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REVIEW

Bone damage in type 2 diabetes mellitus

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Abstract This review focuses on the mechanisms determining bone fragility in patients with type 2 diabetes mellitus (T2DM). Despite bone mineral density (BMD) is usually normal or more often increased in these patients, fracture incidence is high, probably because of altered bone "quality". The latter seems to depend on several, only partly elucidated, mechanisms, such as the increased skeletal content of advanced glycation end-products causing collagen deterioration, the altered differentiation of bone osteogenic cells, the altered bone turnover and microarchitecture. Disease duration, its severity and metabolic control, the type of therapy, the presence or absence of complications, as like as the other known predictors for falls, are all relevant contributing factors affecting fracture risk in T2DM. In these patients the estimate of fracture risk in the everyday clinical practice may be challenging, due to the lower predictive capacity of both BMD and risk factors-based algorithms (e.g. FRAX).

Type 1 and type 2 diabetes mellitus are both associated to bone damage [1,2]. However, the heavy epidemiological impact of type 2 diabetes on Western and developing Countries amplifies the interest on this latter condition. Type 2 diabetes mellitus (T2DM) now affects at least 285 million people worldwide, and this number will raise to 438 million by the year 2030 [3]. Such an increase will mainly occur in people aged over 60 years [3]. On the other hand, osteoporosis affects over 200 million people worldwide, concerning one out of ten women in their 60ies, 40% of women aged 80 and two-thirds of women aged 90 years [4]. Osteoporosis causes about 9 million fractures per year worldwide [5] and by 2050 the incidence of hip fracture is projected to increase by 240% in women and by 310% in men [4]. These epidemiological data underlines as T2DM and osteoporosis are rapidly expanding among older people, that is in a growing proportion of the general population. This in turn will translate not only in staggering financial costs for the communities, but it will also impact on the daily clinical practice of most physicians, who will increasingly deal with elderly patients in whom diabetes and osteoporosis coexist [6]. Moreover, despite T2DM and osteoporosis have been traditionally viewed as separate entities, accumulating evidence indicates that these diseases are tightly linked. Recent reports even advanced the hypothesis that common genetic determinants may contribute to both diseases [7]. Anyhow, although the pathogenesis of bone involvement in diabetes is complex and still not fully elucidated, patients with T2DM have an increased propensity to fracture [1,2], only partly depending on their increased risk of falls due to complications as retinopathy, neuropathy, and macrovascular disease [1,8] (Fig. 1). Qualitative, more than quantitative, alterations of bone

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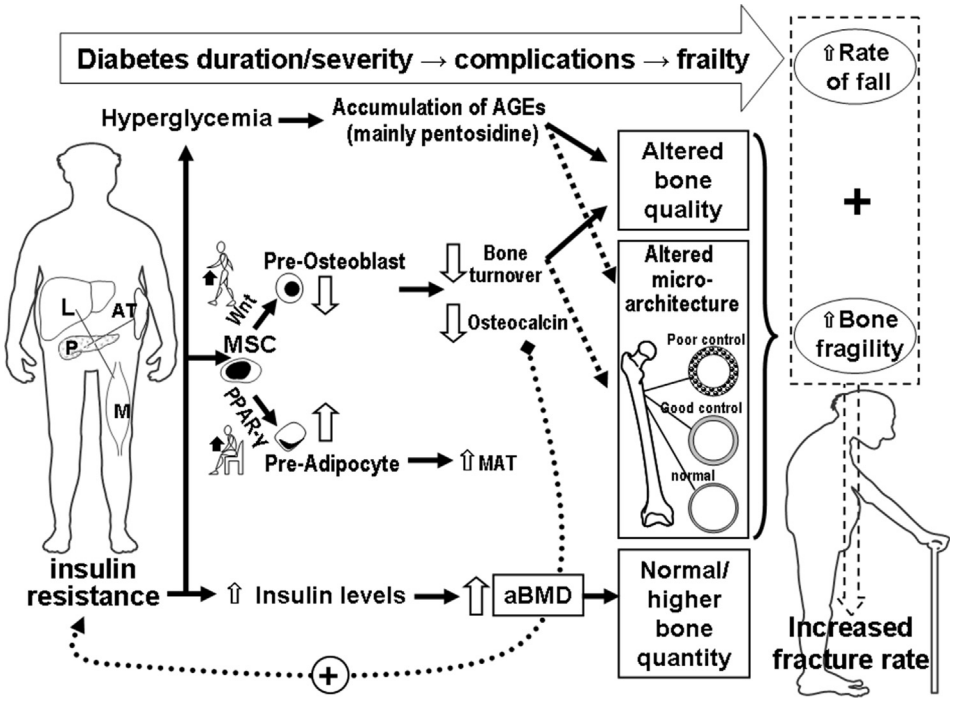

Figure 1 Proposed pathogenetic mechanism of bone fragility and fractures in type 2 diabetes mellitus. Insulin resistance results in higher levels of both insulin (which induce increased aBMD due to its anabolic action on bone) and glucose (which promote the skeletal accumulation of AGEs). Both insulin resistance and AGEs accumulation alter bone quality, microarchitecture (increased cortical porosity), and osteoblast differentiation and turnover (the related decrease of osteocalcin levels in turn worsens insulin-resistance). The consequently increased skeletal fragility, together with extraskeletal factors predisposing to fall, justifies the higher fracture rate of these patients. (L = liver; AT = adipose tissue; M = muscle; P = pancreas; MAT = marrow adipose tissue; aBMD = areal bone mineral density; MSC = mesenchymal stem cells; PPAR-γ = peroxisome proliferator-activated receptor gamma pathway; Wnt = Wingless integrase-1 pathway).

probably account for the increased skeletal fragility of patients with T2DM. The current review mainly focuses on evidence from human studies, but these results are largely consistent with those obtained in animal models [9].

Bone mineral density and fractures

Patients with T2DM, as an apparent paradox, usually have relatively high bone mineral density (BMD), associated to an increased propensity to fracture. Despite some contrasting data [1], most reports on this topic indicated that these patients have normal or higher BMD values in respect to control subjects [1,2,10,11]. Discrepant results from literature probably relate to the non homogeneous composition of the investigated samples, since T2DM patients often differ for body weight, body mass index (BMI), insulin levels, clinical presentation or disease duration, presence or absence of complications, type and duration of anti-diabetic therapy [1]. All the mentioned factors actually could be as many confounders, because previous studies showed significant associations between BMD and obesity, BMI [12], serum insulin levels, drugs [13]. It is worth noting as most studies on this topic have been carried out by the DXA measurement of BMD. However, body or skeletal size affects the results obtained by DXA, which assesses areal instead of "true" volumetric BMD because of its two-dimensional geometry. Moreover, areal BMD assessment by dual-energy X-ray absorptiometry (DXA) in patients with T2DM could be often affected by vascular calcium deposits, osteophytes, and diffuse idiopathic skeletal hyperostosis (DISH) [1]. Even considering these concerns, recent meta-analyses of BMD data [11,14] confirmed that BMD values are increased in patients with T2DM. In particular, Ma and co-workers [11], pooling 15 observational studies, analyzed DXA-BMD of 3437 patients and 19 139 control subjects. The BMD values measured at lumbar spine, femoral neck and total hip were higher in the whole sample of T2DM patients, as like as in male and female patients separately. The higher BMD associated with younger age, male sex, higher BMI, and glycated hemoglobin levels.

Although normal or higher BMD values should portend preserved or increased bone strength, patients with T2DM, counter-intuitively, have an increased fracture risk [1,2,15–20], showing a higher rate both of "classical" osteoporotic fractures, as those of the forearm, vertebrae, humerus, and hip, and of so-called fatigue fractures (i.e. tarsal and metatarsal fractures).

In patients with T2DM the risk of hip fracture, which carries the heaviest burden of morbidity and mortality, is significantly increased [21], attaining a relative risk (RR) between 1.80 and 2.66 [16,18]. Although a recent paper reported no elevation in risk in men with T2DM, and only a minimal increase (RR 1.05) of fracture risk in T2DM women [22], a recent meta-analysis of 12 studies