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Review

Increased fracture risk in patients with type 2 diabetes mellitus: An overview of the underlying mechanisms and the usefulness of imaging modalities and fracture risk assessment tools

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ABSTRACT

Type 2 diabetes mellitus has recently been linked to an increased fracture risk. Since bone mass seems to be normal to elevated in patient with type 2 diabetes, the increased fracture risk is thought to be due to both an increased falling frequency and decreased bone quality. The increased falling frequency is mainly a result of complications of the disease such as a retinopathy and polyneuropathy. Bone quality is affected through changes in bone shape, bone micro-architecture, and in material properties such as bone mineralization and the quality of collagen. Commonly used methods for predicting fracture risk such as dual energy X-ray absorptiometry and fracture risk assessment tools are helpful in patients with type 2 diabetes mellitus, but underestimate the absolute fracture risk for a given score. New imaging modalities such as high resolution peripheral quantitative computed tomography are promising for giving insight in the complex etiology underlying the fragility of the diabetic bone, as they can give more insight into the microarchitecture and geometry of the bone. We present an overview of the contributing mechanisms to the increased fracture risk and the usefulness of imaging modalities and risk assessment tools in predicting fracture risk in patients with type 2 diabetes.

Contents

Abbreviations: AGE, advanced glycation end product; aBMD, areal bone mineral density; BMD, bone mineral density; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; DXA, dual-energy X-ray absorptiometry; eBMD, estimated bone mineral density; GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin; PPAR-γ, peroxisome proliferator-activated receptor-gamma; PTH, parathyroid hormone; SGLT2, sodium-glucose transport protein 2; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione; vBMD, volumetric bone mineral density; WHO, World Health Organization.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a highly prevalent disease, especially in elderly and obese patients. Since the world population is aging and worldwide obesity has nearly doubled since 1990 [1,2], the number of T2DM patients is expected to increase continuously. In 2011 it was estimated that 347 million adults worldwide suffer from diabetes [3]. Ninety percent of all diabetic patients can be classified as type 2 diabetics [4]. T2DM is characterized by insulin resistance and a relative deficiency of insulin, leading to a hyperglycemic state. Long term hyperglycemia results in end organ dysfunction such as neuropathy, retinopathy, cardiovascular disease and nephropathy, making diabetes one of the most important causes of morbidity and mortality in the western world.

More recently, an increased fracture risk has been suggested as another complication of T2DM [5]. Over the past ten years, the relationship between T2DM and overall, hip, vertebral and wrist fracture risk has been studied extensively [5–23]. For vertebral and wrist fractures it is not clear yet whether fracture risk is higher than or comparable to fracture risk in nondiabetic subjects, but hip and overall fracture risk seem to be evidently increased in T2DM patients (an overview of the literature published in the past ten years is presented in Tables 1–4). Fracture risk seems only to be increased in patients with already established T2DM, while patients with newly diagnosed T2DM or with an impaired glucose tolerance or impaired fasting glucose have a fracture risk lower than or comparable to nondiabetic subjects [9,13,16].

In the general population, dual energy X-ray absorptiometry (DXA) is the most commonly used imaging modality to diagnose subjects with osteopenia and osteoporosis and therefore to identify subjects with an increased fracture risk. In T2DM patients, bone mineral density (BMD), as measured with DXA, seems to be normal to elevated [17]. As fracture risk in these patients is higher than would be expected based on their BMD score, other skeletal and extra-skeletal factors should play a role in the increased fracture risk in T2DM.

In this overview we discuss the possible mechanisms leading to the increased fracture risk and the usefulness of current and new imaging modalities and risk assessment strategies in T2DM patients.

2. Mechanisms leading to the increased fracture risk

In general, the mechanisms leading to fractures can be categorized in four groups: 1. An increased falling frequency; 2. Bone fragility; 3. A combination of both an increased falling frequency and bone fragility; and 4. Neither an increased falling frequency nor fragile bones. In T2DM patients, the increased fracture risk partly remains after adjusting for their increased falling frequency, thereby indicating that the increased fracture risk in T2DM patients is probably due to a combination of both an increased falling frequency and bone fragility (Tables 1–4). Below we will discuss some of the mechanisms that lead to an increased falling frequency and factors that cause bone fragility in T2DM patients (see Fig. 1).

2.1. Increased falling frequency

The prevalence of fall incidents is increased in older T2DM patients compared to older adults without diabetes [7,24], whereby T2DM females report more falling incidents than their male counterparts [25]. An increased falling frequency can be observed in both home dwelling T2DM subjects and T2DM subjects living in nursing homes [26]. Younger T2DM patients have a fall frequency comparable to healthy subjects, but because of a worse performance in a timed up and go test (a functional mobility test) when compared to nondiabetic subjects, there fall risk seems to be increased [27]. T2DM patients who have reported a fall in the previous year, are also more likely to have had a prior fracture [28].

Diabetic neuropathy, visual impairment due to diabetic retinopathy, vestibular dysfunction, cognitive impairment and muscle weakness of the lower limbs are common complications of diabetes mellitus, especially in case of longstanding and/or poorly regulated T2DM. All of these complications are associated with an increased risk of falling [24,28–33].

Neuropathy leads to sensory, motor and autonomic dysfunction and hence to neuropathic pain, balance problems, orthostatic hypotension and great variability in step length and step velocity [29,31,34–36], which are all factors associated with falling. Because of neuromuscular impairment, T2DM patients are predisposed to severe falls and to falls to the side, which are both risk factors for hip fractures [37,38]. Cognitive impairment is associated with a decline in walking speed and in gait abnormalities as well [24,39], and could therefore increase the risk of falls in T2DM patients.

Orthostatic hypotension and orthostatic complaints are more common T2DM patients when compared to subjects without diabetes [36,40]. No association between an increased risk of falls and orthostatic hypotension in T2DM patients is found, but the presence of orthostatic complaints is associated with an increased risk of falls, even in patients without established orthostatic hypotension [36]. A strong relationship between orthostatic complaints and initial hypotension (within 15 s after standing up) has been described [41], indicating that the association between orthostatic complaints and falls is probably due to early orthostatic hypotension.

The number of prescribed medications was also reported to be related to fall risk [24,31,42]. The use of four or more prescribed medications was associated with an increased fall risk [42]. As T2DM patients take nine medications on average (seven without their antidiabetic drugs) compared to an average of four prescriptions in nondiabetic subjects [24], polypharmacy could be another contributing factor to the increased fall risk in T2DM patients.

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