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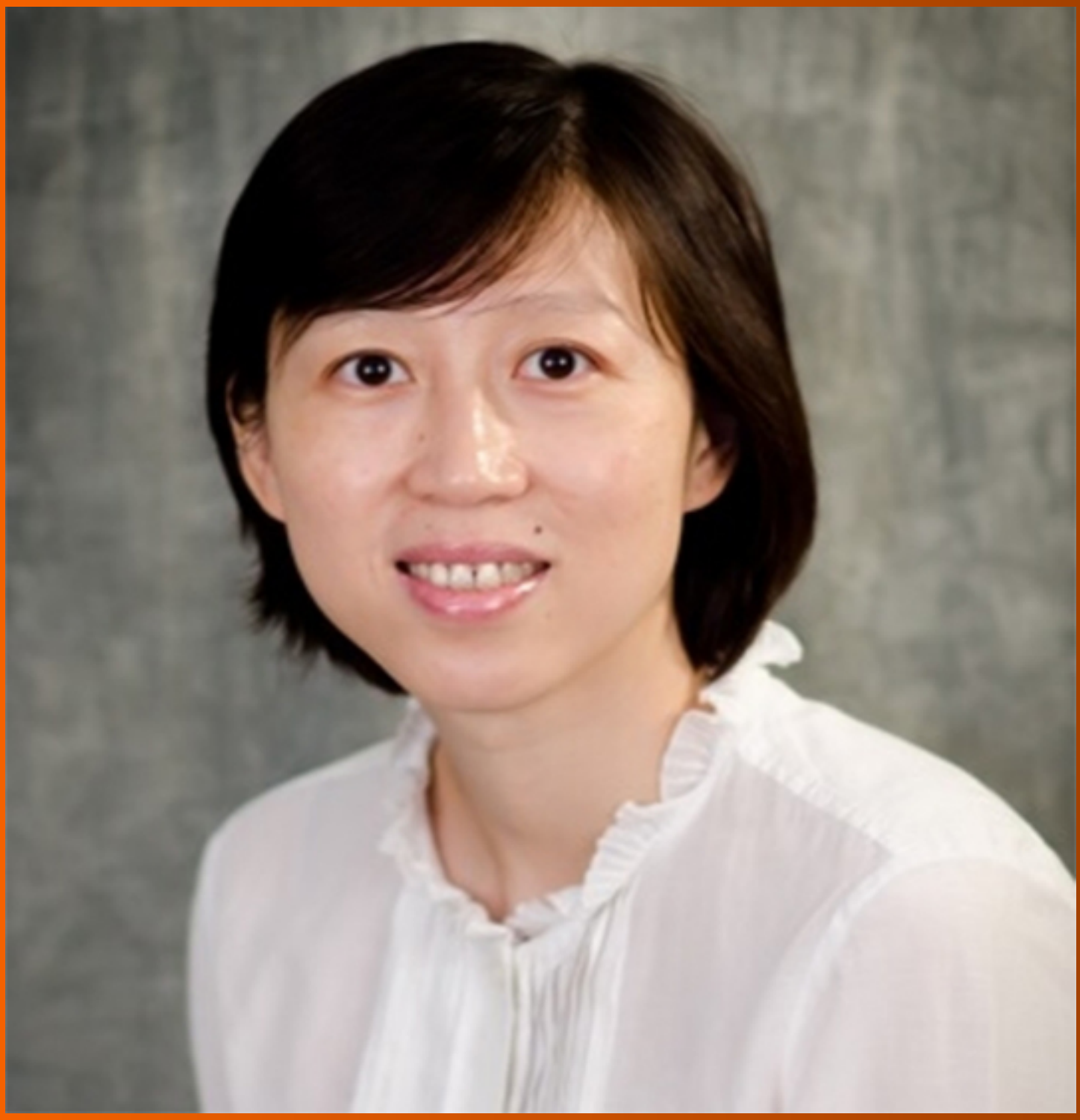

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REVIEW

Bone health in diabetes and prediabetes

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Abstract

Bone fragility has been recognized as a complication of diabetes, both type 1 diabetes (T1D) and type 2 diabetes (T2D), whereas the relationship between prediabetes and fracture risk is less clear. Fractures can deeply impact a diabetic patient's quality of life. However, the mechanisms underlying bone fragility in diabetes are complex and have not been fully elucidated. Patients with T1D generally exhibit low bone mineral density (BMD), although the relatively small reduction in BMD does not entirely explain the increase in fracture risk. On the contrary, patients with T2D or prediabetes have normal or even higher BMD as compared with healthy subjects. These observations suggest that factors other than bone mass may influence fracture risk. Some of these factors have been identified, including disease duration, poor glycemic control, presence of diabetes complications, and certain antidiabetic drugs. Nevertheless, currently available tools for the prediction of risk inadequately capture diabetic patients at increased risk of fracture. Aim of this review is to provide a comprehensive overview of bone health and the mechanisms responsible for increased susceptibility to fracture across the spectrum of glycemic status, spanning from insulin resistance to overt forms of diabetes. The management of bone fragility in diabetic patient is also discussed.

Key words: Bone; Fractures; Type 1 diabetes; Type 2 diabetes; Prediabetes; Diabetes complications; Bone density; Hypoglycemic agents

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Core tip: Diabetes mellitus, either type 1 or type 2, is associated with increased fracture risk. Diabetic hyperglycemia and insulin resistance underlie functional alterations of bone cells and bone marrow fat that affect several determinants of bone strength, including bone matrix proteins and bone mass, geometry and microarchitecture.

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Diabetes-related microvascular complications and certain antidiabetic drugs appear to further increase fracture risk, both directly and indirectly. The prevention and management of bone fragility in diabetes includes identification of patients at risk, correction of modifiable risk factors including appropriate choice of antidiabetic drugs and use of antifracture drugs with proven efficacy.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia leading to serious microvascular and macrovascular complications. In recent years, bone fragility has emerged as a further complication of DM, both Type 1 diabetes (T1D) and type 2 diabetes (T2D). Aim of this review is to provide a comprehensive overview of bone health across the spectrum of glycemic status, spanning from insulin resistance to overt forms of diabetes.

Insulin and bone

Insulin is an anabolic hormone central to the regulation of substrate metabolism in key organs and tissues such as skeletal muscle, the liver and adipose tissue[1]. Both osteoblasts and osteoclasts express the insulin receptor. Insulin stimulates osteoclast formation and promotes proliferation, differentiation and survival of osteoblasts, with an overall balance in favor of bone formation[2]. Studies on insulin receptor knockout mice indicate that insulin signaling is necessary for normal bone acquisition[3,4], likely due to the role of insulin in the regulation of bone energy metabolism. In fact, insulin administration increases ^{18}F-fluorodeoxyglucose ([18F]FDG) uptake by bone in mice, which is markedly reduced in mice lacking the insulin receptor in osteoblasts[5]. Furthermore, activation of the insulin receptor in the growth plate of mice fed with a hypercaloric diet stimulates skeletal growth and growth plate chondrogenesis[6]. Osteoblasts also express the Insulin-like growth factor 1 (IGF-1) receptor[7]. IGF-1 binds both to the IGF-1 receptor and, with lower binding affinity, to the insulin receptor, thus triggering the insulin signaling pathway and exerting osteoanabolic actions.

DM

Depending on the pathogenic mechanism(s) causing chronic hyperglycemia, DM is classified into few main general categories. T1D is distinguished by absolute insulin deficiency due to destruction of pancreatic beta-cells on an autoimmune or idiopathic base. Latent autoimmune diabetes in adults (LADA) is a less common form of autoimmune diabetes that arises in the adult age and is characterized by circulating islet autoantibodies and insulin independence at diagnosis. In T2D, insulin resistance leading to compensatory increase of insulin secretion causes progressive worsening of beta cell function that eventually results in relative insulin deficiency and hyperglycemia. Other forms of DM include monogenic forms (*e.g.*, maturity onset diabetes of the young, MODY), gestational diabetes, and secondary forms either associated with conditions that affect insulin secretion (*e.g.*, pancreatic diseases) or certain drugs (*e.g.*, glucocorticoids and immunosuppressants after organ transplantation). This review will focus on the main diabetes categories, *i.e.* T1D and T2D, as well as on those alterations of glucose metabolism collectively identified as prediabetes[8].

Diabetes and prediabetes: clinical impact on bone

Fracture risk in T1D

Fracture risk is increased in T1D, with a 2- to 6-fold higher risk of fracture as compared with non-diabetic subjects, the risk being greatest in T1D women[9,10]. In a recent analysis that assessed the determinants of fracture risk in T1D adult patients, nearly half of the subjects reported at least one fracture after diabetes diagnosis[11].

Older age, longer T1D duration, age < 20 years at diagnosis and family history of osteoporosis or osteopenia were associated with fracture occurrence.

Fracture risk in T2D and prediabetes

Individuals with T2D have a 1.2- to 3-fold higher risk of fracture as compared with non-diabetic subjects, particularly for hip fractures[9,12], but also for upper arm and ankle fractures[13]. Fracture risk appears to be greater in those with a body mass index (BMI) < 30 kg/m^2 as compared with obese individuals[14], and not to significantly differ by gender[9,15]. Diabetes duration longer than 10 years, low levels of physical activity, use of insulin and systemic corticosteroids and increasing age are also associated with higher fracture risk in T2D[14]. Falls represent another risk factor for fractures, especially in diabetic women[14,16,17]. The association between diabetes, especially T2D, and increased risk of falls is well recognized[18,19] and mainly attributed to diabetes related complications such as therapy-induced hypoglycemic episodes, impaired muscle strength due to sarcopenia, retinopathy-related impaired vision, peripheral artery disease and neuropathy[20,21]. As in a vicious circle, fractures may lead to imbalance, alterations in posture and decreased muscle strength, eventually reducing physical performance and further increasing the risk of falls[22]. Predictive factors of falls and their contribution to fracture risk in T1D patients have not been clearly identified[23].

Despite a clear association between T2D and increased fracture risk[9,19,24], evidence supporting an association between prediabetes and fracture risk is inconsistent. Observations in adolescents suggest that insulin resistance may be detrimental for bone development through puberty, independent of body composition and the level of physical activity[25]. However, no association between insulin resistance and fracture risk was evident after adjustment for BMI and bone mineral density (BMD) in a large cohort of elderly subjects[26]. These findings are consistent with studies that found no statistically significant difference in fracture risk between subjects with or without prediabetes[27,28], but are in contrast with those reporting an association between prediabetes, adjusted for BMI and/or BMD, and lower fracture risk[29].

Assessment of fracture risk in diabetes

Schwartz and colleagues analyzed data from nearly 17,000 older community-dwelling men and women, and found that, for a given T-score and age or FRAX® score (the most widely used fracture risk index), subjects with diabetes had a higher fracture risk than those without diabetes[30]. Similarly, Giangregorio *et al*[31] found that FRAX underestimates the risk of major osteoporotic and hip fractures in individuals with diabetes. Recently, four options have been assessed to enhance the performance of FRAX in patients with DM (using rheumatoid arthritis as a proxy for the effects of DM, trabecular bone score [TBS]-adjustment, reducing the femoral neck T-score input by 0.5 SD, increasing the age input by 10 years)[32]. Although each correction improved the performance of the FRAX tool in predicting fracture risk, no single method was optimal for all fracture outcomes and durations of diabetes.

DIABETIC BONE DISEASE-PATHOPHYSIOLOGY

Several factors might be responsible for the increased fracture risk in diabetic patients. Diabetes-related changes affect bone strength, which in turn depends on different and complex components, *i.e.* BMD, bone microarchitecture and its microenvironment and material properties.

Bone cells

Cellular and molecular components cross-talk to maintain skeletal integrity in an intricate balance that can be altered in DM. It is important to understand alterations in these components, as they have also direct clinical consequences and may represent targets for clinical interventions. Structural elements with a role in physiologic bone formation include support cells like osteoblasts and osteocytes, remodeling cells known as osteoclasts, and non-cellular components like osteoid (hydroxyapatite, collagen, non-collagen-structural proteins) and mineral salts deposited within the matrix. Mesenchymal stem cells (MSC), *i.e.*, the osteoblast precursors, may also differentiate into adipocytes. The fate of MSCs depends on a fine balance between the WNT signaling pathway, which promotes osteogenesis, and the peroxisome proliferator-activated receptor-γ (PPAR-γ) pathway, which promotes adipogenesis[33]. An imbalance between these pathways may result in one cell type predominating over the other. Along with the bone-resorbing osteoclasts, osteoblasts are involved in a fundamental process that lasts the whole human life, bone remodeling, wherein old bone is substituted with new bone to maintain bone strength and mineral

homeostasis, and to repair microdamage[34].

Osteoblasts in T1D: Preclinical studies[25] documented alterations in transcription of osteoblasts promoting genes, in particular Runx2, which is involved in MSC differentiation into pre-OBs and in the regulation of bone matrix protein genes. Some preclinical studies suggested that Runx2 is downregulated by hyperglycemia[35,36], although other studies reported no modification[37,38]. The *Wnt/beta catenin* gene, which is known to promote OB differentiation, is also downregulated[39]. In T1D, low levels of IGF-1, which promotes differentiation of MSCs into OBs[40,41] and bone mineralization[42], may also contribute to reduced bone formation. It is also known that serum from T1D patients decreases collagen production in human OBs when used as a culture medium[43]. Moreover, individuals with T1D have low levels of parathyroid hormone (PTH)[44], which in normal conditions prevents OB apoptosis[45], improves bone density and increases mineralization and enhances, synergistically with IGF-1, osteoblast differentiation into osteocytes[46]. An increase in circulating levels of proinflammatory cytokines such as TNF-a, IL1 and IL6 due to hyperglycemia[47,48], may impair OB proliferation and differentiation *in vitro*[49-53], or even stimulate OB apoptosis[54,55], while inhibiting bone healing *in vivo*[56]. Overall, the evidence suggests that an impairment on OB function and survival may be responsible for reduced bone formation in T1D.

Osteoblasts in T2D: Few studies on OBs from T2D subjects are available. Postmenopausal women with T2D were reported to have higher levels of OB precursor cells than BMI-matched non-diabetic controls. Obs were more immature compared with controls, and Dickkopf-related protein 1 (DKK-1), a regulator produced by bone marrow stromal cells that inhibits OB maturation, was increased[57]. Thus, it appears that individuals with T2D have increased levels of immature Obs, which may explain lower bone quality and higher BMD.

Osteocytes in T1D: In mouse models of T1D, a reduction in osteocyte density and number, and an increase in apoptosis have been reported[58-60]. Sclerostin, an osteocyte-derived protein that inhibits bone formation[61,62] and stimulates OB apoptosis[63], is elevated in adults with long-standing T1D[64] prediabetes[65], or T2D[66]. Surprisingly, however, a large Danish retrospective study of T1D patients found that T1D patients with higher serum levels of sclerostin had a lower incidence of bone fractures[67].

Osteocytes in T2D and prediabetes: As mentioned, osteocyte-derived sclerostin is elevated in adults with T2D and prediabetes[65,66]. In T2D, there is a direct correlation between sclerostin levels, disease duration and glycemic control, and an inverse correlation with bone turnover markers[66,68]. Anti- sclerostin antibodies increased bone mass in diabetic rats[69]. This finding is of particular interest, as an anti-sclerostin monoclonal antibody (romosozumab) is now available for the treatment of osteoporosis in humans[70].

Osteoclasts in T1D: In physiological conditions, the OB-derived receptor activator of nuclear factor kappa-B ligand (RANKL), promotes the differentiation and activation of osteoclasts through the receptor RANK on osteoclast surface. This process is inhibited by osteoprotegerin (OPG), also produced by OBs, which binds to RANKL thereby preventing its interaction with RANK. Patients with T1D and poor glycemic control exhibit more active bone resorption. Consistently, the analysis of peripherally detected osteoclasts in patients with T1D showed a lower sensitivity to inhibitory factors such as OPG[71]. An increased *OPG* gene expression compared to healthy controls has also been reported[72], possibly to compensate for the lower sensitivity to OPG. Other *in vitro* studies, however, showed a reduction in RANKL and its cellular actions in hyperglycemic environments[73] , which could indicate a limited role of RANKL and OPG in the pathogenesis of bone alterations in DM. Finally, a higher concentration of markers of osteoclastic activity (cathepsin K, tartrate-resistant acid phosphatase [TRAP], C terminal telopeptide) has been observed in insulinopenic mice[74,75], although this increase was significant only in the case of severe or long-lasting diabetes. This variability in osteoclastic activation suggests that disease severity and duration may influence the degree of diabetes-induced bone resorption[76,77] .

Osteoclasts in T2D: High glucose levels inhibit osteoclast differentiation and suppress matrix degradation by osteoclasts in animal models of T2D[78]. Accordingly, circulating osteoclast precursors were found to be increased and more immature in T2D postmenopausal women compared with BMI-matched healthy controls, possibly due to lower RANKL levels[57]. It may be speculated that a lower level of maturation compromises OC activity, leading to decreased bone resorption resulting in higher

BMD in T2D.

BMD

BMD in T1D: Low BMD is reported in nearly all studies involving T1D patients of any age compared to non-diabetic controls[79]. The reduction in BMD worsens with longer disease duration[80], poor glycemic control, early age of onset of T1D, and higher insulin dosage[81]. Furthermore, T1D adult patients with microvascular complications have lower BMD than those without microvascular disease[81-86], suggesting a role for bone vascularization in the pathogenesis of diabetic bone disease. Children and adolescents withy T1D have smaller cross-sectional areas and weaker bones despite an increase in bone formation markers, suggesting impaired osteoblast activity during growth[87]. It is likely that an inadequate peak bone mass is reached at the end of the skeletal maturation due to low levels of IGF-1 and the catabolic effects of uncontrolled hyperglycemia during critical growth period[88,89]. Consistently, patients with onset of diabetes before age 10 years reach a lower than average mean near-adult height, adult height being inversely correlated with glycemic control[90].

Altered vitamin D and calcium metabolism due to hyperglycemia may further contribute to reduced BMD in T1D[91]. Reduced BMD, however, might not be the only factor contributing to increased fracture risk. Recent observations suggest that, opposite to what one would expect, BMD does not worsen over time in patients with T1D as compared with nondiabetic individuals[92].

BMD in T2D and prediabetes: Subjects with T2D generally have higher BMD as compared with healthy controls, with significant differences of 0.04 (95%CI: 0.02, 0.05) at the femoral neck, 0.06 (95%CI: 0.04, 0.08) at the hip and 0.06 (95%CI: 0.04, 0.07) at the spine[93]. As insulin is known to exert anabolic effects on bone, high circulating insulin levels may explain the observed increase in BMD in T2D[94]. Accordingly, some studies indicate a positive association between circulating insulin levels and BMD, independent of BMI[95-97]. However, in most studies the positive association between insulin levels or indices of insulin resistance and BMD was lost after adjusting for BMI[26,98-101], implying that the increase in BMD observed in insulin resistant states is mediated by body mass. In fact, obesity has long been considered to be protective towards osteoporosis and osteoporotic fractures, being associated with increased mechanical load stimulating bone formation[102], androgens-to-estrogens conversion in adipose tissue, lower serum levels of sex hormone binding globulin (SHBG)[103], increased circulating leptin[104] and insulin growth factor, and hyperinsulinemia[99]. Recent findings challenge this belief, suggesting that even though BMD increases with body weight, this cannot compensate for obesity-associated greater impact forces during falls. Data from a multiethnic cohort of nearly 2000 pre- or perimenopausal women indicate that higher BMI is associated with higher BMD, but also with lower composite strength indexes[105]. Conflicting data on the association between obesity and fracture risk, with earlier studies demonstrating a protective effect[106-109] and more recent studies indicating an increase in risk[110-114], suggest that BMI is not the only relevant factor in this context, and that body composition and fat distribution may also play a role[115]. Elevated waist circumference and waist-to-hip ratio have been associated with an increased hip fracture risk in a large prospective cohort study[116]. In obese Chinese women, increased fat mass and percent body fat were positively associated with BMD, whereas increased central fat was inversely associated with BMD[117]. Accordingly, visceral adiposity has been associated with increased risk of both vertebral and non-vertebral fractures[118,119]. Central adiposity reflects the amount of visceral adipose tissue (VAT), which is more cellular, vascular, innervated and characterized by the presence of more inflammatory and immune cells, lesser pre-adipocyte differentiating capacity and higher proportion of large adipocytes as compared with subcutaneous adipose tissue (SAT)[120]. VAT is tightly correlated with insulin resistance[121], which, together with low-grade chronic inflammation, possibly mediates the relationship between VAT and increased fracture risk.

In Korean men diagnosed with prediabetes using an oral glucose tolerance test, no significant difference in BMD T-score was found as compared with subjects having normal glucose metabolism[122]. Despite no difference in total body BMD between prepubertal overweight children with prediabetes *vs* non-prediabetic controls (as assessed by OGTT)[123], total body bone mineral content (BMC) was found to be significantly lower in prediabetic children. Inverse associations were found between BMC and markers of insulin resistance and inflammation (C-reactive protein).

Bone turnover

Bone turnover may be assessed by measuring bone turnover markers (BTMs), which reflect the bone resorption and formation processes.

Bone turnover in T1D: In general, both T1D and T2D are considered as states of low bone turnover. Different studies have shown that worse glycemic control is associated with lower bone turnover markers in T1D[124-126], suggesting a negative effect of hyperglycemia on bone turnover. More specifically, patients with T1D exhibit higher sclerostin levels and lower C-terminal telopeptide of type I collagen (CTX) and osteocalcin levels as compared with non-diabetic controls[127].

Bone turnover in T2D and prediabetes: Bone turnover markers are generally reduced in patients with T2D[126,128,129], to a greater extent than patients with T1D[130]. However, not all studies yielded consistent findings. Osteocalcin and CTX are the BTMs most consistently found to be lower in T2D and patients with as compared with subjects without diabetes, whereas sclerostin and osteoprotegerin are generally elevated (Table 1). Conflicting findings have been reported for other markers but, overall, the evidence seems to point towards a suppression of bone formation and bone resorption, both in prediabetes and T2D. Histomorphometric evaluation of bone tissue biopsies from T2D patients confirmed reduced bone turnover[131,132]. The suppression of bone turnover reported in T2D patients is associated with higher risk of vertebral fractures[133,134], independent of BMD. This is consistent with the concept that the impairment in bone strength in T2D is due to impaired material properties, which may be caused by low bone turnover, as well as by elevated concentrations of advanced glycation endproducts (AGEs)[135].

Fewer studies have assessed bone turnover in prediabetes. Impaired fasting glucose (IFG) was associated with lower osteocalcin[128], CTX and N-amino terminal propeptide of T1D procollagen (P1NP)[136,137] in women, and lower CTX and P1NP in men[136], suggesting that, similar to T2D, prediabetes is associated with reduced bone turnover.

Increased bone marrow adiposity

Bone marrow adipose tissue (MAT) has gained increasing attention in recent years as a single anatomic entity, together with its relations with various clinical conditions, including diabetes. MAT consists of MSC-derived adipocytes located within the bone marrow niche. The distribution of MAT around the skeleton is not homogenous, and regulation of marrow adipose depots varies at different skeletal sites. While peripheral depots of MAT (also termed constitutive MAT) rarely change, MAT depots at more central sites (*e.g.*, spine, pelvis and sternum, proximal regions of the long bones) are more diffuse within the red marrow and may increase or decrease in response to environmental or pathological factors (regulated MAT)[138]. Interestingly, hyperglycemia increases the expression of *PPAR* genes, which stimulates differentiation of MSC into bone marrow adipocytes[139]. Similarly, the antidiabetic PPARγ agonists thiazolidinediones (TZDs) are thought to increase fracture risk through promotion of marrow adipogenesis at the expense of osteogenesis[140](Figure 1). Until recently, MAT was thought to be just a reserve of adipose tissue, negatively associated with hematopoiesis, but its complete function has just begun to be revealed. *In vivo* studies using magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) or computed tomography (CT) to assess MAT quantity and composition have helped understand the mechanisms of increased skeletal fragility and metabolic risk associated with several clinical conditions, including diabetes[141].

MAT in T1D: In animal models of T1D, hyperglycemia is associated with increased marrow adiposity and bone loss[37,38,142], whereas no differences in MAT were identified between male patients with T1D and healthy controls[143,144], and neither duration of disease nor glycemic control were related to bone marrow adiposity. This lack of association between MAT and T1D was confirmed in young women with T1D compared with healthy controls[145]. Irrespective of the presence of diabetes, in young women MAT was inversely associated with BMD[145]. Carvalho and colleagues showed that MAT quantity and lipid composition (saturated and unsaturated lipids) were similar between male T1D subjects and controls[144]. There was, however, a significant inverse correlation between MAT saturated lipids and BMD.

MAT in T2D: In T2D men participating in the Osteoporotic Fractures in Men (MrOS) Study, a large epidemiological study of nearly 6,000 men, vertebral MAT was increased as compared with nondiabetic controls, and inversely associate with BMD[146]. Although no differences were detected in total MAT content in postmenopausal women, those with T2D and previous fractures had the lowest MAT lipid unsaturation and highest MAT saturation levels independent of age, race, and BMD, highlighting the importance of MAT composition in addition to the degree of marrow adiposity[147]. Furthermore, gender-related differences have been reported in the association between MAT and visceral adipose tissue (VAT)/subcutaneous

Table 1 Bone turnover markers in prediabetes/insulin resistance and type 2 diabetes

BTM	Meaning	Pre-DM / IR	Ref.	T2D	Ref.
CTX	Bone resorption	↓ or ↔	[136,276,278-280]	↓	[129,132,134,137,281-286]
TRAP	Bone resorption	↑?	[287]	↓ or ↔	[132,281]
uNTX	Bone resorption			↓	[285]
Sclerostin	Inhibition of bone formation	↑	[65]	↑	[284,285,288,289]
OC	Bone formation	↓ or ↔	[128,276-278,280,290]	↓ or ↔	[129,132,134,281,283,285,286,291-294]
P1NP	Bone formation	↓ or ↔	[136,277,280]	↓ or ↔	[88,132,134,137,282,283,285,286]
BAP	Bone formation	Direct association with IR	[295]	↔ or ↓ or ↑	[132,281,284,286,292,294]
ALP	Bone formation	?	?	↔ or ↑	[292-294]
OPG	Inhibition of bone resorption	↑	[296]	↑	[293,296]

BTM: Bone turnover marker; pre-DM: Prediabetes; IR: Insulin resistance; T2D: Type 2 diabetes; CTX: Carboxy-terminal cross-linking telopeptide of type I collagen; OC: Osteocalcin; P1NP: Procollagen type 1 amino-terminal propeptide; TRAP: Tartrate-resistant acid phosphatase; uNTX: Urinary N-telopeptide of type I collagen; BAP: Bone-specific alkaline phosphatase; ALP: Alkaline phosphatase; OPG: Osteoprotegerin; ↑: Increased; ↓: Decreased; ↔: Similar to healthy controls; ?: Unknown.

adipose tissue (SAT) volumes or BMI. While in obese or diabetic women MAT is associated with VAT and SAT[148,149], no such association was found in older men[150]. In men, a negative association between MAT and DXA-derived BMD of femoral neck and total hip was reported. Data on MAT in pre-diabetes is scanty, but a potential relation between hyperglycemia and MAT has been suggested[151].

Advanced glycation end products - bone matrix in diabetes

AGEs are protein or lipid complexes formed through non-enzymatic reactions in the presence of high sugar levels. Their accumulation is thought to play a role in aging and some degenerative diseases[152]. In *in vitro* studies, AGEs deposits have been demonstrated in bone matrix, where they may exert a direct toxic effect on OBs[153]. AGEs inhibit bone remodeling and indirectly up-regulate the production of interleukin 6 (IL-6)[154], a catabolic factor that attenuates OBs activity[53] and vascular endothelial growth factor A (VEGF-A) by osteocytes, inducing also their apoptosis[155].

AGEs in T1D: In murine models of T1D, the AGE pentosidine (PEN) in bone is significantly increased, this increase being paralleled by an impairment in bone mechanical properties[156]. Similarly, PEN levels in bone biopsies from fractured T1D patients were higher than in controls[80], and circulating PEN levels are associated with prevalent fractures in T1D[157]. Carboxymethyllysine (CML), another type of AGE that correlates with fracture risk[158], is increased in mouse models of T1D and inversely associated with bone strength[159].

AGEs in T2D and prediabetes: Bone strength in T2D postmenopausal women is reduced as compared with non-diabetic controls, and this reduction appears to be associated with increased AGE accumulation, as indirectly estimated by skin autofluorescence (SAF)[160]. Consistently, increased urinary or serum PEN levels have been associated with greater fracture risk in T2D[161,162]. To the best of our knowledge, no data are available on AGEs and bone health in prediabetes.

Bone geometry and microarchitecture

Bone geometry and microarchitecture contribute to bone strength. Tools such as high-resolution peripheral quantitative computed tomography (HR-pQCT), micro-magnetic resonance (μ-MRI) and TBS acquired through dual-energy X-ray absorptiometry (DXA) are available to study bone structure in diabetes[163,164], offering enough resolution to assess microarchitecture and providing indirect indexes of bone quality.

Bone geometry and microarchitecture in T1D: In rodent models of T1D, deletion of the insulin receptor from OBs at different stages of maturation leads to anomalous trabecular architecture and higher bone fragility[3,4]. In adults with T1D, trabecular bone quality is lower as compared with non-diabetic age-, BMI-, and sex-matched controls and is negatively associated with insulin resistance, as assessed by the hyperinsulinemic euglycemic clamp[165]. Studies using HR-pQCT demonstrated higher cortical porosity, thicker trabeculae and larger spacing between trabeculae in T1D patients with microvascular complications, compared to those without, and in T1D patients compared with matched non-diabetic controls[166]. Similar findings were

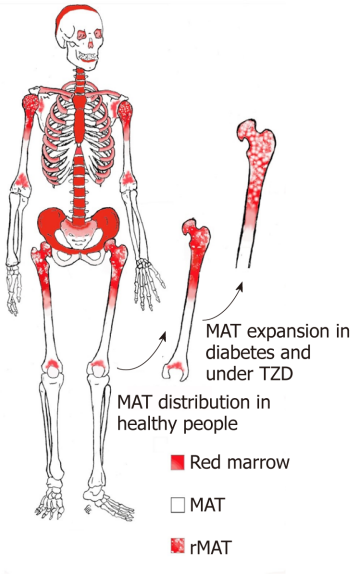

Figure 1 Schematic representation of the anatomical distribution of bone marrow adipose tissue depots. Both hyperglycemia and the antidiabetic drugs thiazolidinediones may induce marrow adipose tissue (MAT) expansion by increasing the expression of peroxisome proliferator-activated receptor genes, which in turn stimulates adipogenesis. rMAT: Regulated MAT (MAT depots that increase or decrease in response to different stimuli).

reported using μ-MRI[167]. Moreover, using μ-CT in T1D subjects without vascular complications, worse bone quality was found in those who did experience fractures as compared with those who did not[166]. An insufficient peak bone mass at the end of skeletal maturation may result in smaller and shorter bones, a geometry that could favor bone fragility[130]. However, the contribute of altered geometry and defective trabecular and cortical bone to the increased risk of fracture in T1D is yet to be clarified.

Bone geometry and microarchitecture in T2D and prediabetes: The increased fracture risk in T2D may be related to distorted bone microarchitecture, especially in cortical bone[168-170].

Bone micro-indentation allows measuring the bone material strength index (BMSi), which estimates the resistance to crack propagation in bone[171]. BMSi is reduced in patients with T2D as compared to healthy controls[88,93], suggesting a lower resistance to fractures. Increased cortical porosity has been identified as a possible causative factor. Patients with T2D have higher porosity in trabecular bones, as assessed by MRI[170]. Studies using HR-pQCT confirmed a similar trend in porosity. Deficits in cortical bone of T2D patients were more marked in patients with previous fractures compared to those without[169], or present only in T2D patients with microvascular complications compared with patients without complications[169]. In a cross-sectional analysis of nondiabetic postmenopausal women, higher levels of insulin resistance were associated with lower cortical bone volume, independent of age and weight[172]. Consistently, female obese late-adolescents had worse trabecular bone microarchitecture at the radius and tibia as compared with non-obese controls, as well as lower bone volume and estimated bone strength[173]. T2D diabetes and insulin resistance are almost invariably associated with obesity and increased central adiposity, which reflects increased VAT. Studies that explored the relationship between VAT and bone microarchitecture suggest a possible detrimental effect of VAT on bone microarchitecture. Studies have reported a negative impact of VAT on bone microarchitecture, as suggested by a negative association between central adiposity measures and TBS[174,175]. Furthermore, a negative effect of VAT on femoral cross-sectional area, cortical bone area and bone strength indexes has been reported[176]. On the other hand, higher VAT was associated with improved microarchitecture with the exception of higher cortical porosity at the distal radius in the Framingham osteoporosis study[177]. However, this association lost significance after adjustment for BMI or weight, suggesting that the effects of VAT may not have a substantial effect on the skeleton independent of BMI or weight. In non-diabetic men at the age of peak bone mass, insulin resistance (as assessed by HOMA-IR) was found to be inversely associated with trabecular and cortical bone size, independent of body

composition[178]. Overall, these data suggest a detrimental role of hyperinsulinemia on bone microarchitecture and geometry. Central adiposity might have a negative effect on bone microarchitecture, but this possibility needs to be further explored.

Vascular disease: microangiopathy

Diabetic microvascular complications such as retinopathy and neuropathy may indirectly potentiate the fall risk, impairing vision or physical perception. Diabetic microangiopathy may involve all organs, including bone, possibly contributing to bone fragility. Histomorphometric assessments found microangiopathy in 82% of bone biopsy specimens from diabetic patients, and a concomitant reduction of bone marrow capillaries[179]. To date, there is no other direct evidence of bone vascular alteration in humans. In mouse models of T1D, administration of an angiogenic factor to ovariectomized mice led to improvements in bone quality[180]. As mentioned, reduced trabecular BMD, cortical BMD, thinner trabeculae and cortex were reported in T1D patients with known vascular complications, as opposite to T1D patients without complications and non-diabetic controls[166]. Similarly, in a cross-sectional study that assessed peripheral bone microarchitecture, bone strength and bone remodeling in T2D patients with or without diabetic microvascular disease only T2D patients with established microvascular disease displayed lower cortical volumetric BMD and cortical thickness and higher cortical porosity at the radius compared to controls without microvascular disease[181]. Impaired microvascular circulation might lead to hypoxia, which in turn may lead to enhanced adipogenesis within the bone marrow and downregulation of OB differentiation[182].

Pharmacological treatments for diabetes

Metformin: Metformin is widely prescribed for the management of T2D, being recommended as the first-line treatment by international guidelines[8,183]. It reduces hepatic glucose production and improves peripheral insulin sensitivity, thereby enhancing peripheral glucose disposal[184]. Metformin has been shown to promote the osteogenic differentiation of adipose-derived MSC, and in general to exert pro-osteogenic effects in preclinical studies[185-188]. Clinical observations indicate that metformin has a neutral[28,189] or even a favorable effect on fracture risk[12,190,191].

Glucagon-like peptide-1 (GLP-1) receptor agonists (RA): GLP-1 RAs (liraglutide, exenatide, lixisenatide, dulaglutide, semaglutide) are recommended as the best choice for a second agent when combination treatment is needed to achieve glycemic control in patients with T2D in whom atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease predominates[8,183]. By activating the GLP-1 receptor, GLP-1 RAs slow gastric emptying, suppress glucagon secretion while also stimulating glucose-induced insulin secretion[192]. These effects result in the suppression of hepatic gluconeogenesis and increased peripheral glucose disposal. *In vitro*, activation of GLP-1 receptors promotes differentiation of MSC into osteoblasts[193] and inhibits osteoblast apoptosis[194], suggesting an anabolic effect on bone. Studies in rats support these findings[195]. Of note, in animal models of T1D administration of liraglutide significantly improved bone strength and reduced collagen degradation in the bone matrix, although no changes in trabecular no cortical microarchitecture were observed[196]. Case-control studies and metanalyses of population-based studies and randomized clinical trials including patients with T2D treated with GLP-1 RAs indicate no effect on fracture risk[197-199]. However, evidence exist that different GLP-1 RAs may exert opposite effects on fracture risk, which appears to increase or decrease in patients treated with exenatide or liraglutide, respectively[200]. Furthermore, liraglutide was reported to prevent a reduction of BMC after weight loss in obese nondiabetic women, although BMD was not affected[201,202].

Dipeptidylpeptidase 4 (DPP4)-inhibitors: DPP4-inhibitors (sitagliptin, linagliptin, saxagliptin,vildagliptin, alogliptin, *etc*.) exert their action by inhibiting the enzyme DPP-4, which is responsible for the rapid degradation of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and GLP-1, thereby enhancing glucose-induced insulin secretion[203]. Preclinical studies indicate a possible anti-osteoclastogenic and anti-resorptive effect of DPP4-inhibitors[204,205]. Clinical data support a neutral[189,206,207] or even favorable[208,209] effect of DPP4-inhibitors on fracture risk. In particular, alogliptin may be associated with a lower risk of bone fracture compared with placebo and other drugs in the same class[210].

Sodium-glucose cotransporter 2 (SLGT2) inhibitors: By inhibiting the renal SGLT2, these drugs (empagliflozin, dapagliflozin, canagliflozin) reduce glucose reabsorption in the kidney, thus increasing urinary glucose excretion and decreasing blood glucose[211]. Associated increases in serum phosphate may lead to changes in PTH and fibroblast growth factor 23 (FGF23) that could affect bone metabolism[212]. Along with

GLP-1 RAs, SGLT2 inhibitors are recommended as the best choice for a second agent when combination treatment is needed to achieve glycemic control in patients with T2D in whom atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease predominates[8,183]. Initial reports of increased frequency of bone fractures associated with SGLT2 inhibitors treatment, particularly with canagliflozin, raised concerns about the skeletal safety of these compounds[213]. Furthermore, increased bone turnover and reduced total hip BMD have been reported in patients with T2D treated with canagliflozin[214]. Nevertheless, recent population studies and metanalyses including several thousands of patients consistently failed to demonstrate an association between SGLT2 inhibitor treatment and increased fracture risk in patients with T2D[215-219].

Sulfonylureas and glinides: Sulfonylureas (*e.g.*, glimepiride, gliclazide, glybenclamide) and glinides (*e.g.*, repaglinide) stimulate glucose-independent insulin secretion by binding to specific sites at the β-cell membrane[220,221]. It has been postulated that sulfonylureas do not affect bone directly, but may increase fracture risk by inducing higher rates of hypoglycemic events[222]. Studies that assessed the effect of sulfonylureas and glinides on fracture risk yielded conflicting results, with most studies indicating increased risk[28,189,223-225], but also no effect[191] even decreased risk[12].

Thiazolidinediones (TZDs): TZDs (rosiglitazone, pioglitazone) are insulin-sensitizing agents that exert their action by activating the peroxisome proliferator-activated receptor γ (PPARγ)[226]. Besides enhancing peripheral insulin sensitivity and suppressing hepatic glucose production, activation of PPARγ stimulates adipogenesis and suppresses osteoblastogenesis, thereby reducing the osteoblast pool in the bone marrow[227]. A detrimental effect of TZDs on bone health has been consistently shown. In a cohort study including more than 5000 patients with T2D, current use of TZDs was associated with increased hip fracture risk[190]. Treatment with pioglitazone significantly increased fracture risk compared with placebo in a randomized double-blind, placebo-controlled study[228]. The increase in risk has been confirmed in population-based studies[189] and metanalyses[229], although the impact on bone seems to be more pronounced in women than in men[190,229].

Insulin in T1D: Insulin is the pillar of T1D treatment. As previously discussed, insulin exerts anabolic effects on bone. Intensive insulin treatment has been associated with increased BMD in patients with T1D[82]. Consistently, no association between insulin treatment and single nor multiple fractures was found in a recent study that assessed risk factors for fragility fractures in T1D[230].

Insulin in T2D: Insulin treatment in patients with T2D is initiated when disease progression overcomes the effect of non-insulin agents[8,183]. Thus, patients with T2D started on insulin generally have longstanding diabetes, and may have developed serious complications such as retinopathy-related impaired vision, peripheral artery disease and neuropathy, which in turn are risk factors for falls[20,21]. Insulin use is associated with a 1.4- to 2-fold increase in fracture risk as compared with no insulin use[189,231], and with a 1.6-fold increase in risk as compared with metformin monotherapy[232]. However, not all studies point towards a negative effect of insulin on fracture risk[12,191]. The association between insulin and increased fracture risk despite the anabolic effects of insulin on bone is likely due to the increased risk of falls and hypoglycemic episodes associated with insulin treatment[222].

Surgical treatments for diabetes

Pancreas and islet transplantation in T1D: Beta cell replacement through pancreas or pancreatic islet transplantation is the only currently available cure for T1D in humans, with pancreas transplantation being more often associated with insulin independence and longer graft function. Successful pancreas transplantation provides physiological insulin repletion, without the risk of hypoglycemia associated with exogenous insulin administration. Evidence exists that combined pancreas-kidney transplantation leads to improvements in BMD[233], and that fracture rates in patients with T1D are lower after transplantation with a simultaneous pancreas–kidney compared with kidney transplantation alone[234], suggesting that T1D remission by pancreas transplantation favorably impacts fracture risk. However, individuals with T1D undergoing pancreas-kidney transplantation also have end-stage renal disease, which strongly affects bone health. A study assessing the effect of diabetes remission following pancreas transplantation alone on bone health in individuals with T1D and preserved kidney function is currently ongoing (NCT03869281).

Metabolic surgery for T2D diabetes: Metabolic surgery is now included as a

treatment option for appropriate candidates with T2D[8,235]. Patients undergoing metabolic surgery experience rapid and massive weight loss, which translates into several metabolic benefits, but may be detrimental to bone health. Most available data relate to the Roux-en-Y gastric bypass (RYGB), a restrictive procedure that also involves a malabsorptive component. Sleeve gastrectomy (SG), which has now overcome RYGB and has become the most common bariatric procedure worldwide[236], is a restrictive procedure. Other bariatric procedures, such as the malabsorptive biliopancreatic diversion and the restrictive laparoscopic adjustable gastric banding (LAGB), are being gradually abandoned. Available data indicate that fracture risk after bariatric surgery varies depending on the bariatric procedure, being lowest in patients undergoing LAGB[237] and greatest in those undergoing malabsorptive procedures[238-241], and increases with time after surgery[237,239-242]. However, weight loss-related reductions in BMD have even been reported 6-12 months after minimally invasive bariatric procedures not involving resection of the stomach and/or intestine, such as use of the intragastric balloon or an intraluminal liner implanted into the small intestine[243,244]. Mechanisms underlying the negative effects of bariatric surgery on bone health may involve nutritional factors, mechanical unloading, hormonal factors, and changes in body composition and bone marrow fat[245]. To the best of our knowledge, no studies have specifically addressed the issue of diabetic bone disease in patients with T2D undergoing bariatric surgery.

PERSPECTIVES: POSSIBLE PREVENTIVE AND THERAPEUTIC APPROACHES

Modifiable risk factors for fracture, including factors that affect fall risk and glycemic control should be tackled to reduce fracture risk, although no prospective studies are available to show the antifracture efficacy of preventive lifestyle and/or treatment strategies. Drugs shown to be associated with increased fracture risk in T2D, such as insulin and TZDs[231,232,246] should be avoided, when possible. Strict monitoring should be implemented for T2D patients undergoing bariatric surgery in order to prevent nutritional deficiencies that could worsen weight loss-associated bone loss.

Several alterations in calcium homeostasis have been described in diabetic patients, including reduced intestinal calcium absorption and renal tubular calcium reabsorption, and impaired vitamin D synthesis[247]. It is also recognized that individuals with diabetes, both T1D and T2D, have lower vitamin D levels as compared with non-diabetic controls[248,249]. Overall, these alterations may negatively impact calcium homeostasis and bone mineralization. International guidelines recommend vitamin D supplementation for the prevention and/or treatment of osteoporosis and osteoporotic fractures in men and postmenopausal women[250-252], although recent findings bring into question the efficacy of vitamin D supplementation in preventing fractures or falls, or improving BMD[253]. Vitamin D supplementation was shown to increase bone formation markers[254] and reduce bone resorption markers[255] in postmenopausal women with T2D, not to affect bone turnover markers in patients with T2D and chronic kidney disease[256], and to preserve femoral neck BMD in men with prediabetes[257]. Few data are available about the effect of the use of osteoporosis medications in patients with diabetes.

Stemming from some positive preclinical results[258], few recent human studies have focused the attention on nutrients containing antioxidants such as resveratrol, providing encouraging results in terms of on bone density and on bone loss prevention in obese patients[259] and patients with T2D[260,261] have been reported.

Recently, hyperbaric therapy[262,263] has been shown to promote bone regeneration in animal models of diabetes, but further studies are needed to clarify whether this could be an effective approach in humans.

Raloxifene, a second generation selective estrogen receptor modulator (SERM) indicated for the prevention and treatment of postmenopausal osteoporosis[264], was shown to improve bone material properties (femoral toughness) in diabetes-prone rats[265]. In postmenopausal women, raloxifene may decrease the bone resorption marker NTX and it has been speculated that it might improve bone quality by reducing AGEs, although no information is available on the effect on reliable bone quality indicators or relevant clinical outcomes such as fracture risk[265]. In a pilot study that assessed the skeletal effects of a third generation SERM, bazedoxifene, in postmenopausal women with T2D, all bone resorption markers decreased significantly after 12 weeks of treatment. Homocysteine and pentosidine, which were used as bone quality markers in this study, were not affected[266].

Little is known about osteoporosis therapies in T1D young patients. As T1D usually manifests in young individuals, it is important to remember that caution must be

taken in women during reproductive age, as bisphosphonates are stored and released from bones for long time and may affect fetal skeletal ossification. In elderly, postmenopausal, osteoporotic obese women with T2D treated with long-term bisphosphonates, no difference in spine BMD but a significantly greater decline in BMD in regions of the hip, femoral neck, and forearm were observed as compared with non-diabetic controls[267]. However, the efficacy of these medications must be assessed based on clinically relevant outcomes. Despite being a condition of reduced bone turnover, epidemiological data indicate that diabetes (either T1D or T2D) was shown not to reduce the antifracture efficacy of antiresorptive drugs, which also reduce bone turnover[268].

In a large study on the efficacy of recombinant PTH (rhPTH 1-34, teriparatide), similar reduction in nonvertebral fracture incidence and increase in BMD were observed in postmenopausal osteoporotic women with or without T2D[269].

Denosumab is a RANKL-specific antibody indicated as osteoporosis treatment known to increase particularly cortical BMD. This property might be of particular value, as cortical compartment is the most involved in the diabetic bone. A phase 2 clinical trial to assess the skeletal effects of denosumab in T2D is ongoing (NCT03457818). Interestingly, denosumab was shown to improve hepatic insulin sensitivity in humans[270,271] and, consistently, to reduce fasting plasma glucose in women with diabetes not on antidiabetic medications[272]. Preclinical studies also indicate that denosumab may stimulate human β-cell proliferation[273].

Sclerostin seems to have a central role in the pathogenesis of diabetic bone disease. In mouse models of T1D[273] and T2D[274], administration of anti-sclerostin antibodies seems to reverse the deficits in bone density and micro-fracture healing. No data are currently available on romosozumab, an anti-sclerostin antibody shown to reduce the risk of clinical and vertebral fractures in postmenopausal women with osteoporosis[275].

CONCLUSION

Diabetes has a strong impact on bone health, and skeletal fragility is now recognized as a complication of both T1D and T2D. Fracture risk is greater in patients with T1D, and increases with increasing disease duration. Individuals with T1D have decreased BMD, possibly due to absolute insulin deficiency and the inability of exogenous insulin to mirror endogenous insulin secretion. However, the relatively small reduction in BMD does not appear to completely explain the increase in bone fragility observed in T1D[276-296]. On the other hand, individuals with T2D have either normal or increased BMD, which is in contrast with the increased fracture risk observed in this population. Therefore, it is likely that factors that affect bone quality, rather than bone mass, impact the resistance of T2D bones to fracture (Table 2). Increased non-enzymatic glycation of bone matrix proteins, impaired microcirculation and glucotoxicity itself, *i.e.*, the direct detrimental effect of high glucose on bone cells, may all play a role. Reduced bone turnover and increased bone marrow adipogenesis at the expenses of osteogenesis may also contribute. Despite a clear association between T2D and increased fracture risk, evidence supporting an association between prediabetes and fracture risk is inconsistent, and further studies are needed to clarify whether insulin excess has either a beneficial or rather detrimental effect on bone health. The incomplete understanding of the mechanisms underlying diabetic bone disease makes it difficult to develop reliable tools for fracture risk prediction. To date, no single method is deemed optimal for predicting all fracture outcomes in patients with diabetes[32]. Fracture history and risk factors should be assessed in older patients with DM, and measurement of BMD is recommended, if appropriate for the patient's age and gender[8]. Caution should be used with antidiabetic drugs known to negatively affect bone health, such as TZDs and insulin in patients with T2D. Healthcare professionals involved in the management of T2D patients undergoing bariatric surgery should be aware of the possible detrimental effects on bone health, and implement appropriate nutritional strategies. Due to the lack of randomized clinical trials to evaluate the efficacy of antifracture drugs in diabetes, and observational data indicating similar efficacy in those with or without diabetes, such drugs should be used according to existing indications.

Future studies should focus on the mechanisms underlying diabetic bone disease, and on preventative and treatment strategies to implement in order to reduce the morbidity associated with fractures in this frail population.

Table 2 Effects of diabetes and prediabetes on bone health

	T1D	T2D	Prediabetes
Fracture risk	↑↑	↑	?
Bone mineral density	↓	↔ or ↑	↔ or ↑
Bone turnover	↓	↓↓	↓?
Bone marrow adiposity	↔	↑	↑?
Bone matrix - AGEs	↑	↑	?
Microarchitecture/geometry	↑ cortical porosity	↑ cortical porosity	↓ trabecular and cortical bone size

AGEs: Advanced glycation endproducts; T1D: Type 1 diabetes; T2D: Type 2 diabetes; ↑: Increased; ↓: Decreased; ↔: Similar to healthy controls; ?: Unknown.

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