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Fracture Risk Assessment in Patients With Diabetes Mellitus

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Abstract

Diabetes mellitus, both type 1 and type 2 (T2DM), is associated with decreased bone strength as well as increased fracture risk. Bone mineral density is decreased in type 1 diabetes but increased in T2DM, compared with controls. This suggests alterations in bone quality are a major player in the pathogenesis of fragility fractures in patients with diabetes. The link between diabetes and bone appears to be mediated by complex pathways, including the insulin-insulin growth factors system, accumulation of advanced glycation end-products in bone collagen, microangiopathy, and increased bone marrow fat content. Bone fragility in T2DM, which is not reflected by bone mineral density and bone mass reduction, depends on deterioration of bone quality. Also, at least in T2DM, the classical diagnosis of osteoporosis by dual-energy X-ray absorptiometry and the fracture risk estimation by FRAX (fracture risk assessment tool) are only partially useful in assessing fracture risk. Trabecular bone score and trabecular bone score-adjusted FRAX offer an enhanced estimation of fracture risk in these patients. Specific risk stratification criteria are needed in the future. The development of improved methods to assess the material properties of bone to better characterize fracture risk is also a priority. Adequate glycemic control is generally associated with decreased fracture risk, with the exception of specific antidiabetics (thiazolidinediones, canagliflozin) that have been shown to have a detrimental effect. Most currently used antiosteoporotic treatments seem equally effective in diabetic patients as compared with patients without diabetes, but clinical data regarding the reduction in fracture risk specifically in patients with diabetes mellitus are lacking.

Key Words: Bone mass; bone quality; diabetes mellitus; fracture risk.

Introduction

Osteoporosis is associated with significant morbidity and mortality, mostly owing to increased risk of fragility fractures (9 million fractures in 2000) *(1)*. Osteoporosis is especially prevalent in postmenopausal women, leading to a very high lifetime risk of hip, vertebral, and wrist fractures, estimated at around 40% *(2)*. Because age is an independent risk factor for osteoporotic fractures *(3)*, increasing life expectancy in developed countries will dramatically increase the magnitude of the problem in the future.

In addition, diabetes mellitus (DM) especially type 2 (T2DM) has reached epidemic proportions: the incidence is continually rising and is currently 4 times more than that recorded a few decades ago *(4)*. The numerous complications and comorbidities associated with long-standing DM contributes to the huge impact of the disease. With current medical advances, both people with type 1 (T1DM) and people with T2DM have significantly improved survival, and with the prevalence of osteoporosis increasing with age, osteoporosis will become a concern, with an increasingly large population of patients with diabetes. The associated costs imposed to health systems are very high for both conditions (overall the costs associated with osteoporotic fractures are greater than those linked to diabetes care) *(5,6)*.

Recent studies have shown that DM, both T1DM and T2DM, significantly increases the risk of vertebral *(7–9)*, hip *(9–13)*, and all nonvertebral fractures *(10,11)*.

The pathophysiology of this connection is still elusive. Bone mineral density (BMD) is lower in patients with T1DM *(14)* but higher in T2DM compared with controls

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(15), which might seem counterintuitive in a population with increased fracture risk. The purpose of this review is to investigate possible mechanisms altering the quality or the strength of bone in patients with diabetes, thus explaining the observed increased fracture risk in this population.

Bone Mineral Density in DM

BMD measured by dual-energy X-ray absorptiometry (DXA) is a widely used tool to diagnose osteoporosis and an important factor in predicting fracture risk in the general population.

Hip and total-body areal BMD (measured by DXA) are significantly lower in women with T1DM than in control subjects (14). High-resolution peripheral quantitative computed tomography (HR-pQCT) measurements of volumetric BMD at ultradistal radius and tibia also demonstrate lower BMD in T1DM cases, especially in those with microvascular diabetic complications (16). Low BMD was associated in patients with T1DM with poor glycemic control, lower insulin-growth factor I (IGF-I) serum levels, less physical activity, and decreased body mass index (BMI) (17,18).

In contrast, in T2DM, the areal BMD measured by DXA is higher than in individuals without diabetes, but paradoxically, despite this finding, their fracture risk is also higher (19). In systematic reviews of the literature, most studies revealed increased BMD in T2DM (15,20,21). At the total hip, all studies reviewed showed significantly higher BMD in subjects with diabetes than in control subjects without diabetes (21). At the femoral neck, many studies found a higher BMD in subjects with diabetes (22–24), whereas some authors reported no significant difference between diabetics and controls (25,26). Volumetric BMD measured by HR-pQCT is also increased in T2DM (27). Younger age, male gender, and higher BMI are positively associated with higher BMD levels in T2DM (21). Disease duration appears to influence only bone quality and not BMD in T1DM or T2DM (28). Metabolic control of T2DM (measured by the serum concentration of glycated hemoglobin [HbA1c]) is not conclusively correlated with BMD: some studies reported a correlation (21), others did not (28,29). In contrast, in T1DM, most studies associated low BMD with poor glycemic control (17,18).

Fracture Prevalence in DM

Bone has not been viewed until recently as a target organ for diabetic complications. However, in the last decade, strong evidence has accumulated in support of the high fracture risk in both types of DM (30,31).

The first studies drawing attention to this connection reported smaller increases in risk compared with the general population. The prospective Study of Osteoporotic Fractures reported a relative risk (RR) of 1.82 for hip fractures and 1.94 for proximal humerus fractures in women with T2DM (10). In a large case-control study, both types of DM were associated with an increased risk of any fracture (odds ratio [OR] 1.3 for T1DM, 1.2 for T2DM) and hip fractures (OR 1.7 for T1DM, and 1.4 for T2DM). T2DM was also associated with an increase in the risk of radius fractures (OR 1.2) (32).

Later studies revealed significantly higher overall risk for fractures, especially in T1DM. A review of the literature published in 2007 concluded that the hip fracture risk is increased in both T1DM (RR 6.94) and T2DM (RR 1.38) compared with controls, but is significantly higher in T1DM (29). Another systematic review on the association between DM and fracture reached very similar conclusions: increase in RR for hip fracture is more significant in T1DM (6.3) than in T2DM (1.7). T2DM was weakly associated with fractures at other sites, such as spine, forearm, or ankle (33). A very recent meta-analysis revealed T2DM was associated with higher risk of hip fracture, but not vertebral fracture (OR 1.134), in postmenopausal women (34). The increase in risk of vertebral fractures seems limited to T1DM cases (OR 2.5) (32). Patients with T1DM also have significantly more asymptomatic vertebral fractures (VF) than controls, but the presence of VF is not correlated with the BMD of the lumbar spine (35).

Some studies suggested a significant gender difference, with the markedly elevated RR for hip fractures in T1DM present especially in men (17.8 in men and 8.9 in women) and in T2DM only in women (36). The validity of these observations and their possible explanations (gender differences in body composition or hormonal milieu) need to be further explored. Studies exclusively recruiting men with diabetes are scarce. Using data from the Osteoporotic Fractures in Men study, after multivariable adjustments (including BMD), the risk of nonvertebral fractures was higher than that in controls only in men with T2DM treated with insulin (RR 1.74) (37). Men with impaired fasting glucose have similar (37) or even lower (38) risk of fracture compared with normoglycemic men.

Pathogenesis of Increased Fracture Risk in DM

The underlying pathogenesis of the higher fracture rate observed in patients with T2DM, in whom BMD is normal or increased, remains ill-defined. Even in T1DM, despite a lower BMD, the fracture risk is disproportionately increased, suggesting that additional factors, other than BMD, also play a role.

Increased Falling Propensity

Increased falling rate in patients with diabetes has been postulated and investigated. Older patients with T2DM have more frequent falls than elderly individuals without diabetes (39). Women with diabetes, poorly controlled cases, and those with mobility problems are especially at risk (40). Diabetic complications (causing neurological, visual, and cognitive impairment) are also associated with increased falling rate (41,42). Falling frequency should clearly be taken into account when estimating fracture risk. However, the overall risk of fracture in women with T2DM is still

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