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REVIEW

Type 2 diabetes and osteoporosis: Current knowledge

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Abstract

Although bone health is primarily associated with age, recent studies have shown that individuals with diabetes mellitus (DM) have up to 6 times higher incidence of osteoporotic fractures compared to the general population. So far, there is no single entity for this condition, primarily due to the different mechanisms of development in type 1 DM (T1DM) and type 2 DM (T2DM), as well as different mechanisms of osteoporosis development. Diabetes affects bone metabolism by various mechanisms including changes in insulin concentration, insulin-like growth factor-1 (IGF-1), and amylin. Hyperinsulinemia (the predominant characteristic of the T2DM) can stimulate bone formation, whereas in contrast to hypothyroidism (the predominant characteristic of T1DM), both lead to bone density reduction. Chronic hyperglycemia leads to the creation and accumulation of advanced glycation end products (AGEs) in collagen. The aforementioned changes in the bone architecture, decreasing its strength and increasing its fragility. In addition, hyperglycemia leads to glycosuria resulting in hypercalciuria, leads to hypocalcemia, accelerated bone resorption, and thus contributes to osteoporosis. Finally, the microvascular complications of DM result in decreased blood flow to the bone and thus additionally contribute to the onset of osteoporosis. Here, we review the current knowledge in epidemiology, pathophysiology, diagnosis, and treatment of osteoporosis in diabetes.

Key words: Type 2 diabetes; osteoporosis; diabetoporosis

1. Introduction

The association between osteoporosis and diabetes was described more than five decades ago in a few case reports among diabetic children [1]. Following several clinical studies and preclinical experiments, there were many attempts to establish a new entity called "diabetoporosis," "diabetic osteopenia," or "diabetic osteopathy [2]." However, it is impossible to introduce a unique entity due to the different pathogenic mechanisms of type 1 diabetes mellitus (T1DM) and type 2 (T2DM). Meta-analyses showed decreased bone mass on several measured sites and consequently increased fracture risk in patients with T1DM, meeting the classic criteria for osteoporosis [3,4]. It is expected that T1DM patients will fail to achieve their peak bone mass due to the metabolic disorder present from childhood, explaining the risk for osteoporosis development.

In contrast to T1DM patients, there is an increased risk of fracture among patients with T2DM, which is paradoxically not accompanied with low bone mineral density (BMD) but usually with normal or even increased BMD [4,5]. Initial clinical studies on T2DM patients showed contradictory results in both trabecular and cortical bone volume [6]. It seems that the stage of T2DM at the time of densitometry contributes to the inconsistent BMD data, thus confirming the direct influence of T2DM on bone, and highlights the complex mechanisms of action and signaling pathways involved in changes in bone metabolism in T2DM.

Collectively, it is difficult to interpret epidemiologic findings due to the different disease stages in cohorts of T2DM patients, which is subsequently connected to various pathophysiological mechanisms and their specific effects on bone metabolism.

In this article, we aim to explain the mechanisms of action that contributes to decreased bone quality and altered bone metabolism in T2DM and outline diagnostic and therapeutic approaches in these patients.

2. Bone Metabolism Changes in T2DM Patients

2.1. Microvascular alteration and cortical porosity

Vascular complications among patients with long-lasting T2DM are well known and described in detail. Before the onset of large vessel complications, microvascular alterations occur, leading to functional disturbances in various organs and tissues, resulting in retinopathy, neuropathy, and nephropathy. Therefore, calcification of small blood vessels due to inflammatory changes in the intimal layer is a direct consequence of altered glucose metabolism in T2DM, resulting in enhanced atherosclerosis. Atherosclerotic changes also affect blood vessels in bone, manifesting as calcification and defective vasodilatation. Patients with T2DM and proven microvascular complications exhibited increased cortical porosity, primarily due to compromised circulation in the cortical bone [7]. Another study showed the development of cortical porosity as a consequence of decreased cortical thickness and volumetric cortical BMD at the radius, while there was only an insignificant trend toward cortical porosity at the tibia [8]. Interestingly, metabolically more active trabecular bone was not affected and showed no difference between T2DM patients with and without microvascular complications.

2.2. Reduced bone turnover rate in T2DM patients and role of advanced glycation end (AGE) products

Despite initial conflicting results regarding the impact of T2DM on bone turnover markers, it was elucidated that markers of bone resorption, more precisely C-terminal cross-linking telopeptide of type I collagen (CTx) and N-terminal cross-linking telopeptide of type I collagen (NTx), and markers of bone formation (osteocalcin and procollagen type I N propeptide) are reduced in diabetes [9-11]. Reduced bone turnover rate will not protect against fracture risk as would be expected, because it enables accumulation of AGEs in bone collagen. The presence of exposed amino acid residues on collagen condition interacts with free-floating sugars in T2DM patients and the subsequent formation and accumulation of irreversible AGEs. Accrual of AGEs in patients with T2DM resulted in their cross-linking within collagen type I and the deterioration of biomechanical bone properties by the loss of elasticity due to bone collagen stiffening [12]. Accumulation of AGEs was significantly accompanied with altered findings of bone material strength index (BMSi), a parameter of cortical bone quality, obtained by reference point indentation [13]. In line with this, higher urinary levels of AGEs could predict fractures in T2DM patients [14]. Moreover, if present,

hyperglycemia can markedly contribute to decreased bone turnover, by disabling bone cells to interact with collagen and produce new bone matrix [9].

Routine practical assessment of bone turnover status is enabled by measurement of serum CTx levels. It should be determined with caution due to the influence of oral ingestion of food and glucose and subsequent change in incretin hormones [15]. Suppression of CTx lasts no more than 6 h after the meal [16]. However, constant lowering of CTx as a result of glucose intake will overtime contribute to decreased resorption and by that to accumulation of old bone, which is more prone to fracture.

2.3. Dysregulation of insulin-like growth factor-1 (IGF-1) level impacts bone volume and quality

The role of insulin in bone formation was clearly explained in children with T1DM and lower BMD and bone size due to lack of insulin and its anabolic effects [17]. The IGF-1 pathway was suggested to be important for insulin to exert its actions on bone metabolism, which includes osteoblast differentiation, chondrogenesis, and collagen synthesis [18,19]. Many preclinical studies support the crucial effect of IGF-1 signaling in bone status in diabetic conditions. Mice models of T1DM showed reduced levels of both IGF-1 and insulin receptors and had significantly reduced bone growth [20]. Overexpression of IGF-1 in osteoblasts is connected with increased strength of cortical bone but has no influence on trabecular microarchitecture [21]. This could at least in part explain the cortical porosity in T2DM. However, a systemic decrease of IGF-1 affects primarily trabecular bone [22]. Although the role of IGF-1 in T1DM is clear, its function in T2DM patients is probable but needs further preclinical and clinical evaluation with thoroughly designed trials and experiments [23]. However, stimulatory effects of IGF-1 were also shown to be compromised by accumulation of AGEs that could potentially trigger resistance of osteoblasts to IGF-1 [24].

2.4. Role of sclerostin in bone turnover process in diabetic patients

The impact of sclerostin level on BMD in patients with T2DM was revealed in a cross-sectional study which enrolled 124 patients. Circulating sclerostin was significantly increased in T2DM patients irrespective of gender and age [25]. Increased sclerostin levels were associated with a higher risk of vertebral fractures among a cohort of T2DM patients [26]. Sclerostin inhibits bone formation primarily by downregulating Wnt signaling pathway, which induces differentiation of osteoblasts and in turn suppresses the development of osteoclasts [27]. The main source of sclerostin is osteocytes, which was once not considered a very active part of bone; however, their central role in orchestrating bone metabolism is now clear. It was recently shown that osteocytes are the main source of receptor activator of nuclear factor kappa-B ligand (RANKL) for osteoclast differentiation and enhancement, thereby confirming the central role of osteocytes in bone metabolism [28]. Mature osteoclasts express RANK, a member of tumor necrosis factor receptors. RANK is activated in the presence of RANKL [29,30]. RANKL function is negatively regulated by its decoy receptor called osteoprotegerin [31]. Genetic deletion of RANKL in the osteoblasts until adulthood surprisingly did not result in osteoporosis, therefore highlighting the key role of osteocytes. Hyperglycemia and increased production of AGEs will likely suppress bone formation by increasing sclerostin expression in osteocytes. In contrast, AGEs are expected to additionally suppress bone resorption by decreasing RANKL expression [32]. Taken together, this mechanism will lead toward a low bone turnover state, which contributes to altered bone quality in diabetic patients. The pathophysiology of osteoporosis development in T2DM is given in Figure 1.

3. Assessment of Bone Volume and Quality in T2DM Patients

Bone loss and fracture risk are routinely assessed by dual X-ray absorptiometry (DXA) measuring BMD at the lumbar spine, proximal femur, and occasionally at additional sites, such as the distal radius. It is considered as a gold standard for verification of bone health [33]. However, due to some limitations, it is not capable to predict real risk for fracture in T2DM patients. Real fracture risk was significantly higher than that estimated with T-score measurement, thus revealing an upward shift to the BMD-fracture risk curve in T2DM patients [34]. The trabecular bone score (TBS) represents a recent upgrade in DXA technology that improved fracture risk prediction among T2DM patients [35,36]. TBS is a unitless texture analysis based on the anterior–posterior DXA that is able to assess the degree of heterogeneity in the bone. Bone with better

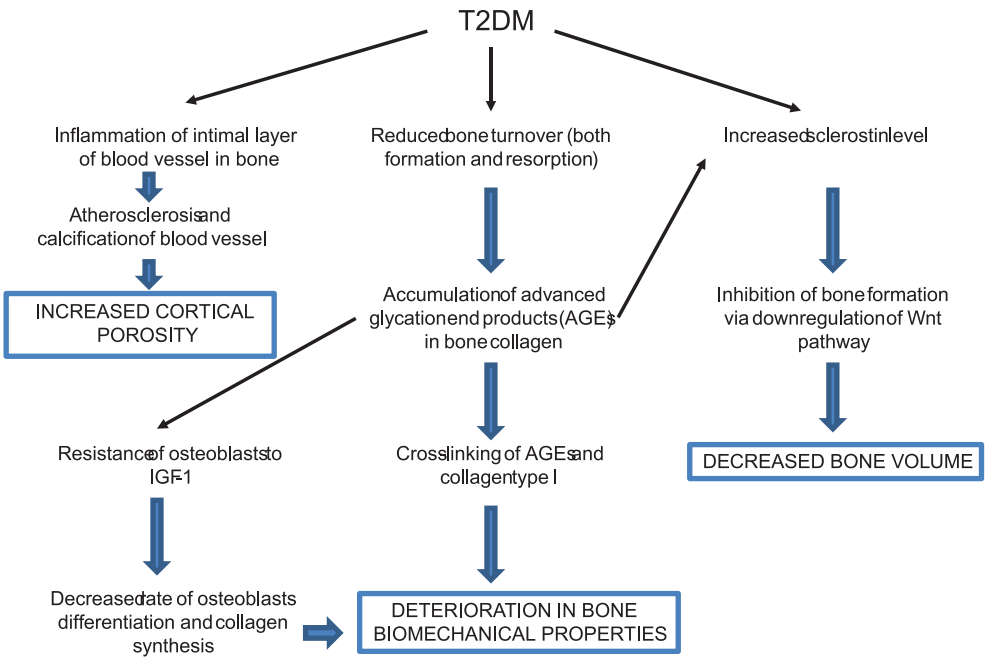

Figure 1. The pathophysiology of "diapetoporosis"

microarchitecture is captured as low level of interpixel variation and expressed as higher TBS, while lower TBS marks altered bone microarchitecture characterized with high interpixel variation [37,38]. Therefore, in T2DM, the value of TBS is reduced, irrespective of better DXA results, which enables more confident prediction of fracture risk.

The fracture risk assessment tool (FRAX), a widely used questionnaire approved by the World Health Organization for prediction of fracture risk, has shown insufficiency in T2DM patients [39]. FRAX summarizes femoral neck BMD and clinical risk factors from anamnestic data, without specific questions regarding glucose tolerance status. The questionnaire was recently adjusted for a subgroup of T2DM patients by substitution of rheumatoid arthritis for calculation with positive T2DM [40]. Another suggestion was to use the validated TBS as a part of FRAX questionnaire [41].

Despite its utilization in several clinical trials, high-resolution peripheral quantitative computed tomography (HR-pQCT) is still not accepted in everyday clinical assessment of bone quality [42]. It enables meticulous analysis of the microarchitecture of both trabecular and cortical bone, which is its main advantage over standard methods focused on trabecular bone. The usefulness of HR-pQCT is supported by trials that revealed altered cortical bone in T2DM patients. A small cross-sectional study compared bone properties of post-menopausal women with T2DM and age-matched controls and described increased cortical porosity of the radius and tibia in the first group for 50% and 118%, respectively [43]. Preliminary data from the Framingham HR-pQCT study confirmed higher porousness of cortical bone, accompanied with reduced volume of cortical bone and preserved trabecular bone volume [5]. Patsch et al. aimed to assess peripheral cortical bone structure in T2DM patients with and without fragility fractures by performing DXA and HR-pQCT of the distal radius and tibia [44]. T2DM patients with fragility fractures exhibited significantly altered cortical bone, shown as deficit in stiffness, failure load, and cortical load fraction at both the tibia and radius, in comparison with the group without fragility fractures. However, few studies failed to show the significant difference in cortical porosity among T2DM patients but still remained in the positive trend that supports the detrimental effect of T2DM on cortical bone [45].

A recently introduced novel technique called impact microindentation enabled direct *in vivo* analysis of cortical bone on the tibia by a reference point indentation

instrument validated on osteoporotic patients as capable to specifically discriminate between patients with and without fragility fracture [46,47]. The measured unit, BMSi, reflects the capacity of cortical bone to endure propagation of the probe. The power of this novel technique was recently recognized in the assessment of cortical porosity in T2DM patients. BMSi was markedly reduced in T2DM patients when compared to matched controls and was inversely correlated with the duration of T2DM [48]. In addition, the diagnostic value was upgraded with a cadaveric study of AGE accumulation, which suggested that reference point indentation may be sensitive to bone quality changes relating to collagen [13].

The diagnostic algorithm for T2DM assessment is given in Figure 2.

4. Management of Bone Loss among T2DM Patients

Choosing an appropriate antiosteoporotic drug is important when treating osteoporosis in patients with T2DM. Vice versa, it is crucial to select antidiabetic medications without negative effects on bone remodeling.

Thiazolidinediones could lead to bone loss and subsequently more frequent fractures, due to stimulation of adipocytes rather than osteoblasts [49,50]. Other drugs used to control glycemia in T2DM patients showed a heterogeneous effect on bone metabolism which is probably influenced by individual glycemic control.

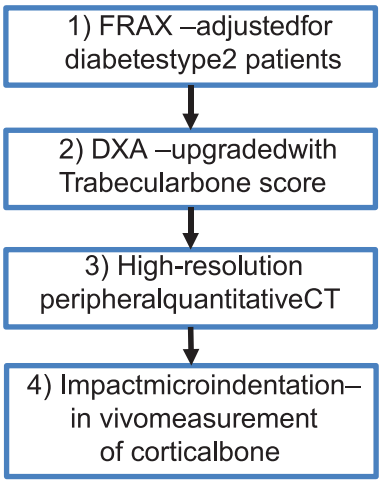

Figure 2. Algorithm for bone assessment in patients with type 2 diabetes mellitus

Among glucagon-like peptide-1 agonists, liraglutide was associated with a decreased fracture risk [51]. A recent meta-analysis suggests that treatment with DPP-4 inhibitors could be connected to a reduced risk of bone fractures [52].

Considering low bone turnover in T2DM patients, osteoanabolic therapy should have some advantages over antiresorptive. However, studies with direct comparison are still missing.

A preclinical study revealed accumulation of AGEs and a reduction in energy absorption of cortical bone after high-dose bisphosphonate treatment. However, no significant changes in AGE amount were noticed after treatment with more common doses of bisphosphonates routinely prescribed for post-menopausal osteoporosis [53].

5. Conclusions

Data from the National Diabetes Statistic Report predict that T2DM is present in a quarter of older adults in the United States [54], which overlaps with those at the greatest risk for fractures [55].

Current gold standards for osteoporosis assessment, including DXA and FRAX, should be used with the proposed enhancements, to approve their diagnostic value. Novel methods based on analysis of cortical bone properties seem to be more useful for fracture risk prediction in T2DM patients. Therefore, we suggest that the guidelines for the diagnosis of osteoporosis among T2DM patients should be adjusted and upgraded from the recent algorithm for osteoporosis assessment.

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