MANAGEMENT OF ENDOCRINE DISEASE

Diabetes and osteoporosis: cause for concern?

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Abstract

Diabetes and osteoporosis are both frequent conditions, and they may thus occur simultaneously by chance. However, a growing body of evidence suggests that hyperglycemia may impair bone matrix formation and biochemical competence. Decreased biomechanical competence may be present even in a setting of increased bone mineral density, as assessed by traditional dual energy X-ray absorptiometry or normal structural parameters by quantitative computed tomography. Also, the absence of endogenous insulin secretion in type 1 diabetes (T1D) and insulin resistance or, in some cases, frank hyperinsulinemia in T2D may play a role.

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Introduction

Diabetes and osteoporosis are both frequent conditions (1, 2), and they may thus occur simultaneously by chance. However, studies have indicated that osteoporosis and fractures may be more prevalent in diabetes than can be expected by chance (3, 4).

Osteoporosis has been defined as ‘a disease characterised by low bone mass and micro architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk’ (5).

In type 1 diabetes (T1D), bone mass is decreased and fracture risk is increased (4), so T1D thus meets the criteria for osteoporosis. However, in T2D, bone mass *per se* may be increased, even though fracture risk is increased (4). Patients with T2D may thus not readily meet the criteria

for osteoporosis, although their bone fragility may be increased (6, 7).

One reason for the occurrence of more fractures despite higher bone density in T2D could be an increased risk of trauma, which is possibly linked to hypoglycemia or an increased number of falls because of complications from impaired eyesight, cerebral ischemia, and poor balance resulting from neuropathy. However, one study indicated that these factors do not explain the increase in the risk of fractures to any significant extent, except to some degree for kidney complications (8). Impaired kidney function may have a number of detrimental effects, including reduced formation of activated vitamin D, secondary hyperparathyroidism, and uremic

Invited Author's profile

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osteodystrophy (9). Impaired eyesight and neuropathy may also be associated with decreased mobility, immobilization, and thus 'disuse' osteoporosis. Microvascular complications may be associated with decreased blood flow to the bones, as may macrovascular disease. These will not be dealt with further in the present review. Hypoglycemia *per se* is often transient, and although it may be associated with trauma (10), it has not been associated with impaired bone strength.

Other factors, such as impaired bone quality, may thus be responsible for the excess fracture risk in T1D and T2D.

The factors that underlie altered bone biomechanical competence may include: i) altered matrix competence (e.g., through the glycation of collagen or an altered crystal structure); ii) altered bone turnover; or iii) altered bone density or microarchitecture or structure, which may be a result of the previous two factors.

Some factors that affect bone biomechanical competence and/or turnover may be common among T1D and T2D, as is the case with hyperglycemia. Others, such as the lack of endogenous insulin secretion in T1D and insulin resistance and, in some cases, frank hyperinsulinemia in T2D, may be less common. In the following sections, we first discuss the evidence for each parameter and subsequently discuss the potential differences between T1D and T2D.

The present paper presents a narrative review of bone structure, biomechanical competence, and biochemical markers of bone turnover in diabetes. Because of the amount of data, not all of the animal and human subject studies have been presented. The main emphasis is on bone density and competence.

Altered bone turnover

Diabetes has been characterized as a disease of low bone turnover both by histomorphometry in rodent studies (11, 12, 13, 14, 15) and in two studies in human subjects (one involving six patients with T2D, two patients with T1D, and the other involving five patients with T2D and four controls) (16, 17). However, another study in 18 T1D human patients did not show any differences in their markers of mineral apposition or bone structure (18). For the biochemical markers of bone turnover, decreases in osteocalcin and C-terminal crosslinks of collagen (CTX) were seen, whereas other markers in general were not altered; there was large heterogeneity in all of the biochemical markers of bone turnover because of the differences in the assays that were used (19).

The link to CTX in particular may be interesting, because it represents the crosslinking of collagen and is thus a contributor to bone biomechanical competence, which may not be fully reflected in bone mass, density, and structure. However, a recent meta-analysis found an increase rather than a reduction in NTX (19), although the number of studies included in that meta-analysis were small and heterogeneous. It may thus not be completely accurate to say that decreased crosslinking is a risk factor.

One factor that may contribute to a reduction in CTX, especially in T2D, is the change in incretin hormones. The oral ingestion of food or glucose is associated with a decrease in CTX (20, 21). The ingestion of food also leads to an increase in glucagon-like peptide type 2 (GLP2) (20) and GLP1 (22). An injection of octreotide inhibits the decrease in CTX after the ingestion of glucose (21), and octreotide has been shown to inhibit GLP1 and to possibly inhibit GLP2 (23), which may explain the effects of octreotide. In both T1D and T2D, GLP1-related insulin release may be impaired (23, 24, 25). This may be associated with a decreased formation of crosslinks (including, among others, CTX) and thus possibly with the accumulation of fragile bone matrix. This decreased resorption could in theory also lead to an accumulation of old bone, which may perhaps be less resistant to load.

The duration of the suppression of CTX (and, to some degree, P1NP) is short-lived and seems to last for only 3–6 h (20, 21). Frequent meals may be prescribed for some patients with T1D in the form of, say, snacks in order to prevent hypoglycemia. Some patients with T2D may eat frequent meals as part of their obesity, and this may contribute to a more permanent suppression of bone turnover. This may perhaps also explain why patients with metabolic syndrome have lower bone mineral density (BMD) than expected after adjustment for confounders (26) and a slightly increased risk of fractures (27). Unadjusted, the higher body mass index (BMI) that occurs in metabolic syndrome is associated with higher BMD (28).

If hyperglycemia is present and collagen is glycated, the bone cells may also be less likely to adhere to collagen and produce new matrix (29), which can thus lead to a decrease in bone turnover.

Bone density and microarchitecture

One meta-analysis has pointed to a decreased BMD in the lumbar spine and proximal femur by bone densitometry (dual energy X-ray absorptiometry (DXA)) in T1D and an increased BMD in T2D in both the lumbar spine and

femoral neck (4). Despite this, an increased risk of fractures was seen in T2D, and a higher risk of hip fractures than could have been predicted from BMD was seen in T1D (4). This has been suggested to indicate a decreased bone biomechanical competence in diabetes (4).

Trabecular bone score (TBS) is a recent development in DXA technology, and it has been suggested that TBS captures fracture risk in diabetes better than traditional DXA does (30). One study that did not separate T1D and T2D reported decreased lumbar spine TBS in diabetic men aged 50 years or older (the age range suggests that the patients mainly represented T2D, although the study did not provide further details, and some of the patients may have been older T1D patients) (31). In women, lumbar spine TBS did not differ between diabetes patients and controls, and femur TBS was also similar in diabetic men and women and controls (31).

Computerized tomography (CT)-based techniques include high-resolution peripheral quantitative CT (HRpQCT), which may scan the forearm or tibia, and QCT, which may scan the lumbar spine, hip, or forearm (32). Magnetic resonance imaging (MRI) is also possible (33).

QCT performed in non-diabetic women has a larger detection rate of osteoporosis than DXA does (34), and it discriminates hip fracture better than DXA does (35); it may thus add to our knowledge of diabetes.

A study using QCTs of the femurs in patients with T2D reported lower proximal femur bone volume, minimal (narrow) neck cross-sectional area, and integral femoral neck volumetric BMD as compared to controls, whereas all other QCT parameters did not differ (including trabecular and cortical neck volumetric BMD, trochanteric and total proximal femur volumetric BMD, cortical and cortical neck femoral thickness, and trochanteric neck thickness) (36). The same group using the same patients reported an increased cortical porosity in T2D patients with fragility fractures using HRpQCT of the distal and ultradistal radius and the tibia (37). However, although trends were present, no significant differences between T2D patients and normal controls were seen in any HRpQCT parameters (37).

As mentioned earlier in the present report, Farr *et al.* (6) also failed to show any differences in HRpQCT parameters, but they only found a decreased resistance to microindentation in diabetes. This underscores that the calcium matrix and microarchitecture may seem to be normal in diabetes when X-ray-based techniques are used, even though bone quality may be impaired.

A recent study using MRI (38) in young women with T1D (median age 22 years, median age at diagnosis 9.7 years) reported reduced bone volume and increased

trabecular spacing. The decrease was especially prominent in patients with signs of microangiopathy (expressed as retinopathy) (38). However, this may reflect some of the growth issues related to T1D in young persons. Because of the disease, patients with T1D may have a reduced growth rate and a growth spurt during puberty; thus, the patients may be shorter and have different body proportions than those of normal controls if they have microvascular complications. The bones may thus be smaller and/or less developed in patients with childhood diabetes with complications.

It thus seems that more research is needed in both young patients with T1D and adults with T1D or T2D.

Altered bone matrix competence

Bone matrix is a composite material consisting of hydroxyapatite, cells, and organic matrix, which among other components contains collagen. These various components all contribute to biomechanical competence, such as resistance to pressure, traction, or torsion. The resistance to these strains may vary, and bone may be less resistant to, say, torsion than it is to pressure.

The inorganic calcium–phosphorous matrix of hydroxyapatite crystals contributes to rigidity and some elasticity, because hydroxyapatite may be more flexible in its crystal structure than, say, calcium carbonate is (39). Collagen contributes to support and elasticity (39), and it may prevent low-energy cracks, which can otherwise be seen if the material is completely rigid, like a piece of chalk, for example.

An *in vitro* study in rats that were made diabetic by streptozotocin showed a normal accretion of BMD with age but also an accumulation of advanced glycation end products (AGEs) and a reduction in stiffness, energy absorption, elastic modulus, and maximum load (40). In particular, the accumulation of pentosidine (41) and the lack of crosslinking of collagen (40) have been suggested to play roles in the diminished strength of the bones. The lack of crosslinking mirrored in low turnover, which is expressed, for example, as CTX in diabetes (19) but also after food intake (21) is discussed later in the present report. In humans, AGE and the receptor for AGE (RAGE) have also been linked to reduced bone biomechanical competence independently of BMD (42), and pentosidine has been linked to reduced bone biomechanical competence in osteoporosis (42).

A low serum level in the endogenous secretory RAGEs also seems to be a risk factor for prevalent vertebral fractures independent of BMD in patients with T2D (42).

In vivo studies using HRpQCT in human subjects showed reduced bone compressive strength by micro-indentation of the tibia despite normal bone micro-structural parameters in patients with T2D (6). Despite normal CT parameters, which are mainly derived by measuring the calcified bone matrix, the decreased structural load may support a role for factors other than calcium content and density, such as a weakening of the organic matrix.

In rats, experimentally induced diabetes has been shown to lead to the imperfect formation of hydroxyapatite crystals (43). Although absolute measures of stiffness, torsional strength, and energy absorption were decreased in the bones of the streptozotocin-treated animals, when torsional strength and stiffness were adjusted for differences in both growth and geometry, the adjusted stiffness values for the diabetic bones increased (43). The increased stiffness may potentially be associated with an increased risk of pathological cracks.

A recent study showed that under hyperglycemia and high osmotic pressure (mannitol), osteoblasts increase the secretion of type 1 collagen by a 12-fold factor, which indicates an excess of organic matrix production. The expression of ALP decreased by 50%, which indicates a deficit in mineralization (44). The authors did not find a link to receptor activator of nuclear factor- κ B ligand secretion by osteoclasts as osteoprotegerin increased (44).

Another *in vitro* study found a decreased pit resorption area for osteoclasts in hyperglycemic conditions (45). Thus, both osteoblasts and osteoclasts are affected by hyperglycemia.

This could support a change in biomechanical properties that are brought about by hyperglycemia *per se*.

Other determinants of fracture risk in patients with diabetes

Impact of insulin status and glucose levels

A number of other factors may also play a role in T1D and T2D. Insulin may have anabolic effects on osteoblasts (46), and endogenous hypoinsulinemia in T1D and perhaps also suboptimal levels of insulin from exogenous insulin administration may thus contribute to bone loss. Hyperinsulinemia in T2D might be protective; however, bone can become insulin resistant and abolish the possible positive effects (47).

Hyperglycemia may lead to an increased loss of calcium in the urine, which can in turn cause a negative calcium balance (48).

Impact of antidiabetic medications

The use of thiazolidinediones (glitazones) may lead to bone loss (49) and more fractures (50), because stem cells preferentially differentiate into adipocytes rather than osteoblasts (51, 52, 53).

Moreover, hyperglycemia may up-regulate peroxisome proliferator-activated receptor type gamma activity (54), and this may have effects that are similar to the thiazolidinediones.

Regarding other drug treatments for diabetes, heterogeneity exists between studies and drugs, which probably reflects differences in glycemic control, hypoglycemia, and so on (55). For the GLP1 agonists, liraglutide was associated with a decreased risk of fractures, whereas an increased risk was seen for exenatide (56). DPP-IV inhibitors may be associated with a decreased risk of fractures (57). However, similar observations have been made for the older antidiabetic drugs and may be related to their ability to control diabetes; for example, metformin may be associated with a decreased risk of fractures (55).

The impact of alterations in the Wnt and LDL receptor-related protein 5 pathways

The Wnt and the related LDL receptor-related protein 5 (LRP5) pathways constitute an important signaling system in bone. In a diabetic microenvironment, the anabolic Wnt pathway may be altered (58). The Wnt pathway has also been linked to diabetic complications (59). However, the Wnt and LRP5 pathways may also be linked to the treatment of hypercholesterolemia with statins, which may play a hitherto overlooked role. Hypercholesterolemia is treated aggressively in diabetes. LDL is known to play a role in bone cells, and the Wnt pathway may be a mechanism for increased fracture risk with low LDL levels as a result of statin treatment. The LRP5, 6, and 8 have been identified as positive regulators of the Wnt pathway and osteoblast differentiation (60). LDL binds to the LRP through apolipoprotein B and E moieties (61) and may therefore stimulate the Wnt pathway. A randomized controlled trial on rosuvastatin showed a non-significant trend toward more fractures in the treated group (62). In another trial (63), LDL levels decreased below 1.8 mmol/l in 5606 of 7716 rosuvastatin treatments (72.7%). It may thus be that very low cholesterol levels may be detrimental in a bone setting.

In terms of lipid levels and metabolism, MRI of bone marrow fat in postmenopausal women showed lower unsaturation and higher saturation of bone marrow fat in T2D patients, whereas patients with fragility fractures also had lower unsaturation of bone marrow fat (64).

Differences between T1D and T2D

A number of factors differentiate T1D and T2D; however, some factors, such as hyperglycemia and late complications, are similar and may represent common factors in the increased risk of fractures.

Hyperglycemia may promote the formation of AGE and thus interact with RAGE, which could weaken bone beyond what is reflected in BMD by DXA, QCT, and HRpQCT. This may thus be a common factor in explaining the increased fracture risk beyond that which is explained by changes in BMD by DXA (4). Glycated collagen resulting from hyperglycemia also interacts with bone cells, which makes bone turnover lower and leads to the low turnover state of both T1D and T2D (19).

Complications to diabetes, such as diabetic eye disease, nephropathy, and atherosclerosis, may all affect bone blood supply, balance, risk of falls, and thus risk of fractures. However, whereas patients with T2D may have complications at the time of diabetes diagnosis, T1D patients only develop such complications after years of often poorly controlled disease. Complications of diabetes may thus also separate T1D from T2D in terms of bone complications.

The differences between T1D and T2D are numerous. T1D often occurs in children and adolescents, whereas T2D is mainly a disease of adults. T1D may affect body growth and cause growth spurts during puberty. Final body height and body weight may thus be impaired when T1D debuts in childhood. Smaller bones may appear 'thinner' by DXA than larger bones because of the 2D scan technique applied by DXA (65), so patients with impaired growth may be deemed to have decreased BMD if they are not compared to subjects with similar body configurations. Patients with T2D, on the other hand, are often obese and thus have larger body frames than those of patients with T1D. Higher body weight and BMI in T2D are linked to a higher areal BMD than that in T1D (66), whereas volumetric BMD by, say, HRpQCT and QCT is the same in T2D as it is in controls (6, 37), because these 3D scans adjust for the 2D bias of DXA, which may be a problem with the larger body frames in T2D (66). A major weakness at the moment is the absence of HRpQCT and QCT studies in T1D patients.

Microindentation has been shown by HRpQCT to be impaired in T2D despite normal parameters (6). Again, studies in T1D are lacking. It may thus only be hypothesized that the impaired quality of bone in T1D is linked to changes in microindentation parameters.

Bone turnover assessed by histomorphometry seems low in both T1D and T2D, but the number of studied subjects is low (16, 17), and not all studies agree on this

finding (18). When it is assessed by biochemical markers of bone turnover, turnover seems low in both T1D and T2D, although variations have been seen between the marker types (19).

In T1D, endogenous insulin production is absent and has to be replaced by exogenous insulin, which may mimic endogenous levels but only to a certain degree; its levels are often lower than those of endogenous insulin. In T2D, both insulin and oral antidiabetics are available, and hyperinsulinemia may be present because of insulin resistance. Because insulin is an anabolic hormone, it may play a role in the higher BMD in T2D as compared to T1D. The often higher food intake, which is linked to obesity, in T2D may also contribute to the higher BMD in T2D as compared to T1D.

Although a decrease in BMD seems to correspond well to the increased risk of fractures in T1D (4), the increase in fracture risk is larger than what can be explained from the decrease in BMD or from falls that stem from, say, hypoglycemia (55). In T2D, a more modest increase in fracture risk is seen by DXA despite the increase in BMD (4). This points at a decreased bone biomechanical competence, which may correspond to the biomechanical competence that seems to be present in T1D.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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