REVIEW

Effect of Antidiabetic Treatment on Bone

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Received June 11, 2019
Accepted September 4, 2019

Summary

Patients with diabetes mellitus are at an increased risk of bone fractures. Several groups of effective antidiabetic drugs are available, which are very often given in combination. The effects of these medications on bone metabolism and fracture risk must not be neglected. Commonly used antidiabetic drugs might have a positive, neutral or negative impact on skeletal health. Increased risk of fracture has been identified with use of thiazolidinediones, most definitively in women. Also treatment with sulfonylureas can have adverse effects on bone. One consequence of these findings has been greater attention to fracture outcomes in trails of new diabetes medication (incretins and SGLT-2 inhibitors). The effect of insulin on bone is discussed and the risk of fractures in patients using insulin seems to be unrelated to insulin as itself. The aim of the review is to summarize effects of antidiabetic treatment on bone – bone mineral density, fractures and bone turnover markers. The authors also try to recommend a strategy how to treat patients with diabetes mellitus regarding the risk of osteoporotic fractures. In this review the problem of how to treat osteoporosis in patient with diabetes is also discussed.

Key words

Diabetes • Osteoporosis • Fracture risk • Antidiabetic drugs

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Introduction

Both osteoporosis and diabetes mellitus (DM) are prevalent diseases with significant associated morbidity and mortality. The relationship between DM and bone diseases is not clear. Recent data seem to suggest that DM and diabetic complications can lead to it, and DM can determine also the bone health (Jackuliak *et al.* 2014, Kurra *et al.* 2011). Both types of DM lead to increased risk of fracture, the most durable clinical end point of osteoporosis, which has a significant impact on morbidity and mortality as well as on the quality of life (Ferrari 2017, Nazrun *et al.* 2014, Raška *et al.* 2017). Although Type 1 diabetes (T1DM) is often associated with decreased bone mass density (BMD) values, patients with Type 2 diabetes (T2DM) usually have normal or higher than expected BMD values (Hough *et al.* 2016, Vestergaard 2007, Vestergaard *et al.* 2009).

Research over several decades has supported a primary role for insulin and insulin like growth factor-1 (IGF-1) in bone formation (Cimrmanova *et al.* 2017). Expression of insulin and IGF-1 receptors has been detected at different steps of osteoblast differentiation, from preosteoblast to mature ones (Fowlkes *et al.* 2011, Zhukouskaya *et al.* 2014). Moreover, insulin and IGF-1 are important factors for osteoblast linage selection, since its receptors have been found also on osteogenic bone mass surface (Zhao *et al.* 2014). Insulin and IGF-1 utilize many of the same cellular proteins to achieve various cellular outcomes. In addition, they are able to cross-talk with two major proosteogenic pathways that ultimately regulate Runx2 activity in osteoblasts, such as the canonical Wnt/β-catenin signaling and the bone morphogenetic protein- BMP-2 pathways (Fowlkes *et al.* 2011).

Insulin signaling in osteoblasts is necessary for

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whole-body glucose homeostasis because it increases osteocalcin activity. To achieve this function insulin signaling in osteoblasts takes advantage of the regulation of osteoclastic bone resorption exerted by osteoblasts. Indeed, since bone resorption occurs at an acidic pH enough to decarboxylate proteins, osteoclasts determine the carboxylation status and function of osteocalcin. Accordingly, increasing or decreasing insulin signaling in osteoblasts promotes or hampers glucose metabolism in a bone resorption-dependent manner in mice and humans (Ferron *et al.* 2010, Pramojanee *et al.* 2014, Torres-Costoso *et al.* 2017).

Good metabolic control of DM may improve bone status, but several anti-diabetic drugs could directly affect bone metabolism (Hayakawa *et al.* 2012). Over the last couple of decades also the impact of oral antidiabetic drugs (OADs) on BMD and fractures has been reported (Gilbert *et al.* 2015, McCarthy *et al.* 2016, Paul *et al.* 2015). Antidiabetic treatment could modulate the risk for fractures in many ways. Most studies have not explored the effect on the incidence of fractures of individual oral hypoglycemic agents, rather all oral treatments as a whole. A higher incidence of fractures has been reported in insulin-treated patients in comparison with non-insulin-treated T2DM diabetic individuals, although some studies disagree (Vestergaard *et al.* 2005).

Diabetes mellitus and anti-diabetic treatment should be taken into consideration when evaluating fracture risk in osteoporotic patients. In a retrospective analysis of patients with osteoporosis to assess the incidence of osteoporotic fractures and associated risk factors regarding concomitant medications only anti-diabetic treatment was significantly associated with the presence of osteoporotic fracture (F=4.260, p=0.042), and had a considerable effect on the 10-year risk of major osteoporotic and hip fractures (Majumdar *et al.* 2016, Yavropoulou *et al.* 2015).

This review presents of antidiabetic drugs and their effect on bone, risk of osteoporosis and fracture rates (Table 1). This issue has clinical significance because many patients receiving anti-hyperglycemic therapy are at the age range of highest fracture risk.

Table 1. Evidence of skeletal effects of diabetes medication (Lecka-Czernik 2013, Palermo *et al.* 2015, Schwartz 2017)

Antidiabetic drug	Bone turnover markers		BMD	Fracture Risk
	Bone formation	Bone resorption		
Insulin	??	??	↑	↑
Sulfonylureas	↑/↔	↓/↔	??	↔
Metformin	↓/↔	↓/↔	↑/↔	↓/↔
Thiazolidinedione's	↓↓/↔	↑↑/↔	↓↓/↔	↑↑
GLP-1 receptor agonists	↔	↓↓	↑/↔	↔/??
DPP-4 inhibitors	↓/↔	↔	??	↓/↔
SGLT-2 inhibitors	↔	↔	↔	↑/↔

Metformin

Metformin is the most commonly oral antidiabetic drug (OAD) used to increase insulin sensitivity in patients with DM. Metformin has been shown to increase osteoblast proliferation and differentiation and also augments type 1 collagen formation in cell culture. In addition, it seems to inhibit adipocyte differentiation and promotes osteoblast differentiation (Molinuevo *et al.* 2010, Sundararaghavan *et al.* 2017). Several studies have documented that metformin is osteogenic *in vitro* (Cortizo *et al.* 2006). In contrast, it is necessary to say, that others studies showed no effect of metformin on the osteogenic differentiation of bone marrow-derived mesenchymal stem cells (Hegazy 2015). Interestingly, in recent *in vivo* and *ex vivo* studies with rats found that orally administered metformin improves bone regeneration and femoral microarchitecture, and increases the osteogenic potential of bone marrow progenitor cells *via* an increase in the expression of Runx2 and in the phosphorylation/activation of AMPK, a well-known sensor of energetic balance. Metformin can additionally prevent the *in vivo* and *ex vivo* anti-osteogenic effects of the insulin-sensitizer rosiglitazone in rats (Gu *et al.* 2017, Sedlinsky *et al.* 2011).

Metformin treatment could also prevent the *in vitro* AGEs-induced decrease in osteoblastic differentiation and induction of apoptosis, in this last case by decreasing caspase-3 activity and intracellular oxidative stress (Melton *et al.* 2008, Russo *et al.* 2016).

Human studies of the *Rochester cohort* suggest that metformin decreases fracture risk in T2D patients (hazard ratio 0.7) (Melton *et al.* 2008). Although the ADOPT studies did not demonstrate beneficial effects of metformin on fracture risk (Kahn *et al.* 2008), they showed decreased levels of bone resorption marker CTX and, contrary to animal studies, decreased levels of bone formation marker P1NP (Zinman *et al.* 2010). In a large case-control study metformin utilization was also associated with a reduction in the risk of fractures (Vestergaard *et al.* 2005). In contrast some authors observed in their case control study no association between treatment with the insulin-sensitizing drug metformin and incident bone fractures in type 2 patients with DM (Monami *et al.* 2008).

In conclusion patients receiving metformin could show a lower incidence of bone fractures as a result of a lower comorbidity.

Sulphonylureas

Sulphonylureas, the potent insulin secretagogues are used as second line agents in the treatment of T2DM. Evidence regarding the detrimental effect of these drugs on bone is limited. However, by improving glycemic control, these may exert a favorable effect on bone health (Lapane *et al.* 2013). Sulfonylureas might have a beneficial effect through the enhancement of IGF-1 secretion. In contrast, both the *ADOPT studies* and the *Rochester studies* were unable to show that glyburide therapy has an effect on bone mass and fracture risk (Kahn *et al.* 2008, Melton *et al.* 2008). However, glyburide therapy decreased serum levels of bone formation marker P1NP in the ADOPT studies (Zinman *et al.* 2010).

Several observational studies have reported a neutral effect of sulfonylureas on fracture risk in patients with DM (Chandran 2017).

In 2014 was presented the first study, suggesting a possible increased fracture risk for sulfonylureas based on retrospectively analyzed data from Invalon's Medical Outcomes for Effectiveness and Economics (MORE) registry of more than 100 million individuals. A total of 99,892 adults were identified as new users of glucose-lowering drugs. The incidence of fractures was 6.8 % among the total 76 924 patients taking metformin, 10.9 % among the 2679 taking TZDs, and 9.7 % in the 15 162 on sulfonylureas. Rates for other glucose-lowering agents ranged from 6.1 % of 799 individuals taking incretin drugs to 10.7 % of the 626 on meglitinide. The hazard ratios for fracture risk compared with metformin were 1.40 for TZDs (P<0.0001) and 1.09 for sulfonylureas (P=0.0054). The increase in fracture risk for the other drug classes compared with metformin did not reach statistical significance (Tucker 2014, Mehta 2014).

Sulfonylureas appear to have a beneficial or at the very least a neutral effect on fracture risk. Attention must be paid to the higher risk of hypoglycemia and the risk of falls. There is the need of further investigation on the association between sulfonylureas and the risk of fractures.

Thiazolidinediones (glitazones)

Thiazolidinediones (TZDs) increase insulin sensitivity by acting as agonists of peroxisome proliferator-activated receptor gamma (PPAR-γ). PPAR-γ is expressed in stromal cells of the bone marrow, osteoblasts, and osteoclasts and plays an important role in the differentiation of precursor cells into osteoblasts (Berberoglu *et al.* 2010). By impairing the differentiation of osteoblast precursors, bone formation is compromised. Additional ways of TZDs action on bone are increasing adiposity of bone marrow, decreasing aromatase activity, and promoting osteoclast differentiation, all of which increase bone resorption. In a study involving PPAR-γ knock-out mice, an increase in osteoblastogenesis has been shown in both in vivo as well as the embryonic stem cell cultures. The TZDs, when used as antidiabetic drugs (PPAR-γ activators), convert mesenchymal stem cells to adipocytes thereby suppressing osteoblast development (Loke *et al.* 2009, Mieczkowska *et al.* 2012).

A study on postmenopausal women using rosiglitazone demonstrated an annual reduction of BMD at the trochanter and lumbar spine of 2.56 % and 2.18 %, respectively (Berberoglu *et al.* 2010). BMD is compromised through an increase in bone resorption and a decrease in bone formation (Lecka-Czernik 2010). A meta-analysis exploring long-term use and risk of fractures found that fracture risk was increased in women (but not men) while using rosiglitazone or pioglitazone (Loke *et al.* 2009).

MSDC-0602, a new TZD analog with low

affinity for binding and activation of PPARγ but whose insulin-sensitizing properties mirror those of rosiglitazone has been recently developed. It activates the nuclear receptor in osteoclasts. MSDC-0602, in contrast to rosiglitazone, minimally activates PPARγ and does not alter CD36 expression in the bone-resorptive cells. Consistent with this finding, rosiglitazone increases receptor activator of NF-kB ligand (RANKL)-induced osteoclast differentiation and number, whereas MSDC-0602 fails to do so (Fukunaga *et al.* 2015).

The use of TZDs has been shown to have deleterious effects on BMD and therefore TZDs should be avoided in patients with established osteoporosis or at high risk for fracture (Mazziotti *et al.* 2010). Risk factors for fracture include female gender, advanced age (>65 years), and longer duration of treatment.

Incretin hormones

The role of incretin hormones in T2DM therapy has recently received much attention, because of the beneficial actions of these molecules on the pancreatic islet (Marchetti *et al.* 2012, Whalley *et al.* 2011). Incretin-based therapy encompasses two classes of drugs – glucagon like peptid 1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors.

After food intake, bone resorption becomes unnecessary and it is consequently inhibited. This event may be mediated by gastrointestinal hormones released after meal ingestion such as GLP-1. In line with this hypothesis, the observation that parenteral feeding is associated with reduced bone mass suggests that a deficit in incretin hormones could have a certain role in bone turnover. Interestingly, some studies found that GLP-1 and other incretin hormones, such as GIP or GLP-2, could have positive effects on bone through antiresorptive and anabolic properties, suggesting beneficial effects of antidiabetic drugs like GLP-1RAs or DPP-4 inhibitors on bone metabolism. These appear to involve Wnt/beta-catenin pathway, Osteoprotegerin (OPG)/RANKL (Receptor activator of nuclear factor kappa-B ligand) ratio and sclerostin levels (Fig. 1) (Ceccarelli *et al.* 2013). Osteoblasts and osteoclasts express receptors for both GIP and GLP incretins (Zofkova 2015).

In a murine model, a genetic disruption of GLP-1 receptor signalling resulted in cortical osteopenia and an increase in bone fragility as a result of greater bone resorption by osteoclasts, which was associated with a reduction in thyroid calcitonin expression (Yamada *et al.* 2008). A GLP-1 agonist, exendin-4 has been shown to decrease the urinary deoxypyridinoline (DPD)/creatinine ratio and serum C-terminal cross-linked telopeptides of type I collagen (CTX-I) and increase serum alkaline phosphatase (ALP), osteocalcin, and N-terminal propeptide of type 1 procollagen (P1NP) levels in ovariectomized Sprague-Dawley rats (Ma *et al.* 2013, Meng *et al.* 2016).

A relationship between incretin hormones and bone has been investigated also in humans. Evidence of incretin effects in humans showed a decrease in nocturnal bone resorption after administration of GLP-2. Results reported the absence of any toxic effect of GLP-2 treatment and more interestingly, a dose dependent increase in BMD. Injection of GLP-2 determined an immediate and sustained decrease in bone resorption markers, while levels of bone formation markers, were

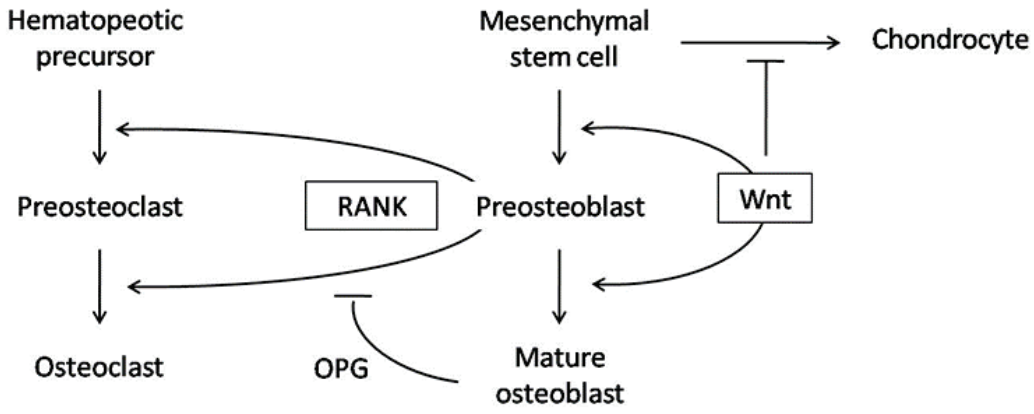

Fig. 1. Role of the Wnt-signalling pathway in regulation of osteoblast (bone-forming cell) and osteoclast (bone-resorbing cell) differentiation. Wnt-signaling diverts the mesenchymal stem cells down the pathway of osteoblast differentiation. The precursors of the mature osteoblast enhance bone resorption by boosting RANKL-induced osteoclastogenesis. Activation of the Wnt-signaling pathway in the mature osteoblast upregulates osteoprotegerin (OPG), which blocks RANKL-induced osteoclastogenesis, resulting in inhibition of bone resorption.

not affected, thus providing evidence of a direct action of incretin hormones in regulation of bone metabolism (Henriksen *et al.* 2009, Holst *et al.* 2016).

In a clinical trial, T2DM patients were randomized to receive GLP-1RAs exenatide or insulin glargine, added to their metformin-based therapy. After 44 weeks of treatment, the different drug regimen did not affect BMD. These findings suggest that, in T2DM patients, long-term injection of exenatide will not lead to an increase in fracture risk (Bunck *et al.* 2011).

Recently was reported that the use of exenatide and liraglutide did not modify the fracture risk in T2DM as compared to placebo or other anti-hyperglycemic medications (glimepiride, sitagliptin, and insulin) in a meta-analysis of 7 RCTs (Mabilleau *et al.* 2013). Another metaanalysis of 16 RCTs variable duration (12 to 104 weeks) exploring the association between fractures and GLP-1RAs in general and liraglutide or exenatide in particular. Overall, the effect of GLP-1RAs on fracture risk seems to be neutral (Su *et al.* 2015). A case-control study using Danish National Health Service concluded that the use of GLP-1RAs was not associated with fracture risk as compared to the use of other anti-hyperglycemic drugs. Additionally, current GLP-1RAs use, stratified by cumulative or average daily dose, is not associated with fracture risk (Driessen *et al.* 2015).

In a meta-analysis which included 28 trials showed a 40 % reduced risk of fractures in patients treated by DPP-4 inhibitors compared with placebo or other anti-hyperglycemic treatments. Neutral role of DPP-4 inhibitors on bone metabolism was demonstrated by treatment with vildagliptin in drug naïve T2DM patients for 1 year. Circulating levels of markers of bone resorption and calcium homeostasis were unaffected compared with baseline and to placebo (Monami *et al.* 2011).

Recently the fracture incidence among participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was examined. During 43,222 person-years follow-up 375 patients (2.6 %; 8.7 per 1000 person-years) had a fracture. In conclusion fractures were common among people with DM in the TECOS study, but were not related to sitagliptin therapy. Insulin and metformin treatment were associated with higher and lower fracture risks, respectively (Josse *et al.* 2017).

Specifically, data so far available both from experimental animal models and man, indicate that the beneficial "extraglycemic" effects of incretin-based drugs include the effects on bone metabolism, either directly on bone cells or indirectly (e.g., via thyroid C cells and calcitonin), appear to favor bone formation and to inhibit bone resorption, thus improving bone strength (Fig. 2).

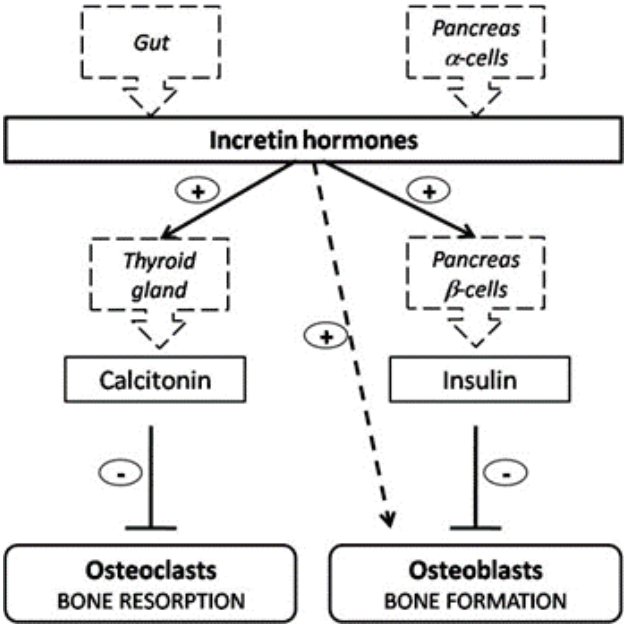

Fig. 2. Effects of incretin hormones on bone metabolism. Incretin hormones are secreted by intestinal L-cells and, in minor amounts, by pancreatic α-cells. Incretin hormones can stimulate osteoblastogenesis indirectly via increased insulin secretion as well as through a direct action on osteoblasts. Moreover, incretin hormones can inhibit osteoclastogenesis by stimulating calcitonin production.

Selective inhibitor of sodium-glucose cotransporter-2

Given the renal tubular mechanism of action of the sodium-glucose cotransporter-2 (SGLT-2) inhibitor class, these drugs may potentially alter calcium and phosphate homeostasis and bone mineral density (BMD).

Dapagliflozin, a selective sodium-glucose co-transporter-2 (SGLT-2) inhibitor, reduces hyperglycaemia in patients with T2D by increasing urinary glucose excretion. Preliminary clinical data showed no changes in serum calcium or vitamin D but small increases in serum magnesium, phosphate and parathyroid hormone with dapagliflozin treatment compared with placebo (List *et al.* 2009, Nauck *et al.* 2011). Furthermore, dapagliflozin-induced urinary caloric loss produces weight loss, which may also potentially reduce BMD. Dapagliflozin had no effect on markers of bone formation and resorption or BMD after 50 weeks of treatment in

both male and post-menopausal female patients whose T2DM was inadequately controlled using metformin (Ljunggren *et al.* 2012).

These data, however, are in contrast with recently published skeletal safety data with increased fracture incidence associated with the use of dapagliflozin and canagliflozin (Kohan *et al.* 2014, Watts *et al.* 2016). In a double-blind, placebo-controlled study of adults with T2DM and moderate renal impairment, substantial increases in fracture numbers were noted in the dapagliflozin groups with a suggestion of dose dependency (Kohan *et al.* 2014). All 13 (7.7 %) fractures occurred after trauma and were mostly of low impact. Similarly, the incidence of fractures was higher with canagliflozin (2.7 %) vs non-canagliflozin (1.9 %) in the overall population of patients from 9 placebo- and active-controlled, randomized, double-blind, phase 3 studies with scheduled exposures to canagliflozin 100 or 300 mg for 1 year or longer, with the same incidence in the canagliflozin 100 and 300 mg groups (Watts *et al.* 2016).

In November 2015, the US Food and Drug Administration (FDA) issued a warning for canagliflozin regarding the risk for bone fractures with new information about decreased bone mineral density. The FDA recommends health care professionals to consider factors that affect the risk of fracture prior to prescribing canagliflozin for patients.

There are plausible pathophysiological mechanisms with potential to mediate detrimental skeletal effects of SGLT-2 inhibitors. Use of these drugs is consistently associated with weight loss (Tahrani *et al.* 2013). This might contribute to bone loss, in part, due to the direct effect of reduced soft-tissue mass on bone through reduced mechanical loading (Martin 2007). Additionally, decreased fat tissue might lead to reductions in aromatase activity, which lowers the production of estradiol and consequently increases bone turnover (Gonnelli *et al.* 2011, Liu *et al.* 2014). The decrease in estradiol in women with canagliflozin is consistent with this hypothesis (Bilezikian *et al.* 2016). SGLT-2 inhibition may reduce sodium transport in the proximal tubule epithelial cells, leading to increased phosphate flux through the sodium-phosphate cotransporter and to increased serum phosphate (Taylor *et al.* 2015). This effect might stimulate the secretion of PTH whose sustained increase enhances bone resorption and increases the risk of fractures.

Other paper reported no significant changes from baseline in bone turnover markers and BMD after dapagliflozin treatment in patients with normal to mild renal impairment (Ljunggren *et al.* 2012). On the other hand, canagliflozin has been reported to increase bone turnover (Bilezikian *et al.* 2016, Rosenstock *et al.* 2012).

In a pooled analysis of >12,000 patients or compared with glimepiride in a 4-year head-to-head study empagliflozin also did not increase the risk of bone fracture compared with placebo. Bone fracture AEs were reported only in 2-4 % of all patients (Kohler *et al.* 2018).

Insulin as a treatment

The distinct reduction of peak bone mass in some patients with T1DM has led to the hypothesis that insulin has osteoanabolic effects although it is unclear whether the effects on BMD are caused by poor glycemic control or other diabetic complications (Hofbauer *et al.* 2007, Klein 2014, Moayeri *et al.* 2017).

In a review, it was suggested that insulin exerts a potent bone anabolic effect on osteoblasts through receptor-mediated mechanisms (Thrailkill *et al.* 2005). Lack of insulin led to low bone mass in an uncontrolled study of 57 patients with T1DM and a mean age of 35 years, who were evaluated before intensive insulin therapy and 7 years later. Treatment was associated with substantial improvement of bone mass and bone turnover biomarkers (Campos Pastor *et al.* 2000).

Insulin has direct effects on bone metabolism in humans and changes in the circulating levels of bone markers can be seen within a few hours after administration of insulin (Ivaska *et al.* 2015).

Hyperinsulinemia in patients with T2DM might contribute to the high BMD, although insulin resistance in bone cells may occur. Differences in skeletal effects between patients with T1DM and those with T2DM are not, therefore, fully explained by the “insulinopenia” hypothesis. In addition to insulin, pancreatic beta-cells produce other osteotropic factors, such as islet amyloid polypeptide (IAPP, also known as amylin) and preptin, both of which are members of the calcitonin-gene-related peptide family. Production of these peptides is abolished in patients with T1DM. IAPP, a 37-amino-acid peptide, is secreted with insulin (Naot *et al.* 2008).

A study on 243 patients with T2DM found that there was no difference in BMD between women with T2DM treated with diet, oral antidiabetics or insulin therapy, but BMD was lower in men with T2DM undergoing insulin treatment (LSMEAN±SE; FN-BMD 0.86±0.02 g/cm^2, LS-BMD 1.035±0.02 g/cm^2) compared

with those treated with other therapies (FN-BMD 0.91±0.02 g/cm^2; LS-BMD 1.13±0.02 g/cm^2) ($p = 0.02$; $p = 0.004$) (Leidig-Bruckner *et al.* 2014). Also some other studies demonstrated that insulin therapy was associated with a higher risk of vertebral fractures (Kanazawa *et al.* 2009). This may be due to the fact that, for example, T2DM patients on insulin therapy are likely to have longer disease duration and/or complications, or a higher risk of hypoglycemic events. According to the studies of osteoporotic fractures, insulin treated older women with DM had more than double the risk of foot fractures, because of falling and diabetic complication like neuropathy, compared with non-diabetics and noninsulin DM users (Schwartz *et al.* 2002). Similarly studies among the *Rochester cohort* showed that insulin slightly but significantly increases fracture rate.

Insulin therapy is associated with an increased frequency of severe hypoglycemic events and therefore an increased risk of falling which can contribute to fracture risk (Ferrari 2017, Chandran 2017).

Interestingly, insulin-treated women with DM have almost a doubled fall incidence (OR 2.78 vs. 1.68), which in part explains the increased fracture rate in the lower extremities (Schwartz *et al.* 2002). Older adults with T2DM are more likely to fall, but little is known about risk factors for falls in this population. A study determined whether diabetes-related complications or treatments are associated with risk of falls in older adults with DM (Schwartz *et al.* 2008). In older adults with DM falls may be prevented by reducing diabetes-related complications. Achieving lower A1C levels with oral hypoglycemic medications was not associated with more falls, but, among those using insulin, A1C≤6 % increased risk of falls. This was also the first study of falls to report an interaction between insulin use and A1C levels. Some, but not all, previous studies have reported increased risk of falls among those using insulin (Quandt *et al.* 2006). Another study group reported increased risk of falls with poor glycemic control (A1C>7 %) (Tilling *et al.* 2006).

Recommendations for the diagnosis and therapy for osteoporosis in patients with DM

Markers of bone resorption and formation seem to be lower in patients with DM (Starup-Linde *et al.* 2016). This can lead to the concerns that antiresorptive therapy may not be effective for fracture prevention in diabetic patient (Zofkova and Blahos 2017). Evidence about the effect of antiosteoporotic treatment remains limited (Table 2). Generally, the trials and also the clinical practice indicate that the antifracture efficacy is similar in patient with and without DM.

Table 2. Established osteoporosis therapies in patient with diabetes – drugs with evidence of reducing the risk of fractures when used with adequate calcium and vitamin D supplementation

Drug	Dose and interval	Route of administration	Anti-Fracture efficacy	Efficacy in diabetes
Alendronate	70 mg weekly	Oral	Hip-fractures Vertebral fractures	Clinical Studies
Risedronate	35 mg weekly 150 mg monthly	Oral	Hip-fractures Vertebral fractures	Daily Practice
Ibandronate	150 mg monthly 3 mg every 3 months	Oral	Vertebral fractures	Daily Practice
Zolendronic acid	5 mg yearly	Intravenous	Hip-fractures Vertebral fractures	Daily Practice
Raloxifene	60 mg daily	Oral	Vertebral fractures	Clinical Studies
Stroncium ranelate	2 g daily	Oral	Hip-fractures Vertebral fractures	Daily Practice
Denosumab	60 mg every 6 month	Subcutaneous	Hip-fractures Vertebral fractures	Daily Practice
TPTD (PTH_{1-34})	20 μg daily	Subcutaneous	Vertebral fractures	Clinical Studies

Clinical studies = mostly retrospective analyses of subgroups with diabetes, few prospective clinical trials
Clinical practice = results from daily practice of treating patient with osteoporosis – the drug is in patient with diabetes effective, without adverse events

FIT trial (*Fracture Intervention Trial*) found that *alendronate* increases BMD in women with DM similar to its effect in women without DM (Keegan *et al.* 2004).

Subgroup analyses of the RUTH trial (*Raloxifene Use for the Heart Trial*) found reduced risk of vertebral fractures in both women with and also without DM treated by *raloxifene* (Ensrud *et al.* 2008).

Direct Analysis of Nonvertebral Fracture in the Community Experience (DANCE) study with 4042 patients (291 with T2DM, 3751 without DM) showed that during *teriparatide* treatment, reduction in nonvertebral fracture incidence, increase in BMD, and decrease in back pain were similar in T2DM and non-diabetic patients (Schwartz *et al.* 2016). The effect of teriparatide in diabetic patients was confirmed also in next study (Real-World Effectiveness of Teriparatide), for patients with and without DM fracture rates decreased significantly in the > 6-month period for all fracture types. The reduction in clinical fracture rate was greater for the diabetic (-77 %) versus the nondiabetic subgroup (-48 %, interaction p=0.046); however, reductions in fracture rates in both subgroups were statistically significant (Langdahl *et al.* 2018). It can be concluded that teriparatide treatment had a significant effect for all fracture types and no impact of diabetes on overall fracture rate.

According the mechanism of action, denosumab should be also effective in treatment of osteoporosis in diabetics. It was shown that denosumab did not affect fasting plasma glucose (FPG) in postmenopausal osteoporotic women with prediabetes or diabetes mellitus. There was evidence of modest FPG lowering with denosumab in those with DM who were not on OADs. It remains to be determined whether blockade of RANKL has a clinically important effect on glucose metabolism (Napoli *et al.* 2018).

In conclusion, DM does not seem to affect the fracture-preventive potential of bisphosphonates or raloxifene (Vestergaard *et al.* 2011). Post hoc analyses of the DANCE (*The Direct Assessment of Nonvertebral Fractures in Community Experience*) observational study compared T2D patients and patients without DM to assess the effect of teriparatide, an osteoanabolic therapy. During teriparatide treatment, reduction in nonvertebral fracture incidence, increase in BMD, and decrease in back pain were similar in T2D and non-diabetic patients (Schwartz *et al.* 2016). The data about the effect of denosumab and strontium ranelate are still missing. An interesting finding is that denosumab, an anti-RANKL antibody, enhanced human β-cell replication in humanized mice. The researchers highlight the potential for repurposing an osteoporosis drug to treat DM (Kondegowda *et al.* 2015).

Algorithm for management of osteoporosis in patient with T2DM

All above mentioned data were given in an algorithm for management of osteoporosis in women and men with T2DM (Fig. 3). First step of the algorithm is how to evaluate osteoporosis risk in a patient with T2DM. According the European guidance, it is recommended that postmenopausal women with a prior fragility fracture should be treated without further assessment, although BMD measurement and incorporation into the FRAX calculation is sometimes appropriate, particularly in younger postmenopausal women. In women without a previous fragility fracture, the management strategy should be based on assessment of the ten-year probability of a major osteoporotic fracture (clinical spine, hip, forearm or humerus) (Kanis *et al.* 2019). Fracture-risk evaulation should be performed in all patient age > 50 years and/or with diabetes specific risk factors for fractures = diabetes duration > 5 years; diabetes medication insulin, TZDs, possibly SGLT2 inhibitors; HbA1c > 7 %; microvascular complications – peripheral and autonomic neuropathy, retinopathy, nephropathy (Ferrari *et al.* 2018).

However, T-score BMDmeasured by DXAmay underestimate fracture risk in patients with diabetes. Thus, a BMD intervention threshold at T-score -2.0 SD at spine or hip could be considered appropriate (Ferrari *et al.* 2018).

The diagnostic algorithm is based on recent guidelines published by IOF working group (Ferrari *et al.* 2018).

All patients should have an adequate intake of vitamin D and calcium, not only to improve bone health, but also to improve the metabolic compensation. If we have a patient with osteoporosis and/or osteoporotic fracture, we should initiate the antifracture treatment with effective antiporotic medication. In general management we have to look also on the bone-effects of antidiabetic drugs.

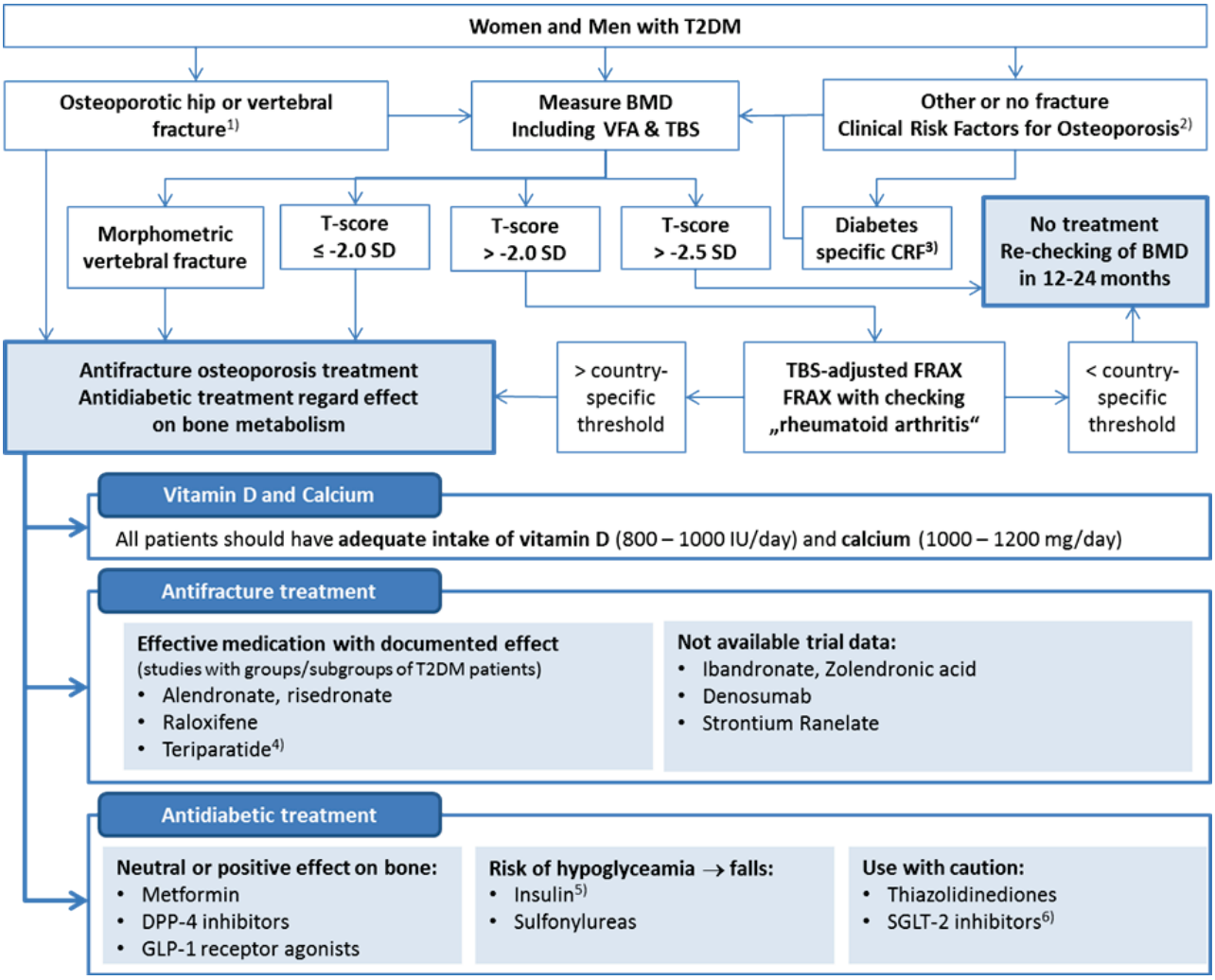

Fig. 3. Recommended algorithm for management in women and men with T2DM. Explanatory Notes: [1)]Osteoporotic fractures – fragility fractures, low-trauma fractures – typical are hip, spine, distal radius. Diabetic patients are also at increased risk of fracture in ankle, humerus and pelvis fracture. [2)]Clinical Risk Factors for osteoporosis: women age > 50 years; men age > 65 years; prior fracture; family history of hip-fracture; alcohol; smoking; glucocorticosteroids use; hypogonadism, high fall propensity, insulin therapy. [3)]In all patients age > 50 years and/or with diabetes specific risk factors for fractures = diabetes duration > 5 years; diabetes medication insulin, TZDs, possibly SGLT2 inhibitors; HbA1c > 7 %; microvascular complications – peripheral and autonomic neuropathy, retinopathy, nephropathy. [4)]TPTD indication according the country-specifics rules for osteoanabolic treatment. [5)]When insulin is indicated/necessary for the (initial) treatment of diabetes it can be used as first line therapy (osteology view: benefit is higher than risk). Insulin treated patients have higher risk of falls, episodes of hypoglycemia, have more serious form of diabetes with complications and other comorbidities → this factors can lead to higher risk of osteoporotic fractures. [6)]Empagliflozin and dapagliflozin are seen to be neutral on bone. Abbreviations: CRF = clinical risk factors; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon like peptide 1; SGLT-2 = sodium-glucose cotransporter 2

Conclusion

Achieving adequate glycemic control in patients with DM is especially important as there are data to suggest that the microvascular complications of DM, such as retinopathy, neuropathy, and macro-vasculopathy which arise from insufficient glycemic control, can lead to falls and subsequent fractures. Several antidiabetic drugs have been demonstrated to influence bone metabolism. From a bone perspective, metformin and DPP-4 inhibitors are safer than TZDs and sulphonylureas, or SGLT-2 inhibitors. Conversely, current treatment with insulin increases the risk of fractures, at the same time exposure to this agent in the longer term does not appear to affect bone frailty. If no contraindications exist, intensive insulin therapy is the standard treatment for DM and seems to be associated with improved skeletal health. The risk of hypoglycemic episodes, which constitute an adverse effect of intensive insulin therapy, should be minimized by comprehensive patient education, frequent self-monitoring of glucose levels and titration of the insulin dose.

The effect on bone metabolism and fracture risk deserves to be included into the evaluation of risk-benefit ratio of anti-hyperglycemic drugs. Positive and negative expectations for the newer drugs still need to be confirmed. Future research could specifically identify patients who are most susceptible to development of drug-induced bone fractures.

Conflict of Interest

There is no conflict of interest.

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