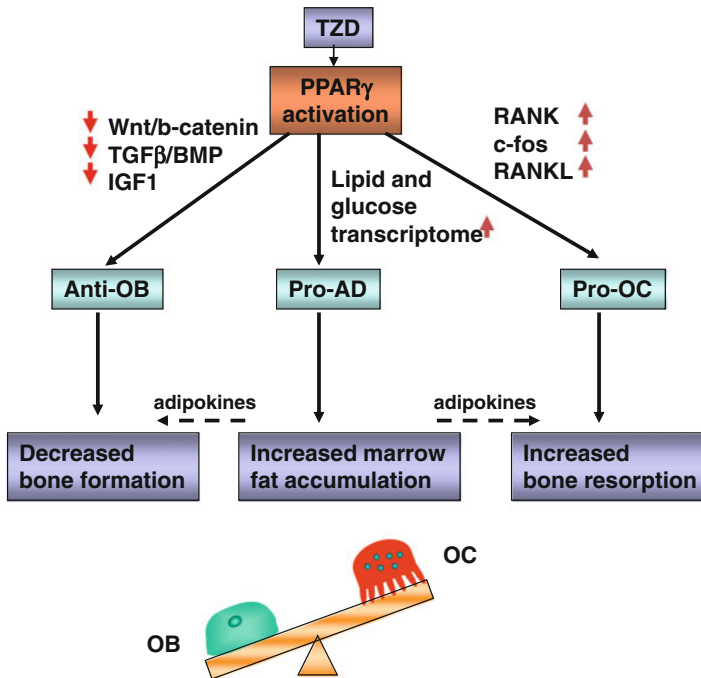
Fig. 7.3 PPARγ activation with TZDs leads to multiple direct and indirect effects in the bone marrow which result in changes in bone cell differentiation, unbalanced bone remodeling and ultimately bone loss. *Anti-OB* PPARγ activity inhibiting osteoblast differentiation, *pro-AD* PPARγ activity stimulating adipocyte differentiation, and *pro-OC* PPARγ activity stimulating osteoclast differentiation

Novel Selective PPARγ Modulators with Beneficial Effect of Insulin Sensitizers and No Effect on Adipocyte Differentiation

The PPARγ 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 PPARγ post-translational modifications (PTMs), including phosphorylation, acetylation and sumoylation, and differential recruitment of coactivators, which determine specific activities of this nuclear receptor [73]. The molecular studies provide evidence for distinct mechanisms regulating the proadipocytic, antiosteoblastic, and insulin sensitizing activities of PPARγ and include the levels of Serine 273 and Serine 112 phosphorylation and functional interaction with other proteins such as β-catenin and molecular chaperons FKBP51 and PP5 [74–77].

The concern of TZDs adverse effects has prompted pharmaceutical efforts to develop selective PPARγ modulators which will retain high potency to treat diabetic disease with minimal adverse effects [78]. The PPARγ selective activators, with a decreased proadipocytic activity but intact insulin sensitizing activity such as

netoglitazone, INT131, MSDC-0602 and telmisartan do not affect bone mass in mice treated with the therapeutic doses [79–82]. A new class of insulin sensitizers with structural similarities to telmisartan, which block Serine 273 phosphorylation but do not stimulate PPARγ transcriptional proadipocytic activity, has been recently developed [74, 83], however their safety for bone is not as yet determined.

Sulfonylureas

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. In addition, sulfonylureas are associated with greater frequency of hypoglycemia which may increase the risk of falls and fractures [84].

In the ADOPT trial, described earlier, fracture incidence was similar in those randomized to a sulfonylurea (glyburide) versus metformin [41]. The results of observational studies have been inconsistent with reports of increased [34], decreased [28, 31] and no difference [29, 30, 32, 35, 50, 85, 86] in fracture risk among those using a sulfonylurea. As noted in a recent review of current literature [87], although a large number of studies have reported no association with fracture, the majority of these studies were not specifically intended to assess the impact of sulfonylureas in particular on fracture. Allocation bias is an important consideration in observational studies, and results from a study in Scotland suggest that patients using sulfonylureas tend to have a higher background fracture risk [33]. Although sulfonylureas increase hypoglycemic episodes, an observational study conducted among Kaiser Permanente members did not find an association between sulfonylurea use and incident falls, identified through inpatient and outpatient medical records [88].

Incretin Analogs and DPP4 Protease Inhibitors

This newest class of antidiabetic drugs enhances the mechanism by which enteric hormones stimulate insulin release from β-cells and inhibit glucagon production in the liver [89]. 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 [90]. Recently, incretin mimetics (GLP1 receptor agonists) and DPP-4 inhibitors have emerged as a new class of pharmacological agents to enhance incretins action and improve glycemic control in patients with T2DM. Incretin mimetics 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 [91–93].

Nutritional hormones are known to be important in bone turnover; as soon as a meal is ingested, bone breakdown is suppressed [94, 95]. 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 [96], while GIP can act both as an antiresorptive and anabolic hormone [97, 98]. 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 [99]. 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 [99]. 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 [100]. In summary, a number of animal studies indicate that incretins have beneficial effects on bone mass and protective effects on bone quality. Therefore, antidiabetic therapies which increase GIP and GLP hormone levels and their bioactivity might exert beneficial effects on human bone.

Since incretin-based therapy is relatively new, the clinical data of its safety for bone is just emerging. The 44-week treatment of T2DM patients with incretin mimetic exenatide did not decrease total body BMD, although it decreased body weight by 6 % [101]. Currently, two meta-analyses of incretin mimetics and fracture outcomes, reported as serious adverse events, have been published. The first meta-analysis included seven trials with placebo or other antidiabetic medications as the comparison group and a total of 19 fractures [102]. There was no difference in fracture incidence between incretin mimetic treatment and the comparator groups (MH OR 0.75; 95 % CI 0.28–2.02), but confidence intervals were wide. A second meta-analysis included 14 trials with 38 fractures and also found no difference in fracture incidence (MH OR 1.05; 95 % CI 0.59–1.87) [103]. However, when examined separately, the investigators found decreased fracture incidence for liraglutide treatment (MH OR 0.38; 95 % CI 0.17–0.87) and increased fracture incidence for exenatide treatment (MH OR 2.09; 95 % CI 1.03–4.21), both compared with placebo or other antidiabetic medications. The reason for this difference is not immediately apparent and may be a chance finding. Liraglutide and exenatide have similar effects on blood glucose and body weight without an increased frequency of hypoglycemia. An important limitation of these trials is their relatively short length for the purposes of assessing fracture risk. Only five of the trials were 52 weeks or longer, and effects on fracture risk that are operating through changes in bone would be expected to develop over periods of a year or more.

A meta-analysis of 28 clinical trials of DPP-4 inhibitors with duration of at least 24 weeks included 63 fractures reported as serious adverse events. Treatment with DPP-4 inhibitors was associated with a reduced risk of fractures (Mantel Haenszel Odds Ratio 0.60; 95 % CI 0.37–0.99) compared to placebo and other treatments [104]. Excluding TZDs or sulfonylurea as comparators yielded similar results (MH OR 0.56; 95 % CI 0.33–0.93). As noted for the trials of incretin mimetics, an important weakness of these results is the short duration of the trials. Only 7 of the 28 trials were 52 weeks or longer. More clinical studies on the effects of incretin mimetics and DPP-4 inhibitors on BMD and fracture risk with stratification according to gender, postmenopausal status, and age are needed.

SGLT2 Inhibitors

In 2013 and 2014 the first of two SGLT2 inhibitors class of diabetes drugs, canagliflozin and dapagliflozin, were approved by FDA for improving glycemic control in T2DM patients in conjunction with diet and exercise. Both drugs are selective and reversible inhibitors of sodium glucose co-transporter 2 (SGLT2), which is responsible for the majority of glucose reabsorption in kidney. Bone safety of dapagliflozin has been evaluated in a randomized trial, adding study drug or placebo to metformin in T2DM patients with inadequate control on metformin. Results have been reported after 50 weeks [105] and 102 weeks [106] of treatment. At 102 weeks, the trial was completed by 140 patients, men and postmenopausal women. The dapagliflozin group lost more weight than the placebo group (difference of −2.42 kg; 95 % CI −3.64, −1.21). In spite of the greater weight loss, no significant differences were identified in changes from baseline in markers of bone formation (P1NP) and bone resorption (CTX). Bone loss was greater at the femoral neck in those treated with dapagliflozin but the difference was not statistically significant (difference −0.94 %; 95 % CI −2.21, 0.35). Differences in BMD changes at the lumbar spine and total hip were smaller and also not statistically significant. There were no significant treatment-by-gender interactions. In a 104-week trial of dapagliflozin to assess efficacy among T2DM patients with moderate renal impairment, 252 patients were randomized to dapagliflozin (5 or 10 mg) or placebo. The treated groups lost weight compared with placebo but glycemic control was not different. More fractures were reported in the treated groups ($N=13$) than the placebo group ($N=0$). Dapagliflozin is not recommended for use in patients with moderate renal impairment [107].

There are no available studies of the effects of canagliflozin on bone turnover or BMD. Increased incidence of upper extremity fractures with canagliflozin treatment was reported in the Prescribing Information by the manufacturer [108]. In a meta-analysis of eight clinical trials with longer mean duration of treatment (68 weeks), the incidence rate of fracture was 14.2, 18.7, and 17.6 per 1000 patient-years of exposure to comparator, canagliflozin 100 mg and canagliflozin 300 mg. FDA approval for canagliflozin included a requirement for postmarketing studies to monitor for bone safety [109].

Amylin Analogs

Amylin, also known as Islet Amyloid Polypeptide (IAPP), is a 37-residue peptide hormone produced in pancreatic β-cells. Amylin is co-secreted with insulin and plays a role in glycemic regulation by slowing gastric emptying, promoting satiety and decreasing glucose levels in circulation. Amylin, like insulin, is absent in individuals with T1DM. Amylin belongs to the family of regulatory hormones that are structurally and functionally related to calcitonin, calcitonin gene-related peptide and adrenomedulin, and signals through the calcitonin receptor modified for amylin-specific activity by binding to receptor activity modifying proteins (RAMP) [110]. Cellular studies have shown that amylin may stimulate osteoblast proliferation and may inhibit osteoclast development and activity through increasing cyclic AMP [111]. These activities have been confirmed in several animal studies which showed a positive effect of amylin on trabecular and cortical bone volume [111] and some of them are indicative that the bone response to amylin may differ depending on diabetes status [112].

Human data suggest that there is a functional link between amylin and skeletal health. Amylin levels decrease with aging and correlate inversely with osteoporosis [113]. In addition, reduced amylin levels are associated with low BMD in women with anorexia nervosa and are significant predictors of BMD and of Z-scores at the femoral neck and at the total hip in this group of patients [114].

An analog of amylin, pramlintide, had been approved for therapy in 2005 by FDA to treat diabetes. It is used as an adjunctive therapy with insulin in both T1DM and T2DM. Pramlintide allows patients to use less insulin, because it improves hemoglobin 1Ac levels, lowers average blood sugar levels, and substantially reduces blood sugar that occurs in diabetic individuals right after eating.

Although animal studies suggest positive effect of amylin on bone, the clinical studies do not provide supporting results. Pramlintide safety on bone was assessed in a study conducted on patients with T1DM who injected the drug for 12 months. BMD measurements of the lumbar spine by dual-energy X-ray absorptiometry (DXA), and biochemical markers of bone metabolism (serum-calcium, PTH, osteo-calcin, urinary pyridinium cross-links) before and one year after starting pramlintide therapy showed no significant changes. It is concluded that a 1-year pramlintide therapy does not affect bone density or bone metabolism in patients with type 1 diabetes mellitus without osteopenia (based on the markers used) [115].

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates, specifically alpha-glucosidase enzymes in the brush border of the small intestines, which subsequently leads to the reduction of blood sugar levels. Therapy with alpha-glucosidase inhibitors is associated with

several side effects which are in close relation to their mechanism of action and include increased levels of carbohydrates in the intestine causing flatulence and diarrhea. There are no available information on bone safety of alpha-glucosidase inhibitors.

Conclusions

In conclusion, the available evidence indicates that antidiabetic therapies may either increase fracture risk (TZDs and insulin), may not affect this risk (sulfonylureas and metformin) or may possibly decrease the risk (DPP-4 inhibitors). 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. Animal studies suggest that aging and estrogen deficiency may modify the effects of TZDs on bone and determine the mechanism of bone loss. The emerging potential of incretin-based therapies as sparing or perhaps even beneficial for bones requires systematic clinical assessment in the future.

References

1. Parfitt AM. Osteonal and hemi-osteonal remodeling: the spatial and temporal framework for signal traffic in adult human bone. J Cell Biochem. 1994;55(3):273–86.
2. Teitelbaum SL, Ross FP. Genetic regulation of osteoclast development and function. Nat Rev Genet. 2003;4(8):638–49.
3. Jiang Y, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature. 2002;418(6893): 41–9.
4. Bianco P, Riminucci M, Gronthos S, Robey PG. Bone marrow stromal stem cells: nature, biology, and potential applications. Stem Cells. 2001;19(3):180–92.
5. Aubin JE. Regulation of osteoblast formation and function. Rev Endocr Metab Disord. 2001;2(1):81–94.
6. Ducy P, Zhang R, Geoffroy V, Ridall AL, Karsenty G. Osf2/Cbfa1: a transcriptional activator of osteoblast differentiation. Cell. 1997;89(5):747–54.
7. Komori T, Yagi H, Nomura S, Yamaguchi A, Sasaki K, Deguchi K, et al. Targeted disruption of Cbfa1 results in a complete lack of bone formation owing to maturational arrest of osteoblasts. Cell. 1997;89(5):755–64.
8. Karsenty G. Minireview: transcriptional control of osteoblast differentiation. Endocrinology. 2001;142(7):2731–3.
9. Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPARgamma 2, a lipid-activated transcription factor [published erratum appears in Cell 1995 Mar 24;80(6):following 957]. Cell. 1994;79(7):1147–56.

10. Rosen ED, Spiegelman BM. PPARgamma: a nuclear regulator of metabolism, differentiation, and cell growth. J Biol Chem. 2001;276(41):37731–4.

11. Lecka-Czernik B, Gubrij I, Moerman EA, Kajkenova O, Lipschitz DA, Manolagas SC, et al. Inhibition of Osf2/Cbfa1 expression and terminal osteoblast differentiation by PPAR-gamma 2. J Cell Biochem. 1999;74(3):357–71.

12. Lian JB, Stein GS, Javed A, van Wijnen AJ, Stein JL, Montecino M, et al. Networks and hubs for the transcriptional control of osteoblastogenesis. Rev Endocr Metab Disord. 2006;7(1–2): 1–16.

13. Bonewald LF. The amazing osteocyte. J Bone Miner Res. 2011;26(2):229–38. Pubmed Central PMCID: 3179345.

14. Fulzele K, Riddle RC, Digirolamo DJ, Cao X, Wan C, Chen D, et al. Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition. Cell. 2010;142(2):309–19.

15. Ferron M, Wei J, Yoshizawa T, Del Fattore A, Depinho RA, Teti A, et al. Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. Cell. 2010;142(2):296–308.

16. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, et al. Endocrine regulation of energy metabolism by the skeleton. Cell. 2007;130(3):456–69.

17. Clemens TL, Karsenty G. The osteoblast: an insulin target cell controlling glucose homeostasis. J Bone Miner Res. 2011;26(4):677–80.

18. Krakauer JC, McKenna MJ, Buderer NF, Rao DS, Whitehouse FW, Parfitt AM. Bone loss and bone turnover in diabetes. Diabetes. 1995;44(7):775–82.

19. Reyes-Garcia R, Rozas-Moreno P, Lopez-Gallardo G, Garcia-Martin A, Varsavsky M, Aviles-Perez MD, et al. Serum levels of bone resorption markers are decreased in patients with type 2 diabetes. Acta Diabetol. 2013;50(1):47–52.

20. Garcia-Martin A, Rozas-Moreno P, Reyes-Garcia R, Morales-Santana S, Garcia-Fontana B, Garcia-Salcedo JA, et al. Circulating levels of sclerostin are increased in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2012;97(1):234–41.

21. Silverman SL, Cummings SR, Watts NB. Recommendations for the clinical evaluation of agents for treatment of osteoporosis: consensus of an expert panel representing the American Society for Bone and Mineral Research (ASBMR), the International Society for Clinical Densitometry (ISCD), and the National Osteoporosis Foundation (NOF). J Bone Miner Res. 2008;23(1):159–65.

22. Zhou S, Schuetz JD, Bunting KD, Colapietro AM, Sampath J, Morris JJ, et al. The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. Nat Med. 2001;7(9):1028–34.

23. Jang WG, Kim EJ, Bae IH, Lee KN, Kim YD, Kim DK, et al. Metformin induces osteoblast differentiation via orphan nuclear receptor SHP-mediated transactivation of Runx2. Bone. 2011;48(4):885–93.

24. Mai QG, Zhang ZM, Xu S, Lu M, Zhou RP, Zhao L, et al. Metformin stimulates osteoprotegerin and reduces RANKL expression in osteoblasts and ovariectomized rats. J Cell Biochem. 2011;112(10):2902–9.

25. Sedlinsky C, Molinuevo MS, Cortizo AM, Tolosa MJ, Felice JI, Sbaraglini ML, et al. Metformin prevents anti-osteogenic in vivo and ex vivo effects of rosiglitazone in rats. Eur J Pharmacol. 2011;668(3):477–85.

26. Kahn SE, Zinman B, Lachin JM, Haffner SM, Herman WH, Holman RR, et al. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). Diabetes Care. 2008;31(5):845–51.

27. Zinman B, Haffner SM, Herman WH, Holman RR, Lachin JM, Kravitz BG, et al. Effect of rosiglitazone, metformin, and glyburide on bone biomarkers in patients with type 2 diabetes. J Clin Endocrinol Metab. 2010;95(1):134–42.

28. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia. 2005;48(7):1292–9.

29. Melton LJ, Leibson CL, Achenbach SJ, Therneau TM, Khosla S. Fracture risk in type 2 diabetes: update of a population-based study. J Bone Miner Res. 2008;23(8):1334–42.

30. Monami M, Cresci B, Colombini A, Pala L, Balzi D, Gori F, et al. Bone fractures and hypoglycemic treatment in type 2 diabetic patients: a case-control study. Diabetes Care. 2008;31(2):199–203. Epub 2007/11/21. Eng.

31. Kanazawa I, Yamaguchi T, Yamamoto M, Sugimoto T. Relationship between treatments with insulin and oral hypoglycemic agents versus the presence of vertebral fractures in type 2 diabetes mellitus. J Bone Miner Metab. 2010;28(5):554–60. Epub 2010/02/24. Eng.

32. Bilik D, McEwen LN, Brown MB, Pomeroy NE, Kim C, Asao K, et al. Thiazolidinediones and fractures: evidence from translating research into action for diabetes. J Clin Endocrinol Metab. 2010;95(10):4560–5. Epub 2010/07/16. Eng.

33. Colhoun HM, Livingstone SJ, Looker HC, Morris AD, Wild SH, Lindsay RS, et al. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia. 2012;55(11):2929–37. Pubmed Central PMCID: 3464390, Epub 2012/09/05. Eng.

34. Napoli N, Strotmeyer ES, Ensrud KE, Sellmeyer DE, Bauer DC, Hoffman AR, et al. Fracture risk in diabetic elderly men: the MrOS study. Diabetologia. 2014;57(10):2057–65. Epub 2014/06/09. Eng.

35. Tzoulaki I, Molokhia M, Curcin V, Little MP, Millett CJ, Ng A, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ. 2009;339:b4731. Pubmed Central PMCID: 2788912, Epub 2009/12/05. Eng.

36. Ivers RQ, Cumming RG, Mitchell P, Peduto AJ. Diabetes and risk of fracture: The Blue Mountains Eye Study. Diabetes Care. 2001;24(7):1198–203.

37. Ahmed LA, Joakimsen RM, Berntsen GK, Fonnebo V, Schirmer H. Diabetes mellitus and the risk of non-vertebral fractures: the Tromsø study. Osteoporos Int. 2006;17(4):495–500. Epub 2005/11/12. Eng.

38. Schwartz AV, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA. 2011;305(21):2184–92. Pubmed Central PMCID: NIHMSID, Epub 2011/06/03. Eng.

39. Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, et al. Older women with diabetes have a higher risk of falls: a prospective study. Diabetes Care. 2002;25(10):1749–54.

40. Volpato S, Leveille SG, Blaum C, Fried LP, Guralnik JM. Risk factors for falls in older disabled women with diabetes: the women's health and aging study. J Gerontol A Biol Sci Med Sci. 2005;60(12):1539–45.

41. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355(23):2427–43.

42. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007;356(24):2457–71.

43. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA. 2007;298(10):1180–8.

44. Yki-Jarvinen H. Thiazolidinediones. N Engl J Med. 2004;351(11):1106–18.

45. Grey A. Skeletal consequences of thiazolidinedione therapy. Osteoporos Int. 2008;19(2):129–37.

46. Lecka-Czernik B. Bone loss in diabetes: use of anti-diabetic thiazolidinediones and secondary osteoporosis. Curr Osteoporos Rep. 2010;8(4):178–84. doi:10.1007/s11914-010-0027-y.

47. Takeda. Observation of an increased incidence of fractures in female patients who received long-term treatment with ACTOS® (pioglitazone HCl) tablets for type 2 diabetes mellitus (Letter to Health Care Providers). Indianapolis: Takeda Pharmaceuticals North America; 2007.

48. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ. 2009;180(1):32–9.

49. Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone. 2014;68:115–23. Epub 2014/09/01. Eng.

50. Douglas IJ, Evans SJ, Pocock S, Smeeth L. The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. PLoS Med. 2009;6(9):e1000154. Pubmed Central PMCID: PMC2741577, Epub 2009/09/30. Eng.

51. Gruntmanis U, Fordan S, Ghayee HK, Abdullah SM, See R, Ayers CR, et al. The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone increases bone resorption in women with type 2 diabetes: a randomized, controlled trial. Calcif Tissue Int. 2010;86(5):343–9. Epub 2010/04/01. Eng.

52. Harslof T, Wamberg L, Moller L, Stodkilde-Jorgensen H, Ringgaard S, Pedersen SB, et al. Rosiglitazone decreases bone mass and bone marrow fat. J Clin Endocrinol Metab. 2011;96(5):1541–8. Epub 2011/03/04. Eng.

53. Bilezikian JP, Josse RG, Eastell R, Lewiecki EM, Miller CG, Wooddell M, et al. Rosiglitazone decreases bone mineral density and increases bone turnover in postmenopausal women with type 2 diabetes mellitus. J Clin Endocrinol Metab. 2013;98(4):1519–28. Epub 2013/03/02. Eng.

54. Grey A, Bolland M, Gamble G, Wattie D, Horne A, Davidson J, et al. The peroxisome-proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. J Clin Endocrinol Metab. 2007;92(4):1305–10.

55. Berberoglu Z, Yazici AC, Demirag NG. Effects of rosiglitazone on bone mineral density and remodelling parameters in postmenopausal diabetic women: a 2-year follow-up study. Clin Endocrinol (Oxf). 2010;73(3):305–12. Epub 2010/02/13. Eng.

56. Borges JL, Bilezikian JP, Jones-Leone AR, Acusta AP, Ambery PD, Nino AJ, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naive type 2 diabetes mellitus patients. Diabetes Obes Metab. 2011;13(11):1036–46. Epub 2011/06/21. Eng.

57. Bone HG, Lindsay R, McClung MR, Perez AT, Raanan MG, Spanheimer RG. 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(12):4691–701. Epub 2013/09/24. Eng.

58. van Lierop AH, Hamdy NA, van der Meer RW, Jonker JT, Lamb HJ, Rijzewijk LJ, et al. Distinct effects of pioglitazone and metformin on circulating sclerostin and biochemical markers of bone turnover in men with type 2 diabetes mellitus. Eur J Endocrinol. 2012;166(4):711–6. Epub 2012/01/24. Eng.

59. Grey A, Bolland M, Fenwick S, Horne A, Gamble G, Drury PL, et al. The skeletal effects of pioglitazone in type 2 diabetes or impaired glucose tolerance: a randomized controlled trial. Eur J Endocrinol. 2014;170(2):257–64. Epub 2013/11/13. Eng.

60. Wan Y, Chong LW, Evans RM. PPAR-gamma regulates osteoclastogenesis in mice. Nat Med. 2007;13(12):1496–503.

61. Ren D, Collingwood TN, Rebar EJ, Wolffe AP, Camp HS. PPARgamma knockdown by engineered transcription factors: exogenous PPARgamma2 but not PPARgamma1 reactivates adipogenesis. Genes Dev. 2002;16(1):27–32.

62. Lecka-Czernik B, Moerman EJ, Grant DF, Lehmann JM, Manolagas SC, Jilka RL. Divergent effects of selective peroxisome proliferator-activated receptor-gamma 2 ligands on adipocyte versus osteoblast differentiation. Endocrinology. 2002;143(6):2376–84.

63. Rzonca SO, Suva LJ, Gaddy D, Montague DC, Lecka-Czernik B. Bone is a target for the antidiabetic compound rosiglitazone. Endocrinology. 2004;145(1):401–6.

64. Sottile V, Seuwen K, Kneissel M. Enhanced marrow adipogenesis and bone resorption in estrogen-deprived rats treated with the PPARgamma agonist BRL49653 (rosiglitazone). Calcif Tissue Int. 2004;75(4):329–37.

65. Soroceanu MA, Miao D, Bai XY, Su H, Goltzman D, Karaplis AC. Rosiglitazone impacts negatively on bone by promoting osteoblast/osteocyte apoptosis. J Endocrinol. 2004;183(1):203–16.

66. Cock TA, Back J, Elefteriou F, Karsenty G, Kastner P, Chan S, et al. Enhanced bone formation in lipodystrophic PPARgamma(hyp/hyp) mice relocates haematopoiesis to the spleen. EMBO Rep. 2004;5(10):1007–12.

67. Ali AA, Weinstein RS, Stewart SA, Parfitt AM, Manolagas SC, Jilka RL. Rosiglitazone causes bone loss in mice by suppressing osteoblast differentiation and bone formation. Endocrinology. 2005;146(3):1226–35.

68. Akune T, Ohba S, Kamekura S, Yamaguchi M, Chung UI, Kubota N, et al. PPARgamma insufficiency enhances osteogenesis through osteoblast formation from bone marrow progenitors. J Clin Invest. 2004;113(6):846–55.

69. Lazarenko OP, Rzonca SO, Hogue WR, Swain FL, Suva LJ, Lecka-Czernik B. Rosiglitazone induces decreases in bone mass and strength that are reminiscent of aged bone. Endocrinology. 2007;148(6):2669–80.

70. Shockley KR, Lazarenko OP, Czernik PJ, Rosen CJ, Churchill GA, Lecka-Czernik B. PPARg2 nuclear receptor controls multiple regulatory pathways of osteoblast differentiation from marrow mesenchymal stem cells. J Cell Biochem. 2009;106(2):232–46.

71. Lecka-Czernik B, Ackert-Bicknell C, Adamo ML, Marmolejos V, Churchill GA, Shockley KR, et al. Activation of peroxisome proliferator-activated receptor gamma (PPARgamma) by rosiglitazone suppresses components of the insulin-like growth factor regulatory system in vitro and in vivo. Endocrinology. 2007;148(2):903–11.

72. Moerman EJ, Teng K, Lipschitz DA, Lecka-Czernik B. Aging activates adipogenic and suppresses osteogenic programs in mesenchymal marrow stroma/stem cells: the role of PPAR-gamma2 transcription factor and TGF-beta/BMP signaling pathways. Aging Cell. 2004; 3(6):379–89.

73. Tontonoz P, Spiegelman BM. Fat and beyond: the diverse biology of PPARgamma. Annu Rev Biochem. 2008;77:289–312.

74. Choi JH, Banks AS, Kamenecka TM, Busby SA, Chalmers MJ, Kumar N, et al. Antidiabetic actions of a non-agonist PPARgamma ligand blocking Cdk5-mediated phosphorylation. Nature. 2011;477(7365):477–81.

75. Rahman S, Czernik PJ, Lu Y, Lecka-Czernik B. β-catenin directly sequesters adipocytic and insulin sensitizing activities but not osteoblastic activity of PPARgamma2 in marrow mesenchymal stem cells. PLoS One. 2012;7(12):e51746.

76. Hinds Jr TD, Stechschulte LA, Cash HA, Whisler D, Banerjee A, Yong W, et al. Protein phosphatase 5 mediates lipid metabolism through reciprocal control of glucocorticoid and PPAR{gamma} receptors. J Biol Chem. 2011;286(10):42911–22.

77. Stechschulte LA, Hinds Jr TD, Ghanem SS, Shou W, Najjar SM, Sanchez ER. FKBP51 reciprocally regulates GRalpha and PPARgamma activation via the Akt-p38 pathway. Mol Endocrinol. 2014;28(8):1254–64. Pubmed Central PMCID: 4116593.

78. Higgins LS, Depaoli AM. Selective peroxisome proliferator-activated receptor gamma (PPARgamma) modulation as a strategy for safer therapeutic PPARgamma activation. Am J Clin Nutr. 2010;91(1):267S–72.

79. Lazarenko OP, Rzonca SO, Suva LJ, Lecka-Czernik B. Netoglitazone is a PPAR-gamma ligand with selective effects on bone and fat. Bone. 2006;38:74–85.

80. Lee DH, Huang H, Choi K, Mantzoros C, Kim YB. Selective PPARgamma modulator INT131 normalizes insulin signaling defects and improves bone mass in diet-induced obese mice. Am J Physiol Endocrinol Metab. 2012;302(5):E552–60. Pubmed Central PMCID: 4116349.

81. Fukunaga T, Zou W, Rohatgi N, Colca JR, Teitelbaum SL. An insulin-sensitizing thiazolidinedione, which minimally activates PPARγ, does not cause bone loss. J Bone Miner Res. 2015;30(3):481–8.

82. Kolli V, Stechschulte LA, Dowling AR, Rahman S, Czernik PJ, Lecka-Czernik B. Partial agonist, telmisartan, maintains PPARgamma serine 112 phosphorylation, and does not affect osteoblast differentiation and bone mass. PLoS One. 2014;9(5):e96323. Pubmed Central PMCID: 4014504.

83. Choi JH, Banks AS, Estall JL, Kajimura S, Bostrom P, Laznik D, et al. Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARgamma by Cdk5. Nature. 2010;466(7305):451–6.

84. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes Obes Metab. 2012;14(7):634–43. Epub 2012/02/18. Eng.

85. Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. Arch Intern Med. 2008;168(8):820–5.

86. Solomon DH, Cadarette SM, Choudhry NK, Canning C, Levin R, Sturmer T. A cohort study of thiazolidinediones and fractures in older adults with diabetes. J Clin Endocrinol Metab. 2009;94(8):2792–8. Pubmed Central PMCID: PMC2730861, Epub 2009/05/28. Eng.

87. Lapane KL, Yang S, Brown MJ, Jawahar R, Pagliasotti C, Rajpathak S. Sulfonylureas and risk of falls and fractures: a systematic review. Drugs Aging. 2013;30(7):527–47. Epub 2013/04/24. Eng.

88. Huang ES, Karter AJ, Danielson KK, Warton EM, Ahmed AT. The association between the number of prescription medications and incident falls in a multi-ethnic population of adult type-2 diabetes patients: the diabetes and aging study. J Gen Intern Med. 2010;25(2):141–6. Pubmed Central PMCID: 2837501, Epub 2009/12/08. Eng.

89. Drucker DJ. The role of gut hormones in glucose homeostasis. J Clin Invest. 2007;117(1): 24–32.

90. Deacon CF. Circulation and degradation of GIP and GLP-1. Horm Metab Res. 2004; 36(11–12):761–5.

91. Wesley UV, McGroarty M, Homoyouni A. Dipeptidyl peptidase inhibits malignant phenotype of prostate cancer cells by blocking basic fibroblast growth factor signaling pathway. Cancer Res. 2005;65(4):1325–34.

92. McGuinness C, Wesley UV. Dipeptidyl peptidase IV (DPPIV), a candidate tumor suppressor gene in melanomas is silenced by promoter methylation. Front Biosci. 2008;13:2435–43.

93. Arscott WT, LaBauve AE, May V, Wesley UV. Suppression of neuroblastoma growth by dipeptidyl peptidase IV: relevance of chemokine regulation and caspase activation. Oncogene. 2009;28(4):479–91.

94. Clowes JA, Khosla S, Eastell R. Potential role of pancreatic and enteric hormones in regulating bone turnover. J Bone Miner Res. 2005;20(9):1497–506.

95. Reid IR, Cornish J, Baldock PA. Nutrition-related peptides and bone homeostasis. J Bone Miner Res. 2006;21(4):495–500.

96. Henriksen DB, Alexandersen P, Hartmann B, Adrian CL, Byrjalsen I, Bone HG, et al. Disassociation of bone resorption and formation by GLP-2: a 14-day study in healthy postmenopausal women. Bone. 2007;40(3):723–9.

97. Xie D, Zhong Q, Ding KH, Cheng H, Williams S, Correa D, et al. Glucose-dependent insulinotropic peptide-overexpressing transgenic mice have increased bone mass. Bone. 2007; 40(5):1352–60.

98. Zhong Q, Itokawa T, Sridhar S, Ding KH, Xie D, Kang B, et al. Effects of glucose-dependent insulinotropic peptide on osteoclast function. Am J Physiol Endocrinol Metab. 2007;292(2): E543–8.

99. Yamada C, Yamada Y, Tsukiyama K, Yamada K, Udagawa N, Takahashi N, et al. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. Endocrinology. 2008;149(2):574–9.

100. Kyle KA, Willett TL, Baggio LL, Drucker DJ, Grynpas MD. Differential effects of PPAR-{gamma} activation versus chemical or genetic reduction of DPP-4 activity on bone quality in mice. Endocrinology. 2011;152(2):457–67.

101. Bunck MC, Eliasson B, Corner A, Heine RJ, Shaginian RM, Taskinen MR, et al. Exenatide treatment did not affect bone mineral density despite body weight reduction in patients with type 2 diabetes. Diabetes Obes Metab. 2011;13(4):374–7.

102. Mabilleau G, Mieczkowska A, Chappard D. Use of glucagon-like peptide-1 receptor agonists and bone fractures: a meta-analysis of randomized clinical trials. J Diabetes. 2014;6(3):260–6. Epub 2013/10/30. Eng.

103. Su B, Sheng H, Zhang M, Bu L, Yang P, Li L, et al. Risk of bone fractures associated with glucagon-like peptide-1 receptor agonists' treatment: a meta-analysis of randomized controlled trials. Endocrine. 2015;48(1):107–15. Epub 2014/07/31. Eng.

104. Monami M, Dicembrini I, Antenore A, Mannucci E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. Diabetes Care. 2011;34(11): 2474–6.
105. Ljunggren O, Bolinder J, Johansson L, Wilding J, Langkilde AM, Sjostrom CD, et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes Obes Metab. 2012;14(11):990–9.
106. Bolinder J, Ljunggren O, Johansson L, Wilding J, Langkilde AM, Sjostrom CD, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab. 2014;16(2):159–69. Epub 2013/08/03. Eng.
107. FARXIGA [package insert]. Wilmington: AstraZeneca Pharmaceuticals LP; 2014.
108. INVOKANA [package insert]. Titusville: Janssen Pharmaceuticals; 2014.
109. Goldenberg MM. Pharmaceutical approval update. P T. 2013;38(8):443–5. Pubmed Central PMCID: 3814443, Epub 2013/11/14. Eng.
110. Bronsky J, Prusa R, Nevoral J. The role of amylin and related peptides in osteoporosis. Clin Chim Acta. 2006;373(1–2):9–16.
111. Cornish J, Callon KE, Bava U, Kamona SA, Cooper GJ, Reid IR. Effects of calcitonin, amylin, and calcitonin gene-related peptide on osteoclast development. Bone. 2001;29(2):162–8.
112. Gutierrez-Rojas I, Lozano D, Nuche-Berenguer B, Moreno P, Acitores A, Ramos-Alvarez I, et al. Amylin exerts osteogenic actions with different efficacy depending on the diabetic status. Mol Cell Endocrinol. 2013;365(2):309–15.
113. Bronsky J, Prusa R. Amylin fasting plasma levels are decreased in patients with osteoporosis. Osteoporos Int. 2004;15(3):243–7.
114. Wojcik MH, Meenaghan E, Lawson EA, Misra M, Klibanski A, Miller KK. Reduced amylin levels are associated with low bone mineral density in women with anorexia nervosa. Bone. 2010;46(3):796–800. Pubmed Central PMCID: 2824019.
115. Borm AK, Klevesath MS, Borcea V, Kasperk C, Seibel MJ, Wahl P, et al. The effect of pramlintide (amylin analogue) treatment on bone metabolism and bone density in patients with type 1 diabetes mellitus. Horm Metab Res. 1999;31(8):472–5.