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Type 2 diabetes and bone fragility in children and adults

Faienza MF *et al*. T2D and bone

Abstract

Type 2 diabetes (T2D) is a global epidemic disease. The prevalence of T2D in adolescents and young adults is increasing alarmingly. The mechanisms leading to T2D in young people are similar to those in older patients. However, the severity of onset, reduced insulin sensitivity and defective insulin secretion can be different in subjects who develop the disease at a younger age. T2D is associated with different complications, including bone fragility with consequent susceptibility to fractures. The purpose of this systematic review is to describe T2D bone fragility together with all the possible involved pathways. Numerous studies have reported that T2D patients show preserved, or even increased, bone mineral density (BMD) compared with controls. This apparent paradox can be explained by the altered bone quality with increased cortical bone porosity and compromised mechanical properties. Furthermore, reduced bone turnover has been described in T2D with reduced markers of bone formation and resorption. All these findings prompted different researchers to highlight the mechanisms leading to bone fragility, and numerous critical altered pathways have been identified and studied. In detail, we focused our attention on the role of microvascular disease. Advanced glycation end products, the senescence pathway, the Wnt/β-catenin pathway, the osteoprotegerin/receptor-activator of nuclear factor kappa B ligand, osteonectin and fibroblast growth factor 23. The understanding of type 2 myeloid bone fragility is an important issue as it could suggest possible interventions for the prevention of poor bone quality in T2D and/or how to target these pathways when bone disease is clearly evident.

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Core Tip: Type 2 diabetes (T2D) patients show increased susceptibility to bone fractures, despite their bone mineral density being normal or increased, leading to difficult identification for clinicians. The prevalence of T2D in adolescents and young adults is increasing alarmingly. Different researchers highlight the mechanisms leading to bone fragility and different critical altered pathways have been identified and studied. In this review, we describe the different metabolic pathways responsible for bone fragility in T2D patients. They can be useful for its management, although further studies are needed to deepen our understanding of the mechanisms underlying bone fragility in T2D.

INTRODUCTION

The prevalence of type 2 diabetes (T2D) mellitus in adolescents and young adults is increasing alarmingly. Data from the SEARCH study show an annual increase of approximately 7% in the incidence of T2D among people aged 10-19 years old in the United States, with increases in all ethnic groups[1]. Increases in children, adolescents and young adults with T2D have been described across most regions of the world[2]. The highest T2D incidence rates in youth have been registered in Canadian First Nations, American Indian and Navajo nation, Australian Aboriginal and Torres Strait Islander, and African American populations (31-94/100000 each year), while youths from non-Hispanic Caucasian populations (*i.e.,* United States and Europe) display the lowest incidence rates (0.1-0.8/100000 each year). Studies show the highest prevalence in youth from Mexico and Brazil, indigenous populations in Canada and the United States, together with black populations in the Americas (160-3300/100000). Differently, the lowest prevalence was registered in European populations (0.6-2.7/100000)[2].

A recent literature review examined country-specific prevalence and incidence data of youth-onset T2D published between 2008 and 2019[3]. The highest prevalence rates of youth-onset T2D were observed in China (520 cases/100,000 people) and the United States (212 cases/100000) and the lowest in Denmark (0.6 cases/100000) and Ireland (1.2 cases/100000). However, the highest incidence rates were reported in Taiwan (63

cases/100000) and the United Kingdom (33.2 cases/100000), with the lowest in Fiji (0.43 cases/100000) and Austria (0.6 cases/100000). These differences in epidemiology data may be partially explained by variations in the diagnostic criteria used within studies, screening recommendations within national guidelines and race/ethnicity within countries.

The main predisposing risk factors for the development of T2D in pediatric age are represented by obesity, family history, and sedentary lifestyle[4]. The mechanisms leading to T2D in young people are similar to those in older patients. However, the severity of onset, reduced insulin sensitivity and defective insulin secretion can be different in subjects who develop the disease at a younger age[5]. In particular, the phase of nutrient-induced insulin secretion might be impaired earlier in children and adolescents than in older subjects[6].

The comorbidities associated with T2D in young people include hypertension, cardiovascular disease, kidney impairment, and retinopathy. Furthermore, psychosocial problems are often observed[7]. Altered bone quality has been reported in T2D patients, possible mechanisms for the effect of T2D on bone mineral density (BMD) include the toxic effects of hyperglycemia which may impair differentiation and proliferation of osteoblasts[8]. In addition, hyperglycemia can increase urine calcium excretion, which inhibits bone formation[8]. Thus, the objective of this systematic review is to describe T2D bone fragility together with all the possible involved pathways.

T2D AND BONE IMPAIRMENT

Most studies have found that patients with T2D have preserved, or even increased, BMD compared with controls, but display bone fragility with consequent increased susceptibility to fractures[9-11]. This apparent paradox is due to the altered bone quality in these patients. In detail, the spine trabecular bone score (TBS) is decreased in T2D patients, and it is a predictor of fracture risk independently of the BMD[12].

Furthermore, different studies have evaluated T2D effects on bone microarchitecture of the peripheral skeleton (radius and tibia) through high-resolution peripheral

quantitative computed tomography. These studies have generally shown preserved, or even improved, trabecular bone microarchitecture in T2D patients compared with controls[12-17]. Furthermore, some[14,15,17-19], but not all[16,20,21], studies report augmented cortical porosity in T2D patients and, interestingly, this parameter independently predicts fracture risk.

Another aspect of bone quality that might be impaired in patients with T2D is the mechanical characteristics which can be assessed through the measurement of the bone material strength index (BMSi). However, discordant results have been reported on this issue. In detail, some authors found reduced BMSi in T2D in comparison with controls[20,23,24], whereas others reported no significant variation[16]. These different results could be associated to the different comorbidities characterizing T2D.

Several studies have noted reduced bone turnover in patients with T2D[20,24,25]. It has been reported that patients with T2D have reduced markers of bone formation [serum levels of procollagen type 1 amino-terminal propeptide (P1NP) and osteocalcin (OC)] as well as resorption [carboxy-terminal telopeptide of type 1 collagen (CTX)][20,24,26,27]. Moreover, Starup-Linde *et al*[28] demonstrated an inverse relationship between glycemic control [hemoglobin A1c (HbA1c)] and OC levels, and a similar trend for CTX and P1NP. Naltrexone, and bone-specific alkaline phosphatase levels are not significantly different between T2D patients and controls[29]. Very recently, it has been reported that thyroid homeostasis could affect bone turnover markers[30], and that follicle-stimulating hormone levels may contribute to the suppression of the same markers[31].

MECHANISMS AND MOLECULAR PATHWAYS/INVOLVED IN T2D BONE FRAGILITY

Indication of mutual regulatory control of both bone and glycemic homeostasis recognizes the close interplay between these two systems. The common regulatory mechanisms involve microvascular disease, advanced glycation end products (AGEs), osteoprotegerin (OPG)/receptor-activator of nuclear factor kappa B ligand (RANKL),

the Wnt/β-catenin pathway, osteonectin and fibroblast growth factor 23 (FGF23) (Table 1).

Microvascular disease

Microvascular disease is a common complication (retinopathy, nephropathy, or neuropathy) of diabetes[32]. Angiopathy has been demonstrated in the iliac crest of diabetic patients[33]. Recently, decreased microvascular blood flow has been demonstrated to be linked with cortical porosity in type 2 myeloid (T2M) patients, suggesting that microvascular disease negatively affects bone microarchitecture in T2M[16]. Consistently, cortical porosity of the distal radius and tibia is most pronounced in T2M patients with microvascular disease[19]. Differently, only in 2022 was it found that the poorest femoral trabecular microarchitecture is associated with vascular complications in T2M patients[34]. T2D patients with microvascular disease display a significantly lower TBS, after adjusting for confounders. Moreover, multivariable analysis demonstrated a significant correlation between low 25(OH) vitamin D levels and microvascular disease[35].

Several mechanisms have been proposed to explain the microvascular disease associated to bone fragility in T2M. It is important to remember that skeletal blood flow provides growth factors, hormones, oxygen and nutrients affecting bone remodeling, suggesting that alteration in microvasculature leads to bone impairment. In the same manner as perivascular cells show stem-cell like properties and may differentiate in osteoblastic cells, blood vessels also release factors affecting the differentiation and activity of osteoblasts and osteoclasts[36]. Blood flow promotes angiogenesis and thus osteogenesis. Bone blood flow is reduced in T2D rats[37], and hypoxia increases the canal network in rat cortical bone[38], suggesting that insufficient oxygen and blood flow associated with microvascular disease alters bone microarchitecture. The recruitment of osteoprogenitors from blood vessels is fundamental for bone formation following osteoclast resorption[39]. Thus, microvascular disease could uncouple resorption and formation in cortical bone by impairing osteoprogenitor recruitment. However, further

studies are needed to deepen understanding of the mechanisms and in particular whether bone fragility is a comorbidity of T2M or a complication: this item is a matter of debate[40].

AGEs

Hyperglycemia disturbs both bone cells and the extracellular matrix. The presence of glucose determines the production of intermediate products, which eventually generate the irreversible accumulation of AGE[41]. AGE accumulation leads to the synthesis of defective collagens as well as of reactive oxygen species (ROS), with consequent structural changes in bone[42]. In detail, considering the organic bone matrix, these products lead to diminished bone strength[43,44]. Elevated AGE levels are associated with increased fracture risk[45].

The AGE-receptor for AGE (RAGE) binding generates ROS production, macrophage and platelet activation, vascular inflammation and inflammatory cell migration[46]. All these events are involved in the onset and progression of typical macro- and microangiopathy associated with diabetes, thus leading to brittle bones with diminished strength and less capability to deform before fracturing[47].

RAGE is also expressed by immune cells and incites activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a central transcription factor of the immune and inflammatory response[46]. The AGE-RAGE interaction in immune cells leads to the increased expression of chemokines and adhesion molecules, secreting further RAGE ligands, supporting the inflammatory tissue response, regulating the activated macrophage reaction to enhance the destructive signals in the tissues and inhibiting the repair and remodeling responses[46]. AGEs may determine osteoclastogenesis and osteoblast alterations in the bone microenvironment due to the increase in inflammatory cytokines, leading to osteoporosis[48].

In detail, pentosidine, the most studied AGE, accumulates in the trabecular and cortical bone in T2D patients and negatively affects their bone strength as well as probably leading to functional changes in osteoblasts and the bone mineralization

process[49,50]. Consequently, trabecular and cortical bones show impaired biomechanical properties and decreased strength, together with altered osteoblast activity as well as adhesion to the collagen matrix, and thus negatively affect bone homeostasis[45,50-52].

AGEs bone content correlates with worse bone microarchitecture, including lower volumetric BMD, bone volume/total volume and increased trabecular separation/spacing[53]. High concentrations of AGEs blunts insuline-like growth factor I (IGF1) mediated osteoblast stimulation and determines the resistance of osteoblasts to IGF1 effects[54]. Consistently, IGF1 serum levels have been found to be inversely correlated with the occurrence of vertebral fractures in T2D postmenopausal women [55].

The role of cellular senescence in mediating skeletal fragility in T2D

Different forms of stress can lead a cell to enter an irreversible permanent growth arrest, known as senescence[56]. This is triggered by cyclin-dependent kinase inhibitors, remarkably p16Ink4a and p21Cip1, that antagonize the activity of cyclin-dependent kinases to stop cell proliferation[57,58]. Senescent cells display a transformed gene expression profile with an increase in senescent cell anti-apoptotic pathways as well as a senescence-associated secretory phenotype (SASP)[59], typically consisting of pro-inflammatory cytokines, chemokines and matrix remodeling proteins[60,61]. Premature increase in senescent cells is evident in T2D, especially pancreatic β-cells and bone[62,63]. In particular, osteocyte senescence has been demonstrated using an inducible obese mouse model of T2D. These mice display bone quality alterations quite similar to bones from humans with T2D, such as reduced biomechanical strength, defective cortical bone microarchitecture and low bone formation rates[63]. Furthermore, in this model, senescent osteocytes were identified for the high levels of p16Ink4a and p21Cip1, senescence-associated distension of satellites, increased telomere-associated foci (another cell marker of senescence), as well as typical increased expression of pro-inflammatory SASP and NF-kB[63].

Additionally, cellular senescence in T2D has also been linked to the incidence of fracture in murine models and patients[64,65]. In detail, using a murine model of T2D

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reflecting both hyperinsulinemia caused by insulin resistance induced by high-fat diet and insulinopenia induced by low doses streptozotocin, increased density of senescent cells has been demonstrated in the callus area in fracture healing[64]. Additionally, the same authors report that cells of the osteoblastic lineage cultured with sera from T2D patients display increased expression of the p53 responsive genes that are typical of a senescent microenvironment[64]. The decreased levels of serum senescent miR-31-5p in older diabetic women is linked to incidents of fragility fracture and can significantly predict fracture risk if combined with femoral neck a BMD measurements[65].

The Wnt/β-catenin pathway

Wnt/β-catenin pathway activation promotes osteoblastogenesis and bone formation but inhibits osteoclastogenesis. Dickkopf-related protein 1 (DKK1) and sclerostin (encoded by *Sost*) antagonize the Wnt/β-catenin pathway by binding to low-density lipoprotein receptor-related protein 5 or 6, thus inhibiting osteoblastogenesis and promoting osteoclastogenesis[66].

Bone expression of sclerostin and DKK1 has been demonstrated to be high in T2D rat models[67,68]. Circulating Sclerostin levels have also been found to be increased in T2D patients[69] and correlated to the decrease in bone formation markers[70]. Differently, in T2D postmenopausal women the high circulating levels of sclerostin are related to vertebral fractures[71]. Interestingly, T2D postmenopausal women with previous fractures display thinner cortical bone, together with a tendency towards larger volumetric bone density and elevated circulating levels of sclerostin compared with diabetic women without fractures and nondiabetic controls with fractures[72]. More recently, Piccoli *et al*[53] has reported that *Sost* expression in RNA extracts from the femoral head of T2D patients is significantly increased compared with the controls, although circulating Sclerostin levels were found to be higher in T2D subjects, but not statistically significant.

OPG/RANKL

OPG is a soluble tumor necrosis factor receptor superfamily member originally discovered in bone[73,74]. It is an anti-resorptive cytokine which works by binding and neutralizing the receptor activator for the RANKL. RANKL is a molecule which induces osteoclast differentiation and activity[73,74]. The OPG/RANKL axis is also linked to the regulation of glucose homeostasis[75,76]. In detail, hyperglycemia downregulates RANKL expression, which inhibits the differentiation and activity of osteoclasts[73,76].

The duration of diabetes seems to negatively affect bone metabolism but poor glycemic control (HbA1c ≥ 7.5%) has also been shown to be associated with an increased risk of fracture[77]. Decreased levels of RANKL have been reported in diabetic patients compared to healthy subjects[78]. This seems to be due to the increased number of immature osteoblasts and osteoclasts[79]. Other authors have reported that serum RANKL levels are reduced and OPG increased in diabetic patients with respect to nondiabetics and prediabetic subjects[80,81].

Furthermore, it has also been reported that high RANKL levels are related to a significantly increased risk of T2D development[82]. However, other authors did not measure significant differences in RANKL levels between T2D patients and controls[29]. Human osteoblast cultures from cancellous bone biopsies of diabetic patients displayed a decreased RANKL/OPG ratio compared to the controls, suggesting that the bone turnover process is suppressed[83].

Osteonectin

Osteonectin is produced by osteoblasts and high osteonectin serum levels represent a marker of bone formation[84]. Osteonectin induces osteoblast differentiation, commitment, and survival. *In vivo*, osteonectin-knock out and -haploinsufficient mice show osteopenia with low bone turnover, a decreased number of osteoblasts, as well as a reduced bone formation rate[85,86]. Additionally, Dole *et al*[87] report that a single nucleotide polymorphism in the 3' untranslated region of osteonectin determined variability in bone mass by modulating its expression. Patients with albuminuria had significantly higher levels of osteonectin compared with normoalbuminuric patients[88].

T2D AND BONE-KIDNEY CROSS-TALK: THE ROLE OF BONE-DERIVED HORMONES

Chronic kidney disease (CKD) represents a serious complication of T2D, and impacts 25%-40% of the diabetic population[89], thus leading to end stage renal disease with the need for dialysis or kidney transplantation[90]. Although kidney replacement therapy improves long term survival and quality of life in CKD patients, this survival highlights bone fragility as an emerging complication[91]. In a large cohort of patients with CKD followed between 1990 and 1999, Bal *et al*[92] demonstrated that the fracture risk was higher with a prolonged period of dialysis before transplantation, and both epidermal growth factor receptor decline and increased albuminuria are considered important risk factors for fracture[93]. Bone fragility in CKD patients is dependent on several risk factors and literature data demonstrate the impact of age, race (white) and gender, low body mass index < 23 kg/m^2, glucocorticoids duration and immunosuppressive agents[94]. However, in addition to the described factors and dialysis vintage, diabetes and pancreas replacement therapy are also important risk factors for bone fragility[95,96].

In 2009, Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-Mineral and Bone Disorder (CKD-MBD) were originally published by Kidney Disease: Improving Global Outcomes[97]. This clinical syndrome defines a systemic disorder in CKD patients responsible for abnormalities in mineral metabolism, bone remodeling and vascular calcification. Despite the completion of several key clinical trials since the 2009 publication of the CKD-MBD guidelines, large gaps in the knowledge still remain[98]. Prospective studies are needed to determine the value of BMD and bone biomarkers as predictors of fractures[99] as well as the impact of different therapeutic approaches on bone fragility, especially in patients with both diabetes and kidney disease. Recent studies have demonstrated that CKD patients with T2D are at increased risk of bone diseases[100], which could involve FGF23.

FGF23

Ribeiro *et al*[101] describe how the FGF-23/klotho axis is a predictive factor for fractures in type 2 diabetic patients with early CKD and demonstrated that α-klotho and FGF-23 independently influence the occurrence of bone fractures. FGF-23 is a bone-derived hormone secreted by osteocytes that regulates phosphate and the vitamin D metabolism. It acts in the kidney through FGF receptors and klotho, thus preventing renal tubular reabsorption of phosphorus. FGF-23 plays an important role in the development of bone and mineral disorders and many studies over recent years, also including patients with CKD and diabetes, have demonstrated that FGF-23 levels increase in CKD patients, and have an impact not only on bone disease, but also on the risk of cardiovascular disease and all causes of mortality[102]. FGF-23 can also induce secondary hyperparathyroidism by increasing the 24-hydroxylation of vitamin D and these changes are associated with an increased risk of fracture in dialysis[103]. FGF-23 levels are also further raised in CKD patients with diabetes who had had a previous fracture[101], thus underlying the association of a history of prior fracture with increased risk of hip fracture, as observed in all dialysis patients[104]. Moreover, FGF-23 may also promote insulin secretion and insulin resistance[105], thus influencing the risk of adverse outcomes, especially under CKD conditions[106]. Thus FGF-23 could represent a potential biomarker not only of CKD progression in diabetes[107], but is also associated with multiple risk factors[108], including bone fragility.

FGF-23 signaling on target tissues is mediated by FGF receptors and klotho, which functions as a co-receptor to increase the binding affinity of FGF-23 for FGF receptors. Klotho can also circulate as a secreted protein and a physiologically active hormone. It has been demonstrated that insulin can stimulate the release of klotho by inducing the cleavage of the extracellular domain of klotho by ADAM10 and ADAM17 in the kidney[109]. Cleaved klotho can thus regulate both the phosphorus and calcium metabolism in the kidney, and mineral homeostasis in the body through 1-alpha hydroxylase activity as well as parathyroid hormone and FGF-23 secretion[110]. Klotho expression is significantly reduced by several kidney injuries such as glomerulonephritis, acute kidney injury, ischemia/reperfusion injury and delayed graft

function[111,112], chronic allograft dysfunction[113,114] and renal cell carcinoma[115]. Low klotho levels are also associated with accelerated aging that can promote dysregulated mineral metabolism and osteoporosis. Thus, reduced klotho levels are considered early factors in the development of CKD-MBD[116,117]. Klotho levels are also compromised in patients with early CKD and diabetes[101], while lower levels of klotho seem to be an independent predictive factor for bone fracture[101].

Sclerostin and OC

The presence of diabetes may also increase Sclerostin, an osteocyte-specific protein that inhibits bone formation and higher serum sclerostin levels are associated with increased fracture rates[118]. Thus, Sclerostin has been described as an important factor contributing to CKD-MBD[119]. In diabetic patients with CKD, Sclerostin levels start to increase in the CKD-G3 stage, while patients in the CKD-G4/5 stages have dramatically increased levels of circulating sclerostin[120].

OC is another bone-derived hormone the levels of which reflect the ability of osteoblasts to form bones[121]. OC is directly associated with glucose metabolism and experimental models show that OC can increase insulin production by pancreatic β-cells and insulin sensitivity in peripheral tissues[122]. Moreover, insulin receptor signaling increases the production of OC in osteoblasts[123]. OC levels have been recently associated with the risk of incident diabetes and kidney complications while increased levels have been described in CKD patients[124,125]. In early CKD patients with diabetes, OC levels independently influence the occurrence of bone fracture[101], however further studies are needed to confirm the specific role of OC in the context of diabetes and CKD.

Further research is also needed to assess the diagnostic and prognostic value of these bone turnover biomarkers in the field of CKD-MBD in the context of diabetes. However, the described hormones represent important factors for the development of bone diseases in the context of CKD and may be considered as targets for future clinical trials.

CONCLUSION

The studies reported in the present review describe altered bone quality and the possible mechanisms underlying its pathophysiology. T2D patients frequently display bone fragility, which is often an underdiagnosed condition in these subjects. The understanding of its pathophysiology is an important issue as it could suggest possible interventions for the prevention of poor bone quality in T2D. Additionally, the discovery of its pathophysiology could help to target these pathways when bone disease is clearly evident. Thus, the simultaneous use of anti-diabetic drugs and bone treating agents could help to ameliorate the quality of life of T2D patients. This issue is of particular interest considering the life extension observed. Nevertheless, the possible interventions to improve bone quality in T2D require further investigation, which could determine different treatment approaches through personalized medicine.

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