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Review

Determinants of bone strength and quality in diabetes mellitus in humans

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ABSTRACT

There is growing evidence that the higher fracture rate observed in patients with type 2 diabetes mellitus (T2DM) is associated with normal, or even increased, areal bone mineral density (aBMD) by DXA. This has led to the hypothesis that patients with T2DM may have abnormalities in bone microarchitecture and/or material composition – i.e., key determinants of bone "quality." Consistent with this hypothesis, several studies using high-resolution peripheral quantitative computed tomography (HRpQCT) have demonstrated preserved indices of trabecular microarchitecture but increased cortical porosity in T2DM patients. In addition, a recent study using a novel in vivo microindentation device found an impairment in a measure of bone material properties (bone material strength index, BMSi) in postmenopausal women with longstanding T2DM; notably, the reduction in BMSi was associated with chronic glycemic control, suggesting that the skeleton should be included as another target organ subject to diabetic complications. The underlying pathogenesis of skeletal fragility in T2DM remains to be defined, although high levels of advanced glycation endproducts (AGEs) may play a role. In addition, T2DM is associated with reduced bone turnover, perhaps with an imbalance between bone resorption and bone formation. Although several studies have found increased serum sclerostin levels in patients with T2DM, the role of these increased levels in mediating the observed increases in cortical porosity or reduction in BMSi remains to be defined. Thus, although bone quality appears to be impaired in T2DM, the pathogenesis of these abnormalities and their relationship to the increased fracture risk observed in these patients needs further study.

Contents

1. Introduction

Because aging is the most significant risk factor for osteoporosis and fractures, skeletal health is an important consideration for older adults in general. However, aging is also a risk factor for a number of chronic diseases, including diabetes, and emerging evidence suggests that diabetes itself affects bone metabolism and exacerbates age-related reductions in bone quality; thus, diabetes is now considered an independent risk factor for fragility fractures [1,2]. In this review, we summarize current evidence of altered bone "quality" in patients with diabetes mellitus, with a focus on in vivo assessment techniques.

Epidemiological data indicate that type 1 diabetes mellitus (T1DM) is associated with greater fracture risk than type 2 diabetes mellitus (T2DM) [3,4]. Whereas patients with T1DM usually have modestly reduced bone mass and areal bone mineral density (aBMD) [3–5], T2DM

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patients typically have normal or increased values for these parameters [3], even when normalized for body mass index (BMI) [6]. Paradoxically, however, despite higher bone mass and aBMD, T2DM is associated with a 50–80% increased extremity fracture risk [7,8], and a meta-analysis of 12 studies found a relative risk of 1.7 (95% CI: 1.3 to 2.2) for hip fracture [4]. Furthermore, large prospective studies in the United States [9] and Canada [10] have shown that patients with T2DM have a higher fracture risk for either a given femoral neck aBMD T-score and age or for a given FRAX probability (defined by the World Health Organization's Fracture Risk Algorithm [FRAX®] score [11]). Collectively, these findings indicate that the higher bone mass in patients with T2DM does not sufficiently protect against fractures, suggesting that other factors are likely responsible for this increased fracture risk.

T1DM typically manifests during childhood or adolescence and results in insulin deficiency, which is commonly accompanied by low body weight. Since insulin has anabolic actions in bone [12], these patients tend to have lower bone formation rates [13] and suffer from suboptimal peak bone mass accrual during growth [5]. Although it is not known whether patients with T1DM have altered bone material properties, a recent study using high-resolution peripheral quantitative computed tomography (HRpQCT) found that patients with T1DM and microvascular disease had significant deficits in both cortical and trabecular bone microarchitectural parameters at the distal radius and tibia as compared to matched non-diabetic control subjects [14]. These data are consistent with abundant evidence suggesting that patients with T1DM are at significant risk for greater bone loss from diabetic complications such as vascular disease, retinopathy, nephropathy, and neuropathy [5]. These complications also increase the risk of falls [15]. Therefore, low bone mass and compromised bone microarchitecture in combination with an increased propensity for falls likely explain the higher fracture risk in patients with T1DM.

The explanation for the higher fracture risk and yet normal or increased aBMD in patients with T2DM is seemingly more complicated. Although the known risk factors for age-related fractures also contribute to fracture risk in patients with T2DM, there appear to be specific fracture risk factors that are either more prevalent in patients with T2DM (e.g., reduced muscle quality, poor balance, and falls [16]) or T2DM-specific (e.g., poor glycemic control, T2DM duration, and diabetic complications [1,2]). In addition, several of the diabetic medications may exacerbate fracture risk in T2DM. For example, long-term use of oral glitazones (e.g., thiazolidinediones [TZDs]) doubles female fracture risk [17]. Also, in a population-based study of Olmsted County, Minnesota, residents with T2DM [18], use of insulin was associated with increased fracture risk, whereas biguanide (e.g., metformin) use and fractures were not related. However, it is also possible that the association of diabetes medications with fracture risk may be driven, at least in part, by the fact that patients on these medications may have worse glycemic control. This possibility is supported by in vitro studies showing that insulin and metformin stimulate osteoblast proliferation and differentiation [12,19]. In addition, there is conflicting evidence regarding the relationship of glycemic control to fracture risk in T2DM patients [20,21]. For example, while evidence exists that poor glycemic control (i.e., a glycated hemoglobin level ≥7.5%) is associated with higher fracture risk in T2DM patients [22], this relationship has not been established unequivocally. Thus, further work is needed to test this important question more rigorously. Moreover, although both the duration of T2DM and the presence of multiple diabetic complications have been associated with fracture risk [4,7,8,18], these risk factors collectively do not explain the increased fracture risk observed in T2DM patients [23].

The normal or higher DXA-derived aBMD [3] and yet increased fracture risk for a given femoral neck aBMD T-score and age in patients with T2DM compared to non-diabetic controls [9,10] has led to the suggestion that fragility fractures in T2DM may result from diabetes-related alterations in skeletal properties not captured by DXA [1,2]. In addition, it is possible that despite their higher BMD cross-sectionally, subsets of T2DM patients may undergo rapid bone loss [24–26], which may be an independent risk factor for fracture regardless of baseline BMD [27,28]. Further work is needed to better identify these potential "rapid losers".

Although widely available and commonly used clinically, DXA has neither the required sensitivity nor specificity for optimal fracture risk assessment [29] and is unable to assess critical aspects of bone's complex design. However, a recently developed analytical tool called the trabecular bone score (TBS) has been shown to capture vertebral trabecular bone "texture" from lumbar spine DXA images [30]. To date, multiple studies have reported negative associations between lumbar spine TBS (lower values reflect worse vertebral bone structure) and fracture risk in both patients with T1DM and T2DM as compared to non-diabetic controls [31–33]. Thus, lumbar spine TBS may serve as an indicator of vertebral skeletal deterioration in patients with diabetes mellitus. Further, it is also possible that bone macrostructure (i.e., geometry) is altered by diabetes. For example, studies using central and peripheral QCT have shown that patients with T2DM have similar or modestly reduced bone sizes (i.e., cross-sectional areas) and load to strength ratios [34,35] as compared to non-diabetic controls. In addition, patients with T2DM may have abnormalities in bone microarchitecture and/or material composition; i.e., determinants of bone "quality" [36,37].

2. Alterations in bone microarchitecture

To test whether bone microarchitecture is altered in patients with T2DM, several studies have used HRpQCT that allows for 3-D assessment of bone macro- and microarchitecture (e.g., cortical porosity and trabecular connectivity), essentially providing a non-invasive "virtual bone biopsy" of the distal radius and tibia. In the first study to utilize HRpQCT in patients with T2DM, Burghardt et al. [38] found that 19 postmenopausal women with T2DM had preserved trabecular microarchitecture but significantly compromised cortical microarchitecture (i.e., higher cortical porosity, by 124% at the distal radius) as compared to 19 non-diabetic postmenopausal control subjects (Table 1 and Fig. 1). By contrast, a later study by Shu et al. [39] reported no significant differences in HRpQCT-derived trabecular or cortical bone parameters at the distal radius or tibia in postmenopausal women with T2DM versus non-diabetic postmenopausal control subjects. However, this study may have been underpowered as only 14 subjects per group underwent HRpQCT scanning and cortical porosity was not reported [39]. More recently, Farr et al. [40] found that radial cortical porosity tended to be higher (by 32%) in 30 postmenopausal women with T2DM as compared to 30 age-matched non-diabetic postmenopausal control subjects after adjustment for BMI, although this difference did not reach statistical significance. Nonetheless, these findings were consistent with the initial study by Burghardt and colleagues [38]. Further, Patsch. et al. [41] reported significantly higher cortical porosity (by 58%) at the distal radius in 20 T2DM facture patients as compared to 20 T2DM patients without fracture. This same group, however, reported no difference in cortical porosity between patients with T2DM and non-diabetic subjects, although with only 20 subjects per group this study may have been underpowered to detect significant differences.

A further potential limitation of studies using HRpQCT is that this technique can only assess bone microarchitecture in vivo in humans at peripheral skeletal sites. However, Liu and colleagues [42] have shown associations between HRpQCT-derived bone microarchitectural properties at the distal radius and tibia and biomechanical properties (assessed by QCT) at central skeletal sites such as the hip and spine. These data suggest that measures of bone microarchitecture at peripheral skeletal sites may have clinical utility in identifying subsets of patients (e.g., patients with diabetes mellitus) who may be at risk for fragility fractures at both appendicular and axial skeletal sites, although this possibility needs further assessment.

Finally, another concern of the studies that have used HRpQCT to assess bone microarchitecture in patients with diabetes mellitus is that

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