MECHANISMS IN ENDOCRINOLOGY

Mechanisms and evaluation of bone fragility in type 1 diabetes mellitus

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Abstract

Subjects with type 1 diabetes mellitus (T1DM) have decreased bone mineral density and an up to sixfold increase in fracture risk. Yet bone fragility is not commonly regarded as another unique complication of diabetes. Both animals with experimentally induced insulin deficiency syndromes and patients with T1DM have impaired osteoblastic bone formation, with or without increased bone resorption. Insulin/IGF1 deficiency appears to be a major pathogenetic mechanism involved, along with glucose toxicity, marrow adiposity, inflammation, adipokine and other metabolic alterations that may all play a role on altering bone turnover. In turn, increasing physical activity in children with diabetes as well as good glycaemic control appears to provide some improvement of bone parameters, although robust clinical studies are still lacking. In this context, the role of osteoporosis drugs remains unknown.

Introduction

Despite the wealth of information available concerning the various systemic complications of chronic diabetes, the effects of this disease on the metabolism of minerals and the integrity of bone, particularly bone fragility, are not yet fully appreciated. The earliest influence of the diabetic environment on bone is seen in the increased

Invited Author’s profile

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prevalence of skeletal malformations in the foetuses of diabetic mothers. Hypoplasia or deformities of the extremities, dislocation of the hips and agenesis of the sacrum or lumbar vertebrae occur three to five times as frequently among these infants as among non-diabetic controls (1). The second category of bone abnormalities known to occur in those with diabetes results from the continuing trauma following diabetic neuropathy and is characterized by focal osteolysis, bone fragmentation, sclerosis and Charcot’s neurogenic arthropathy. This condition is usually evident in the small bones of the feet and less frequently involves the knees, upper extremities or vertebrae (2). Hand abnormalities, including carpal tunnel syndrome, sclerodactyly, acro-osteolysis and Dupuytren’s contracture also occur more frequently in diabetes. Diabetic muscle infarction is a rare complication seen in poorly controlled diabetics with advanced microvascular complications (3). Late complications of diabetes may also impact negatively on skeletal health, e.g. renal osteodystrophy, falls and fractures secondary to poor vision, neuropathy or cerebrovascular disease.

As early as 1927, Morrison & Bogan (4) documented decreased skeletal mass and bone development in children with longstanding diabetes. In 1934 several cases of diabetes associated with vertebral crush fractures were reported from the Joslin clinic (5). Albright & Reifenstein (6) confirmed these findings and Hemberg (7) reported in 1952 that osteoporosis was much more severe in young adults with diabetes at post mortem. Subsequently, Berney and others (8, 9) reemphasized the coexistence of diabetes and radiologic evidence of decreased bone mass. In 1970 Jurist (10), employing resonant frequency analysis, reported decreased skeletal strength in diabetic women compared with age-matched controls. Diabetes was found to occur in more than 20% of patients with vertebral crush fractures in a large epidemiologic study from Israel (11). Applying single photon absorptiometry, Ringe et al. (12), Levin et al. (13) and McNair et al. (14) documented a 31–48% decrease in bone mineral density (BMD) in insulin requiring diabetic patients. A 25–30% decrease in metacarpal cortical thickness was subsequently reported by Santiago et al. (15) and Hough (16).

It is, however, the role of diabetes and its treatment as the cause of a metabolic bone disease resulting in a generalised decrease in bone mass and/or compromised bone quality that has attracted much attention of late. It is now well established that osteoporotic fractures occur significantly more commonly in subjects with type 1 diabetes mellitus (T1DM) (17). Whether this merely reflects the common coexistence of the two diseases or whether involvement of the skeleton should be regarded as yet another unique complication of diabetes needs to be ascertained.

**Fracture risk**

Following earlier (4, 5, 6, 7, 8, 9) suggestions of an increased prevalence of fractures in T1DM, the results of the Iowa Women’s Health Study, an 11-year follow-up of 32 089 postmenopausal women, were reported in 2001 (18). Hip fractures were found to be 12 times more common in women with T1DM compared to matched controls. Men with T1DM were found to have a 17.8-fold increased risk of hip fractures in a 6-year follow up of 27 159 Norwegian subjects (19). Miao et al. (20) reported a similar eight- to 12-fold increase in hip fracture risk in a Swedish cohort of more than 24 000 patients with T1DM. In 2007, two large meta-analyses were published, reporting a near identical 6.9- and 6.3-fold (17, 21) increase in hip fracture risk in patients with T1DM compared to subjects without diabetes. A less marked but significant (OR=2.5 95%CI: 1.3–4.6) increase in vertebral fracture risk has also been reported in T1DM (22). While no large studies evaluating the risk of vertebral fracture in T1DM are available, there is data suggesting higher prevalence of morphometric vertebral fractures, assessed by VFA, in cross-sectional study (23). A more recent meta-analysis showed that T1DM was associated with a threefold higher risk of any fracture, and up to fivefold concerning hip fractures in women (24). T1DM is also associated with higher fracture risk than type 2 diabetes mellitus (T2DM) (17). A retrospective cohort study from the THIN database in the UK determined that the association between T1DM and increased risk of fracture of lower extremities especially was lifelong, starting during childhood and lasting into advanced age (25).

Fracture risk appeared to be related to the duration of diabetes, with some studies revealing a near linear relationship between duration of diabetes and fracture risk (18, 20). Other studies (19) failed to document any association with duration, whereas yet others (22) proposed a bimodal relationship with the highest incidence occurring within the first 2.5 years and again beyond 5 years of diabetes being diagnosed. Most, but not all (26), studies failed to document a relationship between the risk of fracture and glycemic control. An association between the presence of microvascular complications of diabetes and the increase in fracture risk was, however, reported in most studies (17, 18, 19, 20, 21, 22).
Quantitative and structural bases of bone fragility

Bone mineral density and ultrasound parameters

Table 1 lists more recent studies, using more sensitive dual energy X-ray absorptiometry (DXA) techniques, to measure axial BMD in younger subjects with T1DM. Most (27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44), although not all (45, 46, 47, 48, 49), studies report a significant decrease in BMD at either the spine, hip or total body. The magnitude of the decrease in BMD varied quite markedly from 8 to 67%, and large gender differences appear to be present, with many studies documenting changes in BMD in either males or females only. A recent meta-analysis (17) reported an average decrease in spine BMD of $-22\%$ and a hip Z-score of $-37\%$ compared to that of age- and gender-matched controls. Many (27, 30, 36, 43), but not all (29, 35), studies suggested that a decrease in BMD occurred more frequently in those with longstanding diabetes. Some studies, however, documented the presence of osteopenia at diagnosis of diabetes (35). As depicted in Table 1, BMD correlated poorly with glycaemic control in most (29, 33, 34, 35, 36, 37, 38), but not all (28, 31, 32), studies. However many studies reported an association between the presence of microvascular complications of diabetes and the presence and/or progression of a decreased BMD (27, 28, 38, 40, 42, 50). In these studies, the nature of the microvascular complication ranged from nephropathy to neuropathy to retinopathy, and no consistent pattern was apparent. The Vestergaard meta-analysis (17) also documented an association between the decreased BMD observed in patients with T1DM and the presence of a microvascular complication but failed to document an association between BMD and glycaemic (HbA1c) control.

A few studies (45, 51, 52, 53, 54, 55, 56, 57) have employed peripheral quantitative computer tomography (pQCT) or peripheral DXA (pDXA) to study the BMD of the distal forearm or tibia in T1DM. Some (45, 56) have reported no difference in the BMD between diabetics and controls, whereas others (51, 52, 53, 54, 55, 57) have documented a decrease in either trabecular and/or cortical BMD at these sites.

Table 1  DXA measurement of BMD in type 1 diabetes.

<table>
<thead>
<tr>
<th>Decreased BMD</th>
<th>n</th>
<th>F/M</th>
<th>Age</th>
<th>Duration</th>
<th>Site</th>
<th>MVC</th>
<th>GC</th>
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</thead>
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<tr>
<td>Munoz-Torres et al. (38)</td>
<td>94</td>
<td>49/45</td>
<td>30</td>
<td>12</td>
<td>H and S</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Clausen (1997) (27)</td>
<td>36</td>
<td>0/36</td>
<td>48</td>
<td>27</td>
<td>Hip</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Hampson et al. (30)</td>
<td>31</td>
<td>31/0</td>
<td>42</td>
<td>20</td>
<td>Hip</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Tuominen et al. (43)</td>
<td>56</td>
<td>27/29</td>
<td>62</td>
<td>18</td>
<td>Hip*</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rozadilla et al. (40)</td>
<td>88</td>
<td>43/45</td>
<td>29</td>
<td>11</td>
<td>Spine</td>
<td>Yes</td>
<td>NR</td>
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<tr>
<td>Kemink et al. (33)</td>
<td>35</td>
<td>14/21</td>
<td>38</td>
<td>9</td>
<td>H and S</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>campos Pastor (2000) (50)</td>
<td>57</td>
<td>30/27</td>
<td>35</td>
<td>17</td>
<td>H and S</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Lopez-Ibarra et al. (35)</td>
<td>32</td>
<td>10/22</td>
<td>30</td>
<td>0</td>
<td>H and S</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Valerio et al. (44)</td>
<td>27</td>
<td>12/15</td>
<td>13</td>
<td>7</td>
<td>Hip*</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Leger et al. (34)</td>
<td>127</td>
<td>73/54</td>
<td>14</td>
<td>6</td>
<td>S and TB</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rakic et al. (39)</td>
<td>34</td>
<td>11/23</td>
<td>48</td>
<td>14</td>
<td>H and S</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Strodtmeyer et al. (42)</td>
<td>67</td>
<td>67/0</td>
<td>32</td>
<td>5</td>
<td>Hip</td>
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<td>NR</td>
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<tr>
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<td>36</td>
<td>36/0</td>
<td>44</td>
<td>22</td>
<td>Spine</td>
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<td>No</td>
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<td>63</td>
<td>63/0</td>
<td>21</td>
<td>NR</td>
<td>Hip</td>
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<tr>
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<td>11/19</td>
<td>13</td>
<td>5</td>
<td>Spine*</td>
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<tr>
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<td>52/50</td>
<td>38</td>
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<td>NR</td>
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<tr>
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<td>104/71</td>
<td>33</td>
<td>9</td>
<td>H and S</td>
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<td>Yes</td>
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<tr>
<td>Soto et al. (41)</td>
<td>45</td>
<td>45/0</td>
<td>23</td>
<td>13</td>
<td>H and TB</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Joshi et al. (32)</td>
<td>86</td>
<td>22/53</td>
<td>27</td>
<td>15</td>
<td>S and TB</td>
<td>Yes</td>
<td>No</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pascal (1998) (49)</td>
<td>55</td>
<td>29/26</td>
<td>11</td>
<td>3</td>
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<td>Lunt (1998) (48)</td>
<td>99</td>
<td>99/0</td>
<td>42</td>
<td>27</td>
<td></td>
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<tr>
<td>Liu (2003) (47)</td>
<td>72</td>
<td>72/0</td>
<td>16</td>
<td>7</td>
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<td>Ingberg (2004) (46)</td>
<td>38</td>
<td>20/18</td>
<td>43</td>
<td>33</td>
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<td>Bridges (2005) (45)</td>
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<td>0/35</td>
<td>49</td>
<td>20</td>
<td></td>
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</table>

F/M, female/male; Duration, duration of diabetes in years; Site, skeletal site demonstrating a decreased bone mineral density (BMD); MVC, correlation between BMD and diabetic microvascular complication(s); GC, correlation between BMD and glycaemic control (usually the mean HbA1c); NR, not reported; H, hip; S, spine; TB, total body; Hip*, only site measured; Spine*, only site measured.
Although the decreased BMD reported in subjects with T1DM (27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 50, 58) may largely explain the higher fracture risk observed in these patients (17, 18, 19, 20, 21, 22, 26), alterations in bone quality, as described below, may also contribute and actually confer its specific nature to diabetic bone disease.

Quantitative ultrasound (QUS) parameters, including speed of sound (SOS), broadband ultrasound attenuation (BUA) and derived variables like ultrasound BMD or stiffness index of the radius, tibia, calcaneus or phalanges, have been reported in patients with T1DM in a limited number of studies (42, 59, 60, 61, 62, 63). Low values for these parameters were reported in T1DM, which appeared to correlate with the duration of diabetes (59, 60, 61) and the degree of metabolic control (61, 62, 63).

Bone size and microstructure

A number of studies have documented a smaller cross-sectional radial or tibial bone area in T1DM compared to controls (51, 56, 57), especially during childhood (57, 64), but with a normalization with age (65), and reported an association between glycaemic control and decreased bone size (52, 54).

High-resolution (HR)-pQCT measurements at the ultradistal radius and tibia showed in a cross-sectional study that T1DM patients as a group have lower total and trabecular volumetric BMD compared to healthy subjects, and these alterations are more prominent in those subjects with chronic microvascular diseases (MVD). They also exhibit lower trabecular and cortical thickness at the tibia, resulting in decreased estimated bone strength compared to healthy patients with MVD (66). It is notable, however, that cortical porosity, another important determinant of bone strength, was not increased in T1DM subjects, even those with MVD. These data suggest that MVD may be an independent risk factor of fractures. By magnetic resonance imaging (MRI), Adbalrahman confirmed trabecular deficits with reduced bone volume and trabecular number at the proximal tibia of young adults with childhood onset of T1DM, as well as increased medullary fat in the vertebrae (67).

Fracture toughness, the ability of the bone material to resist to crack initiation and propagation is another determinant of fracture risk besides bone strength. Nuclear magnetic resonance spectroscopy (NMR) and reference point indentation (RPI) have been shown to be useful clinical surrogates to assess fracture toughness. In their study, Granke et al. (68) showed that the fracture toughness properties decreased with age. NMR-derived properties such as pore water RPI-derived tissue stiffness correlated with fracture toughness on human femoral bone.

Bone turnover

A variety of animal models of T1DM (streptozotocin-induced, spontaneously diabetic NOD mice) have been shown to exhibit bone loss/impaired bone strength. Both animals with experimentally induced diabetes and patients with T1DM demonstrate similar metabolic bone profiles, namely, impaired bone formation and low levels of osteocalcin/bone-specific alkaline phosphatase, whereas it is less clear whether increased bone resorption also occurs. Employing short-term (2-week) animal models of streptozotocin diabetes, the low BMD observed in insulinopenic diabetes was earlier explained by secondary hyperparathyroidism and increased bone resorption resulting from a negative calcium balance (impaired intestinal calcium absorption; hypercalciuria) (69, 70). Using more appropriate animal models of chronic diabetes (8–10 weeks), and employing time-spaced tetracycline labelled bone histomorphometry, bone formation and resorption were found to be markedly suppressed (71, 72, 73, 74).

Subsequently, low bone formation has been confirmed in patients with T1DM, using biomarkers of bone turnover like serum osteocalcin (33, 75, 76, 77, 78, 79). In some human studies, bone resorption in T1DM is either decreased or unaltered and does not explain the low BMD observed in this disease (80). In children and young adults, T1DM patients had lower PINP and CTX levels compared to controls (67, 81). However enzymatic cross-linking of collagen is reduced in diabetes (82). Thus bone resorption assessed with CTX assay may be underestimated seeing that CTX assay measures cross-linked telopeptides.

Unfortunately, bone histology data in patients with T1DM are scarce. Only one study with two biopsies from patients with T1DM and six with T2DM showed markedly depressed bone formation rate compared to non-diabetic patients (83). Although a larger case-control study of 18 patients with T1DM and relatively good glycemic control (average HbA1C 6.8%) showed no bone structural or dynamic differences between groups, bone formation was significantly less in the small group of subjects who had fractures compared with T1DM patients without fractures (84). A recent reanalysis of these biopsies further indicates an increased degree of bone mineralization and non-enzymatic collagen crosslinks in diabetes subjects, particularly those with fractures, which would...
be consistent with a lower bone turnover. Moreover, these parameters were positively correlated with HbA1C, indicating that poor glycemic control has consequences on material bone properties (85).

**Cellular and molecular mechanisms of diabetes bone disease**

The pathogenesis of diabetic bone fragility is probably multifactorial. T1DM can directly influence bone quantity and quality in a number of ways or indirectly impact on skeletal health by causing hypogonadism (86, 87), hypercalciuria (88, 89), alterations in vitamin D metabolism (89, 90) or because of its association with certain diseases known to adversely influence bone (e.g. Coeliac disease (91)) (Fig. 1).

**Insulin, incretin and IGF1**

Insulin has been shown to have anabolic actions on bone in vitro (92). Furthermore, in knockout models of insulin receptor substrate 1 or 2 (IRS1; IRS2), the main intracellular substrates of the insulin receptor, bone formation and resorption are markedly reduced (93, 94). The administration of insulin to animals with experimental diabetes has also been shown to correct the decreased bone turnover that characterizes the chronic diabetic state (71, 95). Insulin deficiency as a cause of the low bone formation in T1DM therefore appears attractive. However, no changes in bone turnover were observed in global knockout of the mouse insulin receptor (IR), subsequently rescued by transgenic expression of the human IR in the liver, pancreas and brain, but not bone (96). Decreased insulin signalling alone cannot therefore account for the low bone turnover in T1DM. These knockout mice have elevated insulin levels which increase IGF1 signalling. Sufficient signalling through either IR or IGF1 is therefore required for optimal bone turnover (80, 97). Human data support the notion that the lack of insulin may affect negatively osteoblasts. In T1DM adolescents, bone phosphatase alkaline (ALP), osteocalcin and IGF1 levels were significantly lower compared to healthy controls (75) and lower IGF1 were associated with osteopenia (33). The decreased levels of IGF1 seen in T1DM but not in T2DM are not fully explained.

Incretin peptides, especially glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP1) are gut hormones known to potentiate the secretion of glucose-dependent insulin from the pancreas. GLP1 agonists and dipeptidyl peptidase-4 (DDP4) inhibitors are a new class of incretin-based therapies for the treatment of type 2 diabetes, which play an important role in the regulation of bone turnover (98). Recent data suggest that incretins could also have a positive effect on bone quality in T1DM. In streptozotocin-treated mice, incretin peptides were able to prevent the alterations of cortical microarchitecture and the deterioration of bone quality (99). Clinical studies are needed to determine if the rodent data is applicable and to elucidate the effects of incretin on fracture risk.

**Hyperglycaemia and AGES**

Hyperglycaemia is known to suppress osteoblastic differentiation and signalling, potentially resulting in impaired bone formation (80, 100). Chronic hyperglycaemia may also result in the non-enzymatic glycosylation of proteins (e.g. collagen) and other cell components (e.g. DNA), collectively referred to as advanced glycation end products (AGES) (101). Various AGES and their receptors (RAGES) have been implicated in the development of complications of diabetes, including diabetic bone disease. In a cross-sectional study, T1DM people with fracture were having higher serum levels of pentosidine, an AGE product, compared to non-fracture ones, although values largely overlapped with those of non-fractured diabetics (102).

**Marrow adiposity**

In the bone marrow, mesenchymal stromal cells (MSC) are the common progenitors that give rise to osteoblasts,
adipocytes and chondrocytes. A reciprocal relationship exists between adipogenesis, which is largely driven by the pro-adipogenic transcription factor, peroxisome proliferator-activated receptor (PPARγ2) and osteoblastogenesis. Stimulation of PPARγ2 expression in vitro has been shown to promote adipocyte maturation of MSCs and to reduce the number of mature osteoblasts (103). Marrow adiposity has been demonstrated in a number of conditions where increased adipogenesis has occurred at the expense of impaired osteoblastogenesis e.g. glucocorticoid excess, old age. McCabe (80) and others (103) have also demonstrated increased bone marrow PPARγ2 activity and increased bone marrow adiposity in mice with T1DM. Whether marrow adiposity is causally related to the low BMD observed in T1DM remains unclear. A direct link in all forms of bone loss appears unlikely, since PPARγ2 antagonists, capable of preventing marrow adiposity, did not prevent T1DM bone loss (104).

**Inflammation**

Type 2 diabetes is often referred to as a state of accelerated ageing and chronic low-grade inflammation (‘inflammaging’). T1DM is, however, also known to upregulate a number of inflammatory genes, and the pathogenesis of various complications of T1DM is thought to have, at least in part, an inflammatory basis (105).

Inflammatory cytokines like IL1 classically stimulate osteoclastic bone resorption. However, inflammatory cytokines like TNFα have been shown to inhibit osteoblastogenesis from MSC through several mechanisms (106). Moreover, the inflammatory milieu appears to dictate whether osteoblastic bone formation is impaired (e.g., in rheumatoid arthritis) or whether osteoblastic bone formation is stimulated (e.g., at sites of enthesis in ankylosing spondylitis) (107). Further studies are required to determine whether bone loss in T1DM has an inflammatory basis and whether anti-inflammatory agents impact on this process.

**Osteocyte function**

The low bone formation rate that is characteristic of T1DM (see above) suggests that in addition to its direct negative effects on osteoblasts, diabetes could also affect the function of osteocytes, i.e., the master regulator of bone cells functions. Sclerostin is an osteocyte-derived inhibitor of Wnt signalling pathway, essential for osteoblast differentiation and bone formation (108). In humans, sclerostin levels have been shown to be higher in patients with T1DM compared to controls in a cross-sectional study (102). Catalano et al. (109) showed that sclerostin levels are higher in females with T1DM compared to males and that the duration of the disease was associated with higher levels of sclerostin. Sclerostin levels are also higher in prediabetic subjects (110). These findings suggest that sclerostin expression and/or osteocytes viability and functions could be impaired in diabetes. Whether the mechanostatic response to skeletal loading is impaired in these subjects however remains unknown.

**Others**

Nutritional deprivation and keto-acidosis, still too commonly encountered in the patient with poorly controlled T1DM, are well known to impair bone formation (16). Poorly controlled T1DM is often attended by dyslipidaemia, which is associated with increased PPARγ2 expression, impaired osteoblast differentiation and marrow adiposity (80). Finally, theories derived to account for the bone loss in T1DM must also acknowledge reports of abnormalities in circulating levels of the adipokines (leptin, adiponectin), amylin, prostaglandins and glucocorticoids in both experimental and human T1DM, which may negatively impact on bone health (16, 111, 112, 113).

**Evaluation and management of bone fragility in T1DM**

In children and adolescents with T1DM, diagnosis of low bone mass should follow paediatric guidelines, i.e., BMD Z-score below −2.0 and a fragility fracture (114). But it is not clear who should undergo a BMD test among T1DM patients. In young adults, diagnosis of osteoporosis rely not only on aBMD (T-score and not Z-score) but also on multiple fragility fractures (115). Early onset of T1DM can negatively affect bone size and mass. The use of markers of bone turnover to investigate osteoporosis in this age category remains controversial (116).

FRAX algorithm (www.shef.ac.uk/FRAX) was developed to estimate an individual’s 10-year probability of major osteoporotic fracture and hip fracture in subjects older than 40 years of age. T1DM is considered as one of the causes of secondary osteoporosis and not as risk factor and therefore it increases fracture probability only when BMD is not included in the calculation, as illustrated in Table 2. Trabecular bone score (TBS) is a new texture parameter derived from DXA image of the spine and provides information related to bone microarchitecture and fracture risk. TBS was shown not to be significantly
different between T1DM and healthy persons but to be lower in T1DM patients with prevalent fractures (117). A low TBS value increases the predicted fracture probability in T1DM to the same degree as in non-diabetic subjects (Table 2).

In young adults, general recommendations should therefore be followed to diagnose low bone mass in T1DM individuals (118), whereas after the age of 40, fracture risk evaluation can be performed using FRAX, ideally including femoral neck BMD and other DXA-derived information (TBS and VFA).

**Fracture prevention**

It needs to be reiterated that no RCTs are available to guide the treatment of bone fragility in diabetes and that management is entirely empirical and derives from the good clinical practice and experience of the physician. Many osteoporosis guidelines mentioned T1DM as a risk factor for osteoporosis and fracture and suggest earlier bone evaluation in those patients. In contrast, recommendations on osteoporosis screening are not found in most diabetes guidelines. In a recent publication Zhukouskaya proposed a flow chart for evaluation, management and treatment of T1DM patients at risk of poor bone health (119).

**Non-pharmacologic measures**

General measures to prevent osteoporosis also apply to the patient with T1DM, especially to children with early onset of diabetes, who could have difficulties reaching peak bone mass during growth (120). These include a balanced diet rich in dairy, ensuring an adequate calcium (1000 mg/day) and vitamin D (1000 IU/day) intake, regular weight-bearing exercise (40 min walk 3×/week), limiting alcohol to <3 units per day, stopping smoking, the avoidance of other bone toxins and the prevention of falls (121). In children and adolescents, physical activity is the best way to build up bone mass and strength. Maggio *et al.* (81) have shown that regular weight-bearing exercise increases bone mineral accretion in T1DM children similarly to non-diabetic children. In the older patient with T1DM, especially those with neuropathy, poor vision or gait and balance problems, fall prevention is paramount.

**Optimise metabolic control**

Controversy exists as to the role of glycaemic control on BMD and fracture risk. Given the fact that a lot of *in vitro* data (80, 100) suggest that hyperglycaemia and hyperlipidaemia are toxic to osteoblasts, and at least some clinical reports (18, 19, 20) have confirmed a relationship between glycaemic control and fracture incidence, it is our contention that every effort should be made to optimise metabolic control in patients with T1DM at risk of fracture; this is especially relevant to T1DM in the young. Optimization of the insulin treatment remains a major point for normalization of glycaemia, prevention of diabetic complications and even prevention of bone health. In a prospective study, there was a trend for higher BMD in T1DM young adults treated with insulin for 7 years (50). However, in order to avoid hypoglycaemia, insulin is given at a dose that produces a slight hyperglycaemia compared to non-diabetic subjects. Thus it is possible that this slight chronic hyperglycaemia may affect bone quality and account for the increased risk of fracture.

**Management of associated disorders**

T1DM is associated with a number of disorders known to impact adversely on skeletal health. Hypogonadism, although more commonly encountered in T2DM and the metabolic syndrome, also occurs more commonly in T1DM and should be assessed and managed if present. In poorly controlled diabetes, excessive renal loss of calcium and magnesium may occur. Coeliac disease occurs in 4–11% of patients with T1DM as opposed to <1% in the general population and should be screened for with serum endomysial antibody assays in those at risk of fracture (91, 122, 123). If the diagnosis is confirmed with intestinal histology, a gluten-free diet is indicated.

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**Table 2** Ten-year probability of major osteoporotic fracture in T1DM patients (UK).

<table>
<thead>
<tr>
<th></th>
<th>FRAX</th>
<th>FRAX + BMD</th>
<th>FRAX + BMD + TBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No diabetes</td>
<td>Diabetes</td>
<td>No diabetes</td>
</tr>
<tr>
<td>Woman, 52 years old*</td>
<td>3.9</td>
<td>5.3</td>
<td>4.4</td>
</tr>
<tr>
<td>Woman, 62 years old with a vertebral fracture*</td>
<td>14.0</td>
<td>20.0</td>
<td>17.0</td>
</tr>
</tbody>
</table>

*Woman, 52 years old, 60 kg, 163 cm, T-score −1.5, TBS 1.16, no other FRAX clinical risk factor.
*Woman, 62 years old, 60 kg, 163 cm, T-score −2.5, TBS 1.16, with a vertebral fracture.
Bone active medications ► None of the anti-osteoporotic agents have been tested for their anti-fracture efficacy in T1DM subjects. Given the fact that bone formation is generally impaired in T1DM, one would intuitively deduce that treatment with anti-resorptive agents would be less effective and that an anabolic agent should be preferred. Intermittent parathyroid hormone (PTH), known to have bone-forming effects on bone, and more generally to increase bone turnover, has in fact been shown to improve trabecular bone volume in animals with experimental T1DM (124). To date, however, there are no human data on the effect of intermittent PTH in T1DM patients. Sclerostin antibody has been tested in animal models with T2DM, where it increased bone mass and strength, but not in the setting of T1DM (125). Unfortunately no clinical studies are yet available to confirm this in humans. Bisphosphonates, known for their anti-fracture effects in high-turnover (e.g., postmenopausal) as well as low-formation (e.g., glucocorticoid-induced) osteoporosis are usually recommended as first-line treatment for diabetic bone disease, but no studies are available to support this contention. A cohort study showed no difference in anti-fracture efficacy of bisphosphonates in patients with diabetes compared to control non-diabetic patients, or between patients with T1DM and T2DM (126). However, atypical femoral fracture occurred twice more often in postmenopausal women with diabetes (type 1 and 2) compared to those without diabetes (11.6% vs 5.6%) (127), so bisphosphonates should be used with caution and at least for limited durations in T1DM patients with established bone fragility, especially in children and young adults with T1DM. Strontium ranelate is contraindicated in patients at risk of cardiovascular disease. Both bisphosphonates and strontium ranelate are contraindicated in patients with significant renal impairment and a creatinine clearance <30 ml/min. Denosumab has been shown to increase cortical density and thickness but it has not yet been tested in the context of diabetes either in animal models or in humans.

As the onset of T1DM happens often during childhood, specific attention should be directed towards growing children who have not yet reached their peak bone mass.

Conclusions

T1DM confers significant increased fracture risk throughout life. Therefore, fragility fractures should be considered as a (new) major complication of this disease and fracture risk should be properly evaluated and regularly re-evaluated in these patients. Since areal BMD is usually decreased in T1DM, the common fracture prediction algorithms such as FRAX can be used to evaluate fracture probability in T1DM without further adjustments (contrary to T2DM). However, the development of non-invasive or minimally invasive methods to evaluate bone quality parameters, such as HR pQCT and micro-point indentation, might be useful to further identify T1DM subjects at increased fracture risk. Clinical trials evaluating the benefits/risk of osteoporosis drugs on skeletal health in subjects with this common disease are also urgently needed.

Declaration of interest

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

Funding

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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