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REVIEW

Diabetes and Bone Fragility

Camila Romero-Díaz · Daniela Duarte-Montero · Sebastián A. Gutiérrez-Romero · Carlos O. Mendivil

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ABSTRACT

Diabetes is a highly prevalent disease with complications that impact most bodily systems. However, the impact of diabetes on bone health is frequently ignored or underestimated. Both type 1 (T1D) and type 2 diabetes (T2D) are associated with a higher risk of fractures, albeit through different mechanisms. T1D is characterized by near total insulinopenia, which affects the anabolic tone of bone and results in reduced bone mineral density (BMD). Meanwhile, patients with T2D have normal or high BMD, but carry an increased risk of fractures due to alterations of bone microarchitecture and a local humoral environment that stimulates osteoclast activity. Chronic hyperglycemia induces non-enzymatic glycation of collagen in both types of diabetes. Epidemiological evidence confirms a largely increased fracture risk in T1D and T2D, but also that it can be substantially reduced by opportune monitoring of fracture risk and appropriate treatment of both diabetes itself and osteopenia or osteoporosis if they are present. In this review, we summarize the mechanistic, epidemiological, and clinical evidence that links diabetes and bone fragility, and describe the impact of available diabetes treatments on bone health.

Keywords: Bone; Bones; Denosumab; Diabetes mellitus; Fractures; Osteoporosis

C. Romero-Díaz · D. Duarte-Montero · S. A. Gutiérrez-Romero · C. O. Mendivil (✉)
School of Medicine, Universidad de los Andes, Bogotá, Colombia
e-mail: carlosolimpo@gmail.com; cmendivi@uniandes.edu.co

C. O. Mendivil
Department of Internal Medicine, Endocrinology Section, Fundación Santa Fe de Bogotá, Bogotá, Colombia

Key Summary Points
Both type 1 and type 2 diabetes are associated with bone abnormalities and increased fracture risk, especially at the hip
The mechanisms involved in type 1 diabetes involve reduced BMD as a consequence of insufficient anabolic tone from insulin
Meanwhile, patients with type 2 diabetes usually have normal/increased BMD but have microarchitectural bone alterations that increase their risk of fracture
Fracture risk should be taken into account when selecting antidiabetic medications for a patient
Fracture risk should be routinely assessed and addressed in patients with diabetes

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13154408.

INTRODUCTION

There is a strong interaction between insulin action and bone metabolism [1]. Therefore, both type 1 (T1D) and type 2 diabetes (T2D) are associated with a higher risk of fractures. Nonetheless, the mechanisms of the effects on bone in T1D and T2D may be different and do not necessarily involve a reduction in bone mineral density (BMD) [2]. Several studies show that BMD is lower among patients with T1D than healthy controls, while among patients with T2D BMD is equal or higher than in controls [2–4].

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PATHOPHYSIOLOGY OF BONE ALTERATIONS IN DIABETES

Pathophysiology of Bone Alterations in Type 1 Diabetes

Compared to controls matched by age, sex, and body mass index (BMI), patients with T1D usually have a lower BMD in dual-energy X-ray absorptiometry (DEXA) [5]. T1D is characterized by almost absolute insulin deficiency [6], a key anabolic hormone not only in hepatocytes, adipocytes, and myocytes but also in osteoblasts [4]. Insulin action in osteoblasts stimulates mitosis, inhibits apoptosis, and prevents the deleterious effects of hyperglycemia on bone formation [4, 7]. Research shows that the stimulation of insulin receptors in immature mice osteoblasts promotes their proliferation and differentiation [4, 8]. Mature osteoblasts in culture also express insulin receptors [9]. Three signaling pathways are responsible for the effects of insulin in osteoblasts. First, insulin inhibits p27 (an inhibitor of cyclin-dependent kinases), de-repressing proliferation (Fig. 1) [10]. Second, insulin activates phosphatidylinositol 3-kinase, which phosphorylates BAD (BCL2-associated death promoter), blocking its pro-apoptotic effect (Fig. 2) [11, 12]. Third, insulin stimulates IGFR-1 (insulin-like growth factor 1 receptor), leading to anabolic effects [1]. Indeed, intensive insulin therapy stabilizes bone mass in T1D by restoring the anabolic activity of bone [13].

Not only lack of insulin but also hyperglycemia per se may have a negative effect on bone quality. In hyperglycemic states, non-enzymatic glycation of proteins, phospholipids, and nucleic acids leads to the formation of advanced glycation end products (AGE) [14]. Type 1 collagen is not exempt from this process [15]. The aggregation of AGEs causes non-enzymatic cross-linking of collagen, disrupting the adhesion of osteoblasts to the extracellular

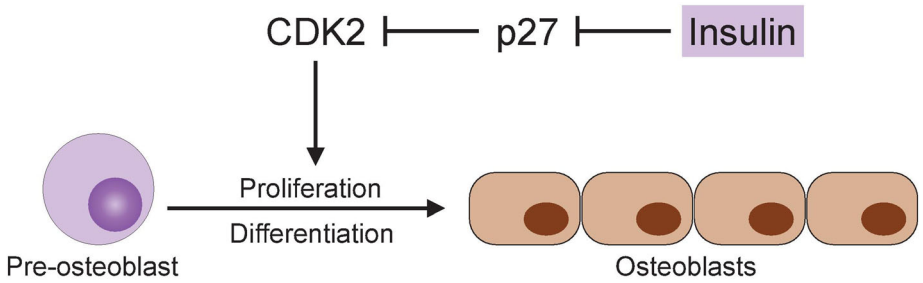

Fig. 1 Insulin enhances differentiation from osteoblast precursors to mature osteoblasts. Insulin signaling inhibits p27. Upon p27 inactivation, CDK2 (cyclin-dependent kinase) is de-repressed and promotes cell cycle progression, resulting in proliferation and differentiation of pre-osteoblasts

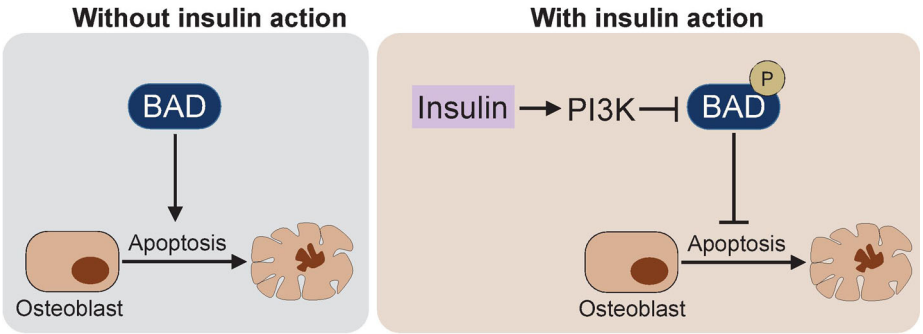

Fig. 2 Insulin inhibits osteoblast apoptosis by blocking BAD (BCL-associated death promoter). In the absence of insulin signaling, BAD induces osteoblast apoptosis. Induction of the insulin signaling pathway in osteoblasts leads to PI3K (phosphatidylinositol 3-kinase) activation. PI3K then phosphorylates and inactivates BAD, preventing apoptosis

matrix and resulting in bone fragility [16] (Fig. 3). These alterations of extracellular matrix also reduce alkaline phosphatase (ALP) activity in mature osteoblasts, affecting bone mineralization [16]. The receptor for AGEs (RAGE) is expressed in human bone cells and its stimulation drives the activation of nuclear factor kappa-B (NF-kB) in osteoclasts, increasing the production of cytokines and reactive oxygen species (ROS) [17]. High proinflammatory cytokine and ROS levels trigger osteoclastogenesis and stop osteoblast differentiation [18, 19]. Hence, accumulation of AGEs promotes chronic inflammation and bone resorption among patients with diabetes. The autoimmune destruction of pancreatic islets decreases the co-secretion of insulin and amylin. Amylin inhibits osteoclasts and stimulates osteoblasts [20]. Thus, amylin deficiency may also affect BMD in patients with T1D.

Pathophysiology of Bone Alterations in Type 2 Diabetes

As mentioned previously, T2D is characterized by normal or high BMD, but an increased risk of fractures. This phenomenon is known as "the diabetic paradox of bone fragility", suggesting that other independent factors aside from BMD may influence fracture risk. Consequently, the National Bone Health Alliance proposed that osteoporosis in T2D should be diagnosed on the basis of bone strength parameters like changes in trabecular microstructure or cortical bone porosity [21]. For instance, high-resolution

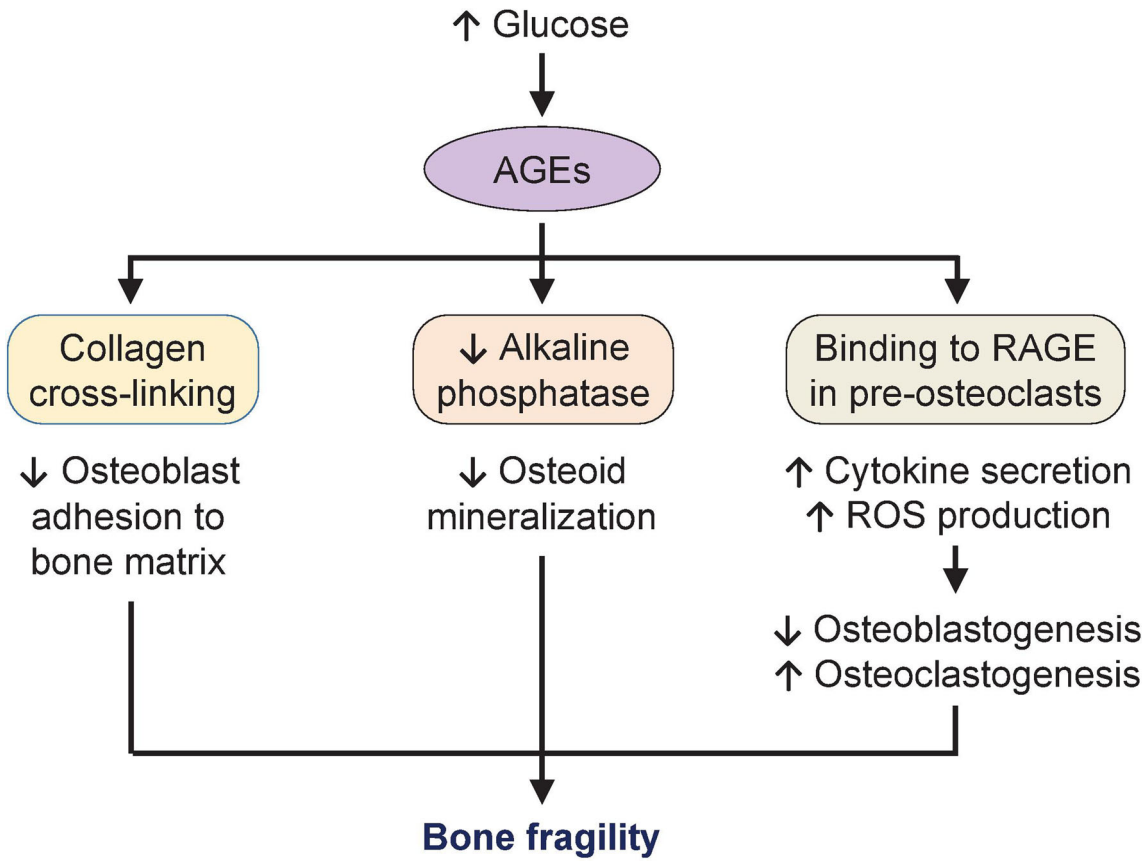

Fig. 3 Bone fragility mechanisms induced by hyperglycemia. AGEs advanced glycation end products, RAGE receptor for advanced glycation end products, ROS reactive oxygen species

peripheral quantitative computed tomography (HR-pQCT) has shown that postmenopausal women with T2D have greater cortical porosity than controls without T2D [22]. A greater cortical porosity results in less bone strength and more fragility fractures in this population [23].

The insulin resistance typical of T2D occurs also in bone tissue, where insulin does not exert its full anabolic effect. There is an inverse relationship between bone strength and insulin resistance measured by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in perimenopausal women [24]. In addition, all the mechanisms connecting hyperglycemia to bone injury are equally active in both T1D and T2D (Fig. 3) [25].

METHODS FOR EVALUATION OF BONE QUALITY IN DIABETES

DEXA (Dual-Energy X-Ray Absorptiometry)

To perform this technique, the patient is placed in a supine position above a C-arm X-ray machine which emits photons at two different energy levels specific for cortical bone and soft tissue [26]. The difference between these two energy photon emissions is detected to create a planar image used to determine BMD in units of bone mass per unit of area (g/cm^2), with the help of associated computer software. Compared to other imaging techniques, DEXA is relatively inexpensive and has a short scan time and less radiation exposure. Even though BMD can be measured in the lumbar spine, hip,

forearm, or in the whole body, lumbar spine and hip are the sites usually evaluated with DEXA [27]. Despite its many advantages, DEXA assesses BMD but not bone quality, which is also a relevant predictor of fragility [28].

HR-pQCT (High-Resolution Peripheral Quantitative Computed Tomography)

Quantitative computed tomography (QCT) measures real bone density in Hounsfield units without reference to other tissues. Hence, it requires an external bone mineral reference phantom to be scanned with the patient in order to obtain the volumetric BMD in milligrams per cubic centimeter [29]. In contrast to DEXA, QCT assesses both trabecular and cortical bone [28]. QCT can be performed using conventional whole-body CT scanners for the spine, or with a smaller CT device for the radius, ulna, tibia, and fibula. This last technique is known as peripheral QCT. Regular CT scanners have a spatial resolution of about 400 μm and a slice thickness of 1 mm. As trabeculae dimensions are 100–400 μm and trabecular spaces 200–2000 μm [30], standard QCT is unable to distinguish morphological parameters of trabecular bone. Therefore, a more sophisticated method (HR-pQCT) has arisen. HR-pQCT makes an in vivo 3D characterization of bone, preferably in the peripheral skeleton (distal radius and tibia), and has a higher resolution (200 μm) and thinner slice images (500 μm). These properties give HR-pQCT the ability to evaluate the microarchitectural, geometrical, and mechanical features of cortical and trabecular bone [22].

μFEA (Micro-Finite Element Analysis)

This technique is a computerized simulation of the stresses and strains induced by mechanical loading on a bone segment. It is used to estimate bone strength and compartment-specific changes in load distribution from HR-pQCT images. By quantifying strength deficits and changes associated with cortical porosity [31], μFEA serves to predict load conditions that increase fracture risk. HR-pQCT combined with μFEA can be used in fracture models to estimate fracture strength, initiation site, and direction as well as a fracture's association with microarchitectural parameters [32].

Spinal X-Ray Images

Although the fracture risk algorithm (FRAX) score may be adapted in patients with diabetes, additional images aside from BMD are needed to assess bone quality. Spinal X-ray images may be a useful tool to detect patients at a higher risk of fracture [33]. A cross-sectional study in Japan found a higher proportion of vertebral fractures in thoracic and spinal radiographs among patients with T2D (31.4% in women and 37.9% in men) compared to controls (24.9% in women and 14.5% in men) [34]. Even though vertebral fractures are associated with consequent fractures in elderly woman [35], there is a lack of prospective evidence among patients with diabetes.

EVIDENCE OF IMPACT OF DIABETES ON BONE QUALITY

Evidence of Impact of T1D on Bone Quality

A host of evidence demonstrates that T1D negatively impacts bone quality. An observational study followed radius BMD in patients with T1D and patients with T2D over a 12-year period, documenting a faster slope of decline for T1D [36]. A cross-sectional study compared BMD in 75 patients with T1D and 140 controls matched by sex, age, and BMI. Patients presented significantly lower BMD in total body and lumbar spine. Furthermore, poor glycemic control, lower physical activity, lower plasma IGF-1, and celiac disease were predictors of worse BMD in T1D [37]. A meta-analysis of 16 studies found a slight difference in femoral neck BMD for individuals with versus without T1D (− 0.055 g/cm^2) [38], whereas the difference in lumbar spine BMD was not significant. This highlights the fact that the large increase in fracture risk (2-fold to 4-fold) in T1D cannot be explained solely by BMD [39].

A recent study of patients with T1D from all age groups found that femoral neck and hip BMD were lower than in controls without diabetes only among postmenopausal women [40]. Thus, T1D accelerates the expected process of postmenopausal bone loss. This also manifests as increased concentrations of bone resorption markers in postmenopausal women with T1D [41].

When Do Bone Effects of T1D Become Manifest?

In a study of 99 pediatric patients recently diagnosed with T1D, BMD was unchanged over the first year after diagnosis [42]. Interestingly though, osteocalcin and P1NP (bone formation markers) decreased, while CTX (bone resorption marker) increased during the same period, revealing that bone turnover disturbances are present since very early stages of the disease.

The Canadian study of longevity in T1D compared BMD in 75 patients with long-standing T1D and 75 age- and sex-matched controls [43]. Despite no significant difference in BMD in lumbar spine, hip, or femoral neck, fragility fractures were more frequent among women with T1D. Therefore, fragility fractures in T1D may be related to other alterations of bone quality, probably resulting from a modified microarchitecture.

Importance of Glycemic Control

In a longitudinal study, 62 patients with T1D were assessed before and 7 years after starting intensive insulin therapy. The improved glycemic control stabilized BMD and reduced circulating tartrate-resistant alkaline phosphatase (TRAP, a bone resorption marker) and parathyroid hormone (PTH). Retinopathy was a correlate of osteopenia or osteoporosis, independently of HbA1c [13]. Similarly, poor control of T1D during childhood affects bone quality by increasing cortical porosity and decreasing trabecular number and density. This was proven in a study of girls with T1D, in which significant disruptions of cortical and trabecular microarchitecture were found only among those with HbA1c > 8.5% [44].

Evidence of Impact of T2D on Bone Quality

Despite the relative increase in BMD in T2D, this does not translate into a lower risk of fractures. On the contrary, absolute risk is comparable between patients with type 1 or type 2 diabetes. Potential mechanisms include changes in bone mechanical properties due to non-enzymatic glycation, mineralization disturbances, and bone microdamage [25].

In a case–control study of 80 postmenopausal women, morphological changes in cortical and trabecular bone were studied using HR-pQCT, while bone strength of the distal radius and tibia was assessed using μFEA. Participants were classified into four groups: diabetes and previous fracture (D-Fr), diabetes and no previous fracture (D-nFr), no diabetes and previous fracture (nD-Fr), and no diabetes and no previous fracture (nD-nFr). In the D-Fr group, there was a 27.8% higher cortical pore volume in the ultradistal radius compared to that in the nD-Fr group [24].

Even though patients with T2D have on average a higher BMD, their bone resorption marker levels have the same correlation with BMD as in the general population. In a cross-sectional study of 1499 patients with T2D, bone resorption markers were negatively correlated with lumbar, femoral neck, and total hip BMD [45].

Metabolic Syndrome and Bone Density

A high BMI is a protective factor against age-associated bone loss. However, there is uncertainty about how mechanisms induced by obesity may have a negative effect on bone [46]. A cross-sectional study assessed central obesity, hyperinsulinemia, inflammatory markers, and bone health (BMD and bone turnover markers) among 114 postmenopausal women with T2D [47]. Femoral BMD was positively associated with BMI, waist circumference, plasma insulin, and PAI-1 (plasminogen activator inhibitor 1). A high BMI is known to increase BMD by decreasing bone turnover [48], whereas chronic inflammation has a pro-resorptive effect on bone and promotes bone fragility [49].

Nonetheless, this increased BMD in obese patients with T2D does not provide any protection against fractures, as explained in the next section.

DIABETES AND RISK OF FRACTURE

Patients with diabetes have a higher risk of fracture, especially at the hip. In addition, patients with diabetes have a poorer prognosis after a fracture because of delayed healing [50], more frequent infections [51], and increased mortality [52]. Likewise, patients with diabetes and hip fracture have on average longer hospital stays and more postoperative cardiovascular events [53].

Risk of Fracture in T1D

A meta-analysis of more than 140,000 patients found a significant association between T1D and any fracture (RR 3.16), hip fracture (RR 3.78), and vertebral fracture (RR 2.88) [39]. The relative risk of any fracture differed by sex, being 4.1 for women and 1.8 for men [39]. In the THIN (The Health Improvement Network) cohort, the age-related increase in risk of fracture occurred 10 years earlier in patients with T1D relative to controls without the disease [54]. Even though patients with T1D have lower BMD, this difference does not completely explain their increased risk of fracture [55].

Diabetes complications may also influence the risk of fracture. Diabetic retinopathy and neuropathy increase the likelihood of falls [56, 57], while nephropathy may induce secondary hyperparathyroidism and osteodystrophy [58]. Similarly, autoimmune diseases associated with T1D (Graves' disease, celiac disease, and rheumatoid arthritis) may have a negative effect on bone health [59].

Risk of Fracture in T2D

The relative risk of hip fracture in patients with T2D has been estimated at 2.8 for men and 2.1 for women, both statistically significant [60]. These findings position hip fracture as an unrecognized chronic complication of T2D [61]. Despite a higher BMD, patients with T2D have an increased risk of fracture, an apparent paradox. For instance, the risk of hip fracture at a *T* score of − 1.9 in a woman with T2D is equivalent to the risk at a *T* score of − 2.5 in a woman without diabetes [61]. Thus, risk of fracture in T2D must be influenced by other factors like trabecular bone quality or cortical bone porosity. The impact of T2D on fracture risk seems to be larger in Caucasians than in other ethnicities [62]. A simple rule to estimate the risk of fracture in patients with T2D consists in adding 10 years to age or replacing rheumatoid arthritis by diabetes in the FRAX [61–63].

T2D complications have also been associated with a higher risk of fractures. In a Danish study retinopathy (OR 2.1), nephropathy (OR 2.0), neuropathy (OR 1.9), and even macrovascular complications (OR 1.9) were associated with fracture risk [64]. It is likely then, that this increased risk results not from an intrinsic effect of each complication, but as part of a systemic deterioration process that negatively affects bone. Peripheral neuropathy in T2D is associated with fracture risk by means of more frequent falls [65]. Fractures are also more common with a T2D duration longer than 10 years [66].

Drug treatment of T2D comorbidities may influence fracture risk in these patients. A post hoc analysis of a clinical trial showed that therapy with thiazide diuretics, calcium channel blockers, or angiotensin-converting enzyme (ACE) inhibitors slightly lowered fracture risk (HR 0.97, $p = 0.04$). By contrast, the relationship between beta-blockers and the incidence of

orthostatism-associated falls is still controversial [67].

Type 2 Diabetes, Sarcopenia, Falls, and Risk of Fracture

Sarcopenia is defined as a decline in muscle mass and function. This condition is highly prevalent among patients with T2D [68]. The association is bidirectional: diabetes-related mechanisms like insulin resistance, inflammation, accumulation of AGEs, and oxidative stress negatively affect muscle health; while low muscle mass decreases metabolic rate and glucose disposal, resulting in accelerated progression of T2D [68]. In a Brazilian cross-sectional study, 15.6% of adults with T2D met criteria for sarcopenia, compared to 2.4% of healthy controls [69]. Evidence from multiple observational studies has documented a positive association between sarcopenia and risk of both falls (pooled OR 1.60, 95% CI 1.37–1.86 in cross-sectional studies; pooled OR 1.89, 95% CI 1.33–2.68 in prospective studies) and fractures (pooled OR 1.84, 95% CI 1.30–2.62 in cross-sectional studies; pooled OR 1.71, 95% CI 1.44–2.03 in prospective studies) [70]. Consequently, sarcopenia may be considered as an extraskeletal factor that increases the risk of falls and fractures in patients with T2D [71].

Vitamin D Deficiency and Fracture Risk in Type 2 Diabetes

Vitamin D deficiency results in secondary hyperparathyroidism, increased osteoclastic activity, and reduced bone mass [72] and has been proven to increase the risk of falls [73], hip fractures [74], vertebral fractures [75], and major osteoporotic fractures [76]. A cross-sectional study reported that men with T2D and a serum 25-hydroxyvitamin D below 20 ng/mL had increased odds of vertebral fractures (OR 7.87, 95% CI 1.69–36.71), compared to sex- and diabetes status-matched controls with normal 25-hydroxyvitamin D [77]. This association was not significant among women.

IMPACT OF ANTIDIABETIC MEDICATIONS ON BONE HEALTH

Metformin

Metformin is considered the first-line therapy for T2D, hence its impact on bone health is highly relevant. In vitro studies show that metformin induces osteoblast differentiation and expression of osteogenesis markers such as osteopontin, alkaline phosphatase, and bone morphogenic protein 2 (BMP-2). These effects are mediated by the activation of AMP-dependent kinase [78]. Multiple clinical trials and long-term observational studies have evaluated the impact of chronic metformin use on BMD and fracture risk among patients with T2D, finding neutral or slightly beneficial effects [79].

Sulfonylureas (SU)

Even though their use has declined, SU still play an important role in the therapeutic arsenal against T2D in several countries. Observational studies have found a neutral effect of SU on biological markers of bone resorption [80]. It should also be considered, nonetheless, that SU may increase the risk of hypoglycemia and subsequent falls, which are associated with fractures [1].

Thiazolidinediones (TZD)

After rosiglitazone was withdrawn from the market because of its adverse cardiovascular profile, the use of TZD has decreased markedly. Despite that, pioglitazone is still in use in

several countries. By binding to and activating the nuclear receptor PPAR-gamma, TZD induce the preferential differentiation of mesenchymal precursor cells towards adipocytes instead of osteoblasts [81]. A meta-analysis including more than 250,000 patients found that the use of TZD was associated with a higher risk of fractures, though only among women. Such risk was not significantly different between rosiglitazone and pioglitazone, did not vary with age, and was not associated to changes in BMD [82]. Results from the ACCORD study follow-up suggest that fracture risk went back to normal after TZD were suspended [83].

Dipeptidyl Peptidase 4 Inhibitors (DPP4i)

DPP4i have become widely used for the treatment of T2D. A meta-analysis of 28 clinical trials and 220,000 patients found a lower risk of fractures among DPP4i users (OR 0.60, 95% CI 0.37–0.99) [84]. Given that SU and TZD might be associated with a higher fracture risk, the authors performed a sensitivity analysis excluding studies in which SU or TZD were the comparators. The results were the same (OR 0.56, 95% CI 0.33–0.93). Thus, the impact of DPP4i on fracture risk seems to be at least neutral and perhaps favorable.

Glucagon-Like Peptide 1 Agonists (GLP-1a)

GLP-1a are an attractive choice of treatment for many patients with T2D with cardio-metabolic comorbidities. A meta-analysis of studies designed to assess glycemic control evidenced a favorable or neutral effect of GLP-1a on fracture risk [85]. An interesting mechanistic study submitted 37 women (mean age 46) to a diet-induced 12% weight loss, and then randomized them to receive 1.8 mg/day of liraglutide or placebo for 1 year [86]. Measures were taken to maintain a constant weight in both groups throughout the study. Surprisingly, at the end of follow-up the loss of bone mineral content was four times higher in the placebo than in the liraglutide group. The bone formation marker P1NP increased only in the liraglutide group. Hence, GLP-1a might aid in the prevention of bone mass reduction related to weight loss, although these findings should be confirmed in larger studies.

Sodium–Glucose Co-Transporter 2 Inhibitors (SGLT2i)

SGLT2i are a novel group of oral antidiabetics with positive effects on many diabetes outcomes. In the CANVAS study, a cardiovascular endpoint trial, the cumulative incidence of fracture was 4.0% in the canagliflozin group and 2.6% in the placebo group [87]. However, a review of randomized trials with canagliflozin did not show a higher rate of fractures compared to other therapies (1.7% in canagliflozin group vs. 1.5% in comparators, OR 1.09, 95% CI 0.71–1.66) [87]. A meta-analysis of 20 studies with SGLT2i (canagliflozin, dapagliflozin, and empagliflozin) reported a pooled fracture risk ratio of 0.67 (95% CI 0.42–1.07) between SGLT2i and comparators [88]. The pooled risk ratio was not different among SGLT2i (canagliflozin 0.66 [95% CI 0.37–1.19], dapagliflozin 0.84, [95% CI 0.22–3.18], and empagliflozin 0.57, [95% CI 0.20–1.59]).

Insulin

So far, no clinical trial has assessed specifically the effect of insulin treatment on bone health and fracture risk. Observational studies have shown a higher risk of fracture for patients on insulin therapy [79]. Some factors frequently found in patients on insulin therapy may contribute to the risk of fracture, such as a longer disease duration, presence of chronic complications, and hypoglycemia-induced falls [79]. In a nested case–control study of more than 12,000 participants in Spain, insulin therapy was associated with a higher risk of fracture, even after adjustment by age and time since T2D diagnosis (aOR 1.63, 95% CI 1.30–2.04) [89].

Bariatric Surgery

Recently, bariatric surgery has been positioned as an effective therapy in patients with obesity-

Table 1 Summary of the effect on antidiabetic therapies on bone health

Antidiabetic intervention	Effect on bone	Implications
Metformin	AMPK activation favors bone integrity. Neutral or slightly beneficial effect on fracture risk	No special consideration
Sulfonylureas	Neutral effect on bone resorption markers. May induce hypoglycemia and falls	Use with caution or prefer a different agent in patients with known osteoporosis or high risk of fracture
Thiazolidinediones	Activation of PPAR-gamma in mesenchymal precursor cells may reduce their differentiation to osteoblasts. Use is associated with slightly increased fracture risk among women	Measure BMD and fracture risk in patients who are candidates for therapy with TZD
DPP4 inhibitors	No known effect on bone physiology. Associated with slightly reduced fracture risk	No special consideration
GLP-1 agonists	Short-term studies show preservation of bone mass. No association with fracture risk	No special consideration
SGLT2 inhibitors	Initial signal of increased fracture risk with canagliflozin, later dispelled in meta-analysis. No signal of fracture risk with other agents	Advise the patient to take enough fluid to prevent orthostatism and falls
Insulin	Observational association between insulin use and fracture risk	Take measures to prevent hypoglycemic events. In patients with long disease duration, guarantee proper treatment of retinopathy/neuropathy
Bariatric surgery	Increased risk of fractures, especially for malabsorptive procedures	Measure bone mineral density. Provide adequate replacement of calcium, vitamin D, and dietary protein

induced T2D. Evidence shows that malabsorptive procedures increase fracture risk, particularly biliopancreatic diversion [79]. A nested case–control study in Canada found an increased relative risk of fracture in upper limbs (1.64, 95% CI 1.40–1.93), spine (1.78, 95% CI 1.08–2.93), and hip or femur (2.52, 95% CI 1.78–3.59) after bariatric surgery [90]. Most of the excess risk was accounted for by 21% of participants, who underwent biliopancreatic diversion. Unexpectedly, the relative risk of lower limb fracture was reduced (0.66, 95% CI 0.56–0.78). Similar findings have been reported in Taiwan [91].

The effect on antidiabetic interventions on bone health is summarized in Table 1.

SHOULD OSTEOPOROSIS TREATMENT BE DIFFERENT FOR PATIENTS WITH DIABETES?

Anti-osteoporotic therapies seem to have a similar effect on fracture risk reduction for patients with and without diabetes [92]. Consequently, international guidelines recommend the same therapeutic approach for osteoporosis regardless of diabetes status [79]. In a sub-analysis of the FREEDOM study (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) and its 7-year extension, the incidence of fractures was compared between denosumab (n = 266) and placebo (n = 242) in patients with diabetes [93]. The rate of vertebral

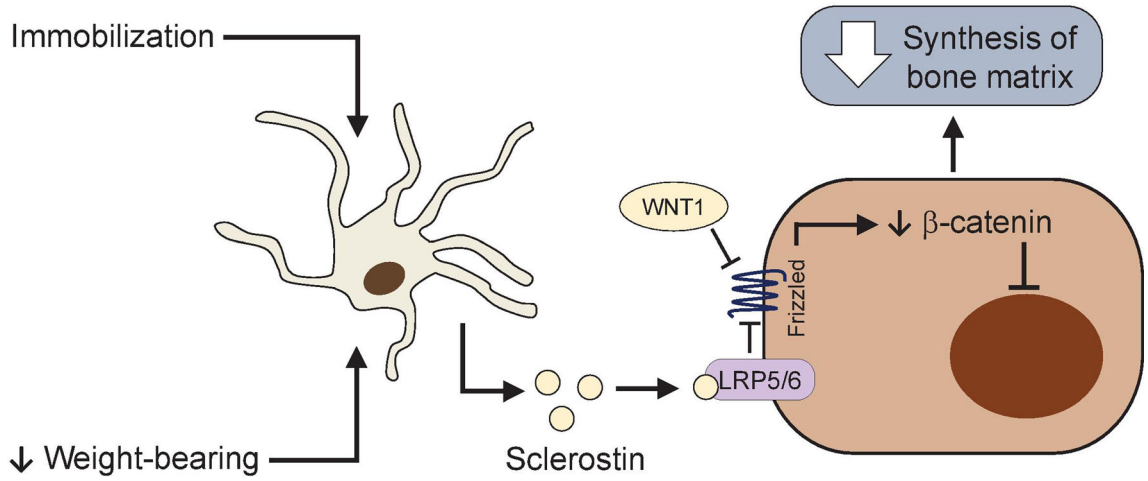

Fig. 4 Effects of sclerostin on bone physiology. Immobilization stimulates the secretion of sclerostin by osteocytes, while weight-bearing reduces it. Sclerostin binds the LRP5/6 (low-density lipoprotein receptor-related protein 5) receptor in osteoblasts, preventing its binding to Frizzled and blocking the formation of an LRP5/6–Frizzled–Wnt1 complex. When this occurs, cytoplasmic beta-catenin is degraded and no longer enters the nucleus to stimulate the expression of genes involved in bone matrix synthesis. Thus, sclerostin reduces bone matrix production

fractures was drastically lower with denosumab compared with placebo (1.6% vs. 8.0%, RR 0.20, 95% CI 0.07–0.61). By contrast, the rate of non-vertebral fractures was higher in the denosumab group (11.7% vs. 5.9% in the placebo group, RR 1.94, 95% CI 1.00–3.77). Therefore, denosumab seems to be particularly effective against vertebral fractures among patients with diabetes. Furthermore, denosumab seems to have a positive effect on insulin resistance, as it slightly reduces fasting serum glucose in postmenopausal woman with diabetes who are not using antidiabetic medications [94]. In the DANCE (Direct Analysis of Nonvertebral Fractures in the Community Experience) study, treatment with teriparatide (a synthetic peptide comprising the first 34 amino acids of parathyroid hormone) for 6–24 months [95] showed a similar reduction in the incidence of non-vertebral fractures and back pain, and a similar increase in BMD in participants with or without diabetes [96]. A promising approach to osteoporosis treatment in diabetes is blocking the hormone sclerostin with monoclonal antibodies, positively impacting bone health through different pathophysiological mechanisms (Fig. 4). Animal and human studies of sclerostin blockade with the monoclonal antibody romosozumab show an anabolic effect on bone mass and significant improvements of bone microarchitecture and strength [97, 98]. In the FRAME study (The Fracture Study in Postmenopausal Women with Osteoporosis), romosozumab treatment reduced the risk of fracture and increased BMD among women with osteoporosis [99]. In 2019, the US Food and Drugs Administration and the European Medicines Agency approved romosozumab for treatment of osteoporosis in postmenopausal women at high risk of fractures. However, the specific impact of romosozumab in humans with T1D or T2D warrants further investigation. Regarding in-hospital management, patients with diabetes and fracture should be treated with insulin to achieve appropriate glycemic control, avoiding oral antidiabetics until the acute stress of fracture is overcome [100].

CONCLUSION

Bone fragility is a frequent and underdiagnosed condition among patients with diabetes. A host of pathophysiological, clinical, and epidemiological evidence supports early detection and proper treatment of bone fragility in patients

with diabetes. Future research directions include the differential effects of osteoporosis therapies in patients with T2D, and the study of the impact of fracture prevention on long-term mortality and quality of life among patients with T2D.

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