New insights on diabetes and bone metabolism
Novos conceitos em diabetes e metabolismo ósseo

ABSTRACT

Diabetes mellitus is a common chronic metabolic disease worldwide whose prevalence has increased during the last decades. Besides its more commonly recognized complications, such as macrovascular disease, retinopathy, nephropathy and neuropathy, diabetes related bone disease has gained growing attention. Diabetic patients are more prone to fracture than the general population as well as to low turnover bone disease in the chronic kidney disease setting. In this review, we discuss the relationship between diabetes and bone as well as the pathogenesis of bone fragility in T2D.

Keywords: bone fragility; diabetes mellitus; kidney failure, chronic.

INTRODUCTION

Diabetes mellitus (DM), in particular type 2DM, is a common chronic metabolic disease worldwide. Its prevalence has increased along with the increase in obesity resulting from lifestyle changes of modern life. Patients with type 2 diabetes (T2D) are at significant risk for well recognized diabetic complications, including macrovascular disease, retinopathy, nephropathy, and neuropathy. However, recently, one more complication has been associated with DM, an increased risk of fragility fractures which appears to be somewhat independent of bone mineral density (BMD). In fact, T2D patients have, in general, normal BMD, implicating abnormalities in bone material strength and/or bone microarchitecture. In this regard, a study using high resolution peripheral quantitative computed tomography (HRpQCT) has demonstrated an increase of cortical porosity in T2D. Moreover, a large study using trabecular bone score (TBS), which is a texture parameter that evaluates pixel gray-level variations in the spine DXA, demonstrated low lumbar spine TBS which is associated with worse bone structure. Taken together, it seems that microarchitecture including trabecular and cortical bone are disrupted in T2D and may contribute to bone fragility. In addition to a disrupted architecture, a decrease in bone formation and turnover demonstrated by histomorphometric analysis of bone may play a role in the increase of risk of fragility fractures seen in T2D.

RESUMOS

O diabetes mellitus é uma desordem metabólica crônica cuja prevalência tem aumentado no mundo todo ao longo das últimas décadas. Além de suas complicações mais reconhecidas, como a doença macrovascular, retinopatia, nefropatia e neuropatia, as alterações ósseas relacionadas ao diabetes têm ganho um crescente interesse. Os pacientes diabéticos são mais suscetíveis a fraturas do que a população geral e à doença de baixa remodelação entre os pacientes com doença renal crônica. Nesta revisão, iremos discutir a relação entre diabetes e o tecido ósseo, assim como a patogênese da fragilidade óssea no diabetes tipo 2.

Palavras-chave: diabetes mellitus; fragilidade óssea; insuficiência renal crônica.
The aim of this review is to discuss the relationship between diabetes and bone as well as the pathogenesis of bone fragility in T2D.

**Epidemiology of T2D and Fractures**

There is convincing evidence that older adults with T2D have an elevated risk for all clinical fractures, particularly in African-American and Latino populations. In this regard, a meta-analysis demonstrated a relative risk (RR) of fracture of 1.2 (95% CI 1.0 to 1.5) in patients with T2D. Longer duration of diabetes appears to increase fracture risk; however, newly diagnosed T2D was related to a significantly increased risk of any fracture (adjusted hazard ratio, HR, 95% CI: 1.36, 1.32-1.40), as well as for hip, spine, wrist/hand, forearm, and upper arm/shoulder fractures. Furthermore, diabetes control also influences bone fragility as showed in a recent meta-analysis indicating that poor glycemic control contributes to increased fracture risk. However, aggressive lowering of A1C does not appear to be effective in preventing fracture.

The increased fracture risk in T2D is thought to be due to both an increased falling frequency and decreased bone strength. The increased falling frequency is mainly a result of complications of the disease such as a retinopathy and polyneuropathy.

**The Pathogenesis of Bone Changes in Diabetes**

**Hyperglycemia**

Hyperglycemia affects the skeleton at both cellular and extracellular bone matrix levels. *In vitro* studies have shown that high glucose levels augment osteoclast differentiation/fusion resulting in a more resorptive environment. At the tissue level, hyperglycemia affects the organic bone matrix through the accumulation of advanced glycation end products (AGEs) leading to inferior bone strength. Indeed, the contribution of AGEs to the development and progression of complications of diabetes is well demonstrated in the literature. In general, the pathological effects of AGEs are related the ability of these compounds to modify the chemical and functional properties of several biological structures. In all tissues, AGEs generate free radicals and promote oxidative stress, and increased expression of inflammatory mediators.

There are several AGE receptors or AGE-binding proteins, but the RAGE receptor is probably the best characterized. There is evidence for involvement of RAGE in the development of diabetic macro- and microangiopathy.

In the skeleton, the accumulation of AGEs leads to more brittle bone with reduced toughness and therefore, less ability to deform before fracturing. The most studied AGE is pentosidide, the concentrations of which in cortical and trabecular bone are negatively associated with bone strength. Patients with fracture present higher concentrations of pentosidide than nonfractured controls. It was demonstrated *in vitro* that incubation of osteoblasts with pentosidide caused a significant decrease in alkaline phosphatase, collagen 1α1, osteocalcin, and RAGE gene expression. These data suggest a detrimental effect of AGEs on bone that leads to functional alterations in osteoblasts and in the bone mineralization process.

In addition, serum concentrations of pentosidide in T2D were shown to be higher than those in control subjects and were correlated with cortical bone pentosidine. One Japanese study evaluated serum pentosidine levels in postmenopausal women with diabetes and demonstrated an association with prevalent vertebral fractures, which was independent of BMD. This study suggested that serum pentosidine was more sensitive than BMD in assessing the risk of prevalent vertebral fractures in women with diabetes. The relationship between pentosidide and bone fragility has been also demonstrated in type 1 diabetes (T1D).

Recently, bone biopsies from T1D patients with fracture were analyzed by high-performance liquid chromatography to assess pentosidide concentrations in trabecular and cortical bone. In addition, the degree of mineralization of bone (DMB) was assessed by digitized microradiography, and mechanical properties by micro- and nanohardness tests. Positive correlations were found between HbA1c and pentosidide and between HbA1c and DMB. Both modifications resulted in less flexible bone (reduced modulus of elasticity) increasing the probability of low-energy fractures in T1D patients. Based on the correlation between pentosidide and fractures, it is reasonable to speculate that serum pentosidide levels could serve as a marker for fracture risk in diabetic patients, since BMD is less effective in the identification of those patients with diabetes at risk for fragility fractures.
**Insulin and IGF-1**

Insulin is an anabolic hormone which has effects on the skeleton. It acts on bone tissue through insulin receptors (IRS-1 and IRS-2) expressed by osteoblasts. In normal physiological conditions, stimulation of these receptors stimulates bone formation by increasing osteoblast proliferation and promoting collagen synthesis. In the same way, insulin growth factor-1 (IGF-1) is a key regulator of bone and acts to increase osteoblast recruitment and bone matrix deposition and reduce collagen degradation. Indeed, studies have demonstrated a positive correlation between IGF-1 and BMD and also a negative correlation with hip and vertebral fractures.

**Bone turnover**

Studies have shown that serum markers of bone turnover (BTM), especially the formation markers (osteocalcin and P1NP) are decreased in patients with diabetes. Moreover, bone histomorphometry has demonstrated that remodeling parameters such as bone formation rate and mineralizing surface are significantly lower in T2D than controls indicating a low turnover state. In this regard, sclerostin a regulator of bone formation, has emerged as an important player in this scenario. Sclerostin is an osteocyte product which inhibits the wnt B-catenin pathway by binding to LRP5 or 6 and, thereby, negatively regulates bone formation. Patients with T2D have been shown to have higher levels of circulating sclerostin that were associated with time and control of the disease. A Chinese study evaluated 265 postmenopausal women with T2D and showed that the serum sclerostin level was significantly higher than that in a non-diabetic control group (48.2 ± 19.4 vs. 37.2 ± 18.6 pmol/L, p < 0.001). Serum sclerostin concentration was positively correlated with hemoglobin A1c level and negatively associated with biochemical bone turnover markers, intact parathyroid hormone and bone-specific alkaline phosphatase. In addition, sclerostin levels were associated with increased risk of vertebral fractures, independent of BMD, indicating that the low bone formation caused by high levels of sclerostin impaired bone quality. A significant association between bone formation markers and IGF-1 was demonstrated and confirmed that IGF-1 is linked to osteoblast function. Moreover, an inverse association of IGF-1 and sclerostin was demonstrated in postmenopausal women with T2D and vertebral fractures. It, therefore, appears that the association of low IGF-1 and high sclerostin levels contribute to the bone fragility observed in T2D patients.

Osteocalcin is a non-collagenous matrix protein that is linked to glucose metabolism. It is a 49-amino acid peptide synthesized exclusively by the osteoblasts and stored in matrix. In its undercarboxylated form, it has some hormonal features and has been associated with glucose metabolism and fat mass. Osteocalcin stimulates insulin secretion and enhances insulin sensitivity in adipose tissue and muscle (Figure 1). A negative association between osteocalcin and markers of metabolic syndrome, such as serum glucose, insulin, high-sensitivity C reactive protein, interleukin-6, body fat and body mass index (BMI) has been demonstrated, suggesting that reduced osteocalcin levels may play a role in the pathophysiology of bone fragility in T2D.

**Figure 1.** Endocrine link between bone and energy and glucose metabolism. Insulin stimulates the secretion of undercarboxylated osteocalcin, which improves insulin secretion and adiponectin production by fat cells. Figure from reference 27, with permission.

**Obesity and adipocytes in the bone marrow**

Obesity was once believed to be protective for osteoporosis. An elevated BMI is very frequent in T2D patients and is strongly associated with higher BMD, however obesity is not protective against fractures. Indeed, results from the GLOW study (Global Longitudinal study of Osteoporosis in Women) demonstrate that obesity is not protective against fracture in postmenopausal women and is associated with increased risk of ankle and upper leg fractures. In addition, interesting interactions between fat and
bone may play a role in the pathophysiology of bone fragility.

There is growing interest in the relationship between bone marrow fat (BMF), BMD and fractures. This interaction occurs due to the fact of osteoblasts and adipocytes differentiate from the same mesenchymal stem cells (MSC). Recent studies on bone marrow adipocytes have shown that they are not only lipid storage cells, but also secrete adipokines, such as leptin and adiponectin in an autocrine and paracrine manner. An inverse relationship between BMF and BMD was observed; however, no study has yet demonstrated an association with bone fragility. BMF can be measured by sophisticated techniques such as magnetic resonance imaging, with or without spectroscopy, and by bone biopsy, in which the adipocyte volume, perimeter and density can be quantified. Bone histomorphometry studies demonstrated that enhanced adipogenesis in the bone marrow of osteoporotic patients was inversely correlated with trabecular bone volume. Further, the increase in BMF was associated with reduced bone formation, supporting the postulated switch in differentiation of MSCs from the osteoblastic to the adipocytic pathway in osteoporosis.

Recently, we evaluated BMF of 41 patients on peritoneal dialyses by bone histomorphometry and found an association between increased marrow adiposity and reduced osteoblast activity and bone turnover. Interestingly, diabetic patients presented with higher marrow fat than non-diabetic patients (Figure 2).

Figure 2. Adynamic bone disease in an ESRD patient. An isolated trabecula among a great number of adipocytes in the bone marrow. (Bone section stained with hematoxylin and eosyn; magnification x 20.)

In summary, it is clear that there are complex interactions among the skeleton, obesity and BMF and these interactions have important implications for the development of skeletal fragility in T2D.

DM and renal osteodystrophy

Diabetes mellitus predisposes chronic kidney disease (CKD) patients to a low bone turnover state, called adynamic bone disease (ABD). Importantly, the prevalence of ABD has increased during the last decades and it has been found as the most prevalent bone disorder among pre dialysis and peritoneal dialysis (PD) patients. The growing prevalence of DM among the CKD population has been suggested as one of the possible explanation for these findings. Furthermore, the pathological significance of ABD in CKD has been demonstrated through its association with vascular calcification, bone fragility and mortality.

A recent study in which renal osteodystrophy was evaluated in 41 PD patients, de Oliveira et al. have further confirmed the association between DM and ABD, which could be, at least partially, explained by the presence of higher bone and serum levels of sclerostin in diabetic patients. This hypothesis still needs to be tested in pre dialysis and hemodialysis populations. Notably, accumulation of uremic toxins may potentially exacerbate the suppressive effect of diabetes on bone turnover through their deleterious effects on bone cell function. Hyperglycemia and insulin deficiency both inhibit parathyroid hormone secretion and may act, synergistically, with the direct effects of DM and uremic toxins on bone cells to further suppress bone turnover in CKD. Finally, despite of being considered a classical risk factor for ABD, it remains to be demonstrated whether a better glycemic control would ameliorate bone turnover in diabetic CKD patients.

Conclusion

There is an interesting relationship between T2D as well as glucose metabolism and the skeleton. Further, an interaction among fat and bone has been demonstrated. In this regard, a great number of features, discussed above, play a role in the impairment of bone quality seen in T2D. An adequate glycaemic control is important and might help reduce
the risk of bone fragility, since it may decrease the accumulation of AGEs in bone matrix. In addition, a delay in the complications of DM, such as neuropathy and retinopathy, achieved with improved glucose control may help decrease the risk of falls.

However, besides the glucose control, all patients with DM should be encouraged to prevent osteoporosis and falls, by reducing all of the other risk factors, such as smoking, sedentary lifestyle and vitamin D deficiency. It is interesting to point out, that the bone disease in diabetes has some similarities with ABD, where along with a low bone remodeling rate there are also higher levels of circulating sclerostin and lower levels of circulating PTH. All these findings may indicate that a new class of drug, sclerostin inhibitors, might be a promising therapeutic option in diabetic patients with bone fragility.

**CONFLICT OF INTERESTS**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**REFERENCES**


32. Tanaka S, Kuroda T, Saito M, Shiraki M. Overweight/obesity and underweight are both risk factors for osteoporotic fractures at different sites in Japanese postmenopausal women. Osteoporosis Int 2013;24:69-76. DOI: http://dx.doi.org/10.1007/s00198-012-2209-1


38. Barreto FC, Aguiar CM, Hernandez MJ. Marrow Adiposity Is Associated with Low Bone Turnover and Sclerostin levels in Peritoneal Dialysis Patients. ASBM Annual Meeting; oct 9-12, 2015. Seattle, USA.


