

The Impact of Diabetes Mellitus on Skeletal Health: An Established Phenomenon with Inestablished Causes?

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Abstract: Diabetes mellitus and osteoporosis affect a large proportion of older adults. In this context, diabetes may influence the bone in multiple pathways, some with contradictory effects. These mechanisms include changes in insulin and insulin-like growth factors levels, hypercalciuria associated with glycosuria, reduced renal function, obesity, higher concentrations of advanced glycation end products in collagen, angiopathies, neuropathies and inflammation. Although it is assumed that the decreased bone strength in diabetes may contribute to fracture risk, a very high number of available clinical and/or epidemiological studies as well as animal model studies brought about heterogeneous or even contradictory results on the skeletal involvement in patients with diabetes mellitus. In addition, bone mineral density (BMD) is a convenient predictor for fracture and the type 1 diabetes is associated with modest reductions in BMD. However, type 2 diabetes can be related to the elevated BMD. The immediate improvement in these discrepancies is to consider the complex pathophysiology of diabetes as well as influences of gender, age, treatment and duration of the disease. It is important also to improve further the choice of investigated biochemical markers and the standardization of the bone mass measurements. Along these lines, several recent cohort studies undeniably indicated that diabetes itself is associated with increased risk of osteoporosis.

Key words: Diabetes mellitus, skeletal health, fracture risk, bone mineral density

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Introduction

During the previous century, diabetes mellitus (DM) became a serious health problem of the developed world. It affects about every fifth person among older adults and has well-known vascular complications.

Skeletal health is an important problem among the older population as well. The skeleton is an efficient feedback-controlled steady state system that continuously integrates signals and responses, which sustain its functions of delivering calcium while maintaining strength [1, 2]. The strength and integrity of our bones depends on maintaining a delicate balance between bone resorption by osteoclasts and bone formation by osteoblasts. In many individuals, bone mass homeostasis starts failing in midlife, leading to bone loss and osteoporosis, and the risk of debilitating fractures exponentially increases with age. Osteoporosis is characterized by low bone mass, architectural deterioration, increased fragility and increased fracture risk [3, 4]. DM is generally not considered a risk factor for osteoporosis.

The involvement of DM in skeletal health has been considered for almost 80 years and conclusions of several recent cohort studies claim that diabetes of both type 1 and type 2 are themselves associated with increased risk of certain fractures, those of proximal humerus, foot, and hip [5–10]. This being said, it has to be emphasized that many hundreds of available clinical and epidemiological studies on skeletal involvement in DM patients have resulted in rather non-uniform and even contentious results, possibly because of the pathogenetic complexity associated with DM. Also, different bone quality measurement approaches, including bone histology and different sets of biochemical parameters with apparently highly variable prediction values, have been implemented in such studies. The BMD value is a strong predictor of fracture, but its significance for either more cortical or more trabecular bone may differ. Along these lines, the issue from the experimental studies employing animal models, such as acquired or induced diabetes in rodents, also remains to some extent controversial with regard to the involvement of diabetes in the bone fractures [4, 10].

The complex pathophysiology of DM is characterized by hyperglycemia and a variety of metabolic conditions due to insufficient insulin action [3]. This may result from impaired insulin secretion and/or lowered tissue responses to insulin at one or more target organs. Therefore, the endocrine and metabolic alterations of type 1 and type 2 diabetes could determine unequal alterations of calcium homeostasis, skeletal metabolism, and bone mass. The reduced insulin secretion and impaired insulin action may coexist in the same patient. In this sense, although the terms type 1 and type 2 diabetes are usually used as labels in clinical and/or epidemiological research, in specific cases they become not enough adequate to depict the true pathogenic complexity of the disease [4, 10].

In this review provides a short survey of clinical and epidemiological studies with regard to metabolic disturbances as well as to fracture risks in DM patients, and it comments the possible issues involved.

Metabolic disturbances in DM affecting skeletal health

The pathogenesis of diabetic osteopenia is far from being completely understood. Negative calcium balance can both accelerate and lower the bone turnover state; alterations in vitamin D metabolism and abnormal collagen metabolism have been implicated as the pathogenetic mechanisms of diabetic osteopenia [11].

In diabetic patients, the bone can be affected through several mechanisms, the combination of which may also have opposing effects. This can be one reason why the studies on the metabolic disturbances leading to skeletal involvement of diabetes frequently generate non-uniform conclusions.

Osteoblasts possess receptors for insulin and insulin-like growth factor-1 (IGF-1). It is known that these two substances function as skeletal growth factors and enable the recruitment of osteoblasts [4, 10]. This should lead to the promotion of bone formation [12, 13]. Low circulating insulin levels may sometimes account for the low peak bone mass and/or for bone loss seen in type 1 diabetes. Higher insulin levels may partially account for the higher bone density seen in type 2 diabetes. In this context, it should be also noted that hyperinsulinemia is associated with reduced sex hormone-binding globulin and with increased androgenicity and hyperestrogenemia [14–16] both conditions promoting bone formation. With regard to the action of insulin-like growth factors, their serum levels found in patients with type 1 diabetes were significantly lower than in type 2 diabetes patients and controls, and a positive correlation was found between IGFs and bone mineral density [13]. An increase in inflammation and associated cytokines could accelerate bone turnover and bone loss [17, 18]. Also, the increased content of advanced glycation end product-modified proteins in bone may lead to an imbalance in the secretion of IGFs and its binding proteins by proliferating preosteoblasts [4, 10, 19].

Patients suffering from chronic non-compensated diabetes exhibit decreased collagen strength that could be due to abnormal glycosylation and cross-linking of skeletal collagen [4, 20, 21]. These qualitative changes may induce bone fragility, this feature being potentially more important, with regard to the risk of fracture, than lowered bone mass.

In diabetic patients that exhibit low extent of metabolic control accompanied by renal excretion rates correlating positively with the degree of hyperglycemia and glycosuria, elevated urine levels of calcium, phosphate, and magnesium were found [4, 22, 23]. To some extent, this could be related to bone loss. Hypercalciuria can be traced back both to the osmotic diuresis promoted by glycosuria and to renal hemodynamic changes induced by prostaglandin excess.

More recently, however, it was demonstrated that urinary calcium levels of patients with type 1 diabetes did not differ from those of control subjects [4, 24].

Declining renal function, more prevalent in diabetes, is associated with lower BMD in older women [25]. The increased renal calcium leak appears to be connected with lower duodenal calcium absorption [4]. It has been speculated that hyperphagia, although it determines higher calcium intake, may limit the efficacy of active calcium transport, inducing an overall decrease in intestinal absorption [4, 26]. The reduced concentrations of the calbindin binding protein in the duodenal mucosa could contribute, in contrast to previous findings, to calcium malabsorption [4]. Also, the inclusion of patients with celiac disease [27] could partially explain the reduction of calcium absorption in diabetes as the celiac disease has higher incidence in DM patients of type 1 with regard to general population [4, 28].

Lowered intestinal absorption, together with the increased urinary calcium excretion, may induce a compensatory increase of parathyroid hormone (PTH) secretion [4]. Also, the reduction of serum ionized calcium due to higher concentration of the complexed ion [29] should promote PTH secretion in DM patients. Even though increased circulating parathyroid hormone has been reported in one study on a small group of poorly controlled type 2 diabetic patients [22], most studies demonstrated normal or even low PTH concentrations [24, 30]. The discrepant data could be partly related to the different assays employed for PTH measurement. However, overall, PTH secretion seems to be lower than expected for homeostatic needs as also confirmed after citrate-induced hypocalcemia [31], or hyperinsulinemic hypoglycemia [32], or following an oral glucose tolerance test [33]. Such a functional hypoparathyroidism has been related to magnesium deficiency and has been considered responsible for the low bone turnover [4, 10, 34, 35].

The possible role of vitamin D in the pathogenesis of skeletal involvement has been addressed in several studies. In contrast to healthy subjects, 24, 25-dihydroxyvitamin D levels are, in DM patients, markedly reduced and not correlated with those of 25-hydroxyvitamin D [4]. Islet cells of the pancreas possess calcitriol receptors and vitamin D deficiency could alter insulin secretion. This could explain reports of a significant inverse correlation between glucose levels after oral glucose load and serum 25-hydroxyvitamin D concentrations in elderly men [36, 37]. Even though a relevant role of vitamin D status in diabetic bone disease can be hypothesized, there are also disagreements. With regard to healthy subjects, some studies indicated normal 25-hydroxyvitamin D levels in diabetic patients [38], while other reports [39] pointed out that patients with type 1 diabetes had lower serum concentration of this substance [4]. Results of Broulík et al. [40] showed that the predominance of bone resorption over bone formation is not involved in the pathogenesis of diabetes associated with osteopenia. Nitric oxide is not involved in the pathogenesis of diabetic osteopenia.

Fat tissue is often reduced in type 1 diabetes while it is increased in type 2 diabetes [4, 41, 42]. With respect to the impact of obesity on skeletal health, either a lower or higher load on the skeletal tissue is applied. It appears that obesity is strongly associated with BMD, possibly through mechanical loading and hormonal factors including insulin and estrogens. It has been shown that apart from mechanical stress, the increased production of estrogens protects against osteopenia in type 2 diabetic patients [4]. The change of androgens to estrogens in postmenopausal women actually represents the main source of oestrogen, the latter positively correlating with fat tissue [43]. The peripheral estrogen production, especially in women after menopause, could affect BMD [4, 44].

A peptide produced by the adipocyte, leptin, has been found to contribute to protective effects of fat on the bone tissue [4, 45, 46]. Thus, leptin administration increases osteoblastic differentiation [47]. Leptin may also reduce osteoclastogenesis by inhibiting the expression of receptor activator of nuclear factor NF- κ B ligand and by stimulating that of osteoprotegerin in stromal cells [48]. These findings could explain the positive correlation observed between serum leptin levels and BMD at several skeletal sites [46, 49, 50]. However, such an association has not been confirmed by other authors [51]. An adipocyte-derived hormone, adiponectin, has been also proposed to play a role in the frame of fat tissue. It may regulate fat cell formation in bone marrow. Fat marrow is increased with ageing and in patients with osteoporosis [4, 52, 53].

Diabetic complications such as neuropathy and angiopathy are preventable with strict metabolic control. On the other hand, these complications may obviously contribute to fall-related fracture risk, and it has been hypothesized that angiopathies as well as neuropathies might also negatively influence skeletal tissue [4, 10, 54–58].

How should we summarize the published data on possible mechanisms through which DM affects skeletal health? There are very high numbers of publications dealing with the involvement of DM on skeletal health. On one hand, it seems that lowered bone strength in diabetes might contribute to the fracture risk, whereas, on the other, these publications generate a number of important results which, however, are frequently heterogeneous, not to say contradictory. We firmly believe this problem is mainly due to the pathogenic complexity associated with DM. Still today, there is considerable disagreement upon the possible influences on bone tissue exerted by gender, metabolic control of diabetes, and disease duration. Thus, the different design of studies involving the investigations of populations of varying ages and genders contribute to the conflicting results. Also, the plain inclusion in the investigated samples of diabetic patients with different pathogenesis, or assuming different therapies, or with various disease duration, or presence/absence of renal complications could have provided as many confounding factors in both clinical and epidemiological investigations. Obviously, one has to be aware of the fact that in DM patients, the morbidity associated with

fractures is likely to be exacerbated by diabetic complications and possibly by slower fracture healing [4, 6, 10, 59–62]. Also, different mass and quality measurement approaches, including different sets of measured biochemical parameters; with apparently highly variable prediction values have been implemented in such studies. For instance, the BMD is a strong predictor of fracture, but its value either in more cortical or more trabecular bone may differ. Finally, the assessment of bone quality and mass with various techniques could have been catastrophic to a unified conclusion. A better understanding of the factors that determine bone strength and integrity in DM patients is therefore needed. In a positive tone, the recent cohort studies, claiming the involvement of DM in the increase risk of certain fractures, have to a large extent met such criteria [4–10].

Bone fracture risk in diabetes

Patients suffering from type 1 diabetes usually exhibit a modest lowering of BMD [4, 10]. The risk of hip fracture appears to be substantially increased even though the number of studies of fractures, that involve patients with type 1 diabetes, is limited. Two cohort studies reported a significant increase in the risk of hip fracture [5, 7], but two previous case-control studies did not find any evidence of increased risk [63, 64]. In animal model studies, bone histology and bone markers in rodents with type 1 diabetes indicate a low turnover state of decreased osteoblast activity combined with normal or decreased osteoclast activity [23]. In contrast, human studies on bone turnover in type 1 diabetes have usually reported increased resorption [65–68] even though a different conclusion was reached in other study as well [69]. Reports on formation markers are inconsistent across studies and markers [66, 70–72]. In summary, it is generally believed that the type 1 of DM increases the risk of fractures at certain sites, although the causes of the bone turnover profile and of the lower BMD in type 1 diabetic patients are not well understood [4, 10].

With regard to type 1 diabetes, type 2 diabetes involvement in the skeletal health is even less characterized [10]. Historically speaking, an increased risk of fracture has not even been systematically claimed to represent one of the consequences of type 2 diabetes [4, 10]. It was reported in a large case-control study that diabetes was not associated with increased risk of fracture except at the ankle [63]. In addition, type 2 diabetes is associated with increased weight, a factor that somehow provides protection from most fractures. However, more recent cohort studies have reported increased risk of hip fracture with type 2 diabetes [5–8]. Diabetes appears to increase fracture risk at some other sites, including the proximal humerus, foot, and possibly ankle, but not the distal forearm or wrist [6, 7, 9]. In contrast, it was found in one large cohort study that a risk of fracture in older diabetic women, considering all nonvertebral fracture sites combined, is decreased [73]. Taken together, we can conclude that these

studies show an increased risk of fracture at specific sites for older adults suffering from type 2 diabetes [10].

What is the impact of BMD results on fracture prediction? While studies of type 1 diabetes that have generally found a modest decrement in BMD, studies of type 2 diabetes have reported a broader range of data that show more frequently average or slightly increased value of BMD [10, 22, 73–82]. The high variation in results may be due in part to variations in the severity, duration, and treatment of diabetes represented in the different studies. Two of the studies that reported elevated BMD identified diabetes using the glucose tolerance test in addition to self report and therefore probably included a greater proportion of newly diagnosed diabetics [73, 75]. Possible contributing factors to higher BMD in type 2 diabetes, in addition to obesity, include hyperinsulinemia and, in women, increased androgen levels associated with lower levels of sex hormone-binding globulin [83, 84]. This paradox of higher BMD but increased fracture risk in type 2 diabetes might be explained in two, not excluding ways [10, 85]. First, diabetics are more likely to fall and may therefore be exposed to more incidents that could produce a fracture. Additionally, diabetes may be associated with poor bone quality that is not captured in cross-sectional BMD measurements [10].

For future studies, it is of utmost importance to take into consideration the possible drawbacks associated with the complexity of DM as well as influences of gender, age, treatment, and duration of disease. Also, it is important to further improve the choice of relevant investigated biochemical markers and the standardization of the bone mass measurements planification of the study and the measurements of the bone quality and mass, we are of the opinion that several recent reports have indeed shown the higher risk of certain fractures in DM patients [4–9, 31]. However, despite numerous publications addressing this problem, many questions remain unanswered.

Prospect

We are of the opinion that the major breakthrough in the knowledge of the causal involvement of DM in skeletal health is to be expected in the years to come. It will occur as a result of studies devoted to molecular mechanisms governing bone formation and maintenance in animal models. Imbalances in bone remodelling can result in gross perturbations of the skeletal structure and function, and potentially in diseases like osteoporosis. Osteoporosis is a multigenic disease, with tens of identified genes being involved, and results from the interplay between genetic and environmental factors [2, 86]. Indeed, spectacular progress has been achieved in the last 5 or 6 years in the knowledge of the control of osteoclasts and osteoblast functions in experimental systems that also include animals with knock-out genes Accordingly, this progress will allow for major advances in new therapeutic approaches, including tissue engineering and stem cells, in human medicine [1, 2, 86, 87]. However, the diabetic animal models somehow evade,

for the time being, the primary interest of investigators working in this field. In the first instance then, the interest of scientists in diabetic rodent models has to change.

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