

Mechanisms of diabetes mellitus-induced bone fragility

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Abstract | The risk of fragility fractures is increased in patients with either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). Although BMD is decreased in T1DM, BMD in T2DM is often normal or even slightly elevated compared with an age-matched control population. However, in both T1DM and T2DM, bone turnover is decreased and the bone material properties and microstructure of bone are altered; the latter particularly so when microvascular complications are present. The pathophysiological mechanisms underlying bone fragility in diabetes mellitus are complex, and include hyperglycaemia, oxidative stress and the accumulation of advanced glycation endproducts that compromise collagen properties, increase marrow adiposity, release inflammatory factors and adipokines from visceral fat, and potentially alter the function of osteocytes. Additional factors including treatment-induced hypoglycaemia, certain antidiabetic medications with a direct effect on bone and mineral metabolism (such as thiazolidinediones), as well as an increased propensity for falls, all contribute to the increased fracture risk in patients with diabetes mellitus.

The prevalence of diabetes mellitus is increasing worldwide, reaching 15% in some regions, with diabetes-related complications, in particular renal and cardiovascular, imposing a tremendous burden on all health-care systems¹. As in excess of 9 million osteoporotic fractures occur annually worldwide, osteoporosis is a significant contributor to morbidity and lost life years globally, accounting for an estimated 0.83% of the global burden of noncommunicable diseases in terms of disability-adjusted life years (DALY)². The lifetime risk of an osteoporotic fracture is ~30–40% in white women and 20% in men³. The global effect of reduced BMD, including osteoporosis and also milder reductions in BMD, theoretically translates to >5 million DALY and 188,000 deaths annually⁴. Fragility fractures are increasingly recognized as an important complication of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), and are associated with excess morbidity, mortality and health-care costs⁵. Evidence from both the bench and the bedside have shown a strong interaction between glucose levels and bone metabolism, and opened-up new, unexpected scientific scenarios to explain the increased fracture risk in patients with diabetes mellitus. In this Review, we focus on the complex interactions between glucose homeostasis and bone fragility, the epidemiology of fractures in patients with diabetes mellitus and the effects of antidiabetic mediations on bone health.

Fracture risk and diabetes mellitus T1DM

Fracture risk is significantly higher in the T1DM population, as well as in patients with T2DM, than in the general population⁶. This risk is increased at all ages in both male and female individuals and increases further above that of the general population with ageing⁷. In the large prospective Nurses' Health Study⁶, the incidence of hip fractures in patients with T1DM was reported as 383 per 100,000, that is, sixfold higher than the overall incidence of hip fracture in this population (mean age 65 years) and 2.5-fold higher than in the T2DM population. A meta-analysis of five cohort studies found that T1DM is associated with an overall relative risk (RR) of 8.9 (95% CI 7.1–11.2) for hip fractures compared with an age-matched nondiabetic population⁵. The RR of hip fractures in patients with T1DM ranges from 1.7 to 12.3 (REF. 5), and increases with age, particularly after age 40 years⁷. The wide range in RR of fractures found in different studies might be explained by differences in the age of study participants, ethnicity, duration of disease, level of glucose control and diabetic complications. Fractures at the spine and proximal humerus are also moderately increased in diabetic populations^{8,9}. In one study, the prevalence of morphometric vertebral fractures was found to be higher in 30 year old patients with T1DM (24%) than in a control population (6%)¹⁰.

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doi:10.1038/nrendo.2016.153
Published online 23 Sep 2016

Key points

- Patients with type 1 diabetes mellitus or type 2 diabetes mellitus (T2DM) have an increased risk of fractures; BMD underestimates this risk in individuals with T2DM, making risk assessment challenging
- Patients with diabetes mellitus with long-term disease, poor glycaemic control, β -cell failure and who receive insulin treatment are at the highest risk of fractures
- Low bone turnover, accumulation of advanced glycation endproducts, micro and macro-architecture alterations and tissue material damage lead to abnormal biomechanical properties and impair bone strength
- Other determinants of bone fragility include inflammation, oxidative stress, adipokine alterations, WNT dysregulation and increased marrow fat
- Complications of diabetes mellitus, such as neuropathy, poor balance, sarcopenia, vision impairment and frequent hypoglycaemic events, increase the risk of falls and risk of fracture; preventive measures are advised, especially in patients taking insulin
- Use of thiazolidinediones, or some SGLT2 inhibitors might contribute to increased fracture risk; antidiabetic medications with good bone safety profiles such as metformin, GLP1 analogues or DPP4 inhibitors are preferred

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Several studies have reported an association between fracture risk and diabetic complications such as retinopathy¹¹, neuropathy¹², cerebrovascular disease¹³ and nephropathy¹².

T2DM

The risk of hip fracture, in particular, is increased in patients with T2DM^{14–16} and the risk is increased further in those treated with insulin^{6,17}, as well as in those with poor glycaemic control (that is, high levels of HbA_{1c})¹⁸, which could reflect the severity of the disease. Conversely, observational studies have shown an increased fracture risk with more frequent hypoglycaemic episodes¹⁹. Two large meta-analyses that assessed studies involving 1.3 million individuals found that patients with T2DM have a moderately increased risk of hip fractures (RR 1.7, 95% CI 1.3–2.2; and RR 1.38, 95% CI 1.25–1.53, respectively)^{5,20}. When restricting the analysis to four cohorts with >10 years of follow-up, the RR of hip fractures increased to 2.7 (95% CI 1.7–4.4)⁵. The Study of Osteoporotic Fractures (SOF)²¹ also found that a history of T2DM was the strongest independent predictor of low-energy intertrochanteric and subtrochanteric and/or diaphyseal

fractures (hazard ratio 3.25, 95% CI 1.55–6.82) in a model that included the use of bisphosphonates and total femur BMD.

Fractures of the wrist²² and the foot^{14,23} also seem to be more frequent in patients with T2DM than in healthy individuals⁵. By contrast, very little data is available regarding the risk of vertebral fractures in patients with T2DM. A study conducted in Japan found that T2DM was associated with an increased risk of vertebral fractures in women (OR 1.9, 95% CI 1.11–3.12) and men (OR 4.7; 95% CI 2.19–10.20)²⁴.

According to two different cohorts^{25,26}, the absolute rates of hip fractures (per 1000 patients) ranges from 3.0 to 4.1 in men (compared with 3.3 to 3.5 in nondiabetic controls) and from 9.1 to 13.4 in women (compared with 7.8 to 11.1 in nondiabetic controls). In elderly individuals with and without diabetes mellitus, the absolute risk of non-vertebral fractures is 15.7 in men and 51 in women, compared with 16.5 and 42.5, respectively²⁶. Among patients with hip fractures, diabetes mellitus has repeatedly been shown to be predictive of increased post-fracture mortality risk^{27–29}. Moreover, patients with diabetes mellitus and a hip fracture have been reported to have more comorbidities, a reduced health status preoperatively and more pain than patients without diabetes mellitus.

Causes of increased risk

Increased risk of falls. Diabetes mellitus is associated with the risk of hypoglycaemic events and falls¹⁹. Impaired balance, poor muscle strength^{30,31} and low ability in physical performance tests have consistently been observed in patients with diabetes mellitus and are well-known risk factors for falls³². Data from the Study of Osteoporotic Fractures (SOF) indicate an increased risk of falls in women with diabetes mellitus, which is accounted for, in part, by poorer balance in those women than in nondiabetic controls. Those individuals treated with insulin had a particularly high risk of falls compared with women without diabetes mellitus (OR 2.76, 95% CI 1.52–5.01)³⁰. Similarly, data from the Osteoporotic Fractures in Men Study shows that men using insulin report more falls than men not using insulin¹⁷.

These data can probably be explained by the fact that patients with diabetes mellitus who are treated with insulin usually have more severe disease or long-term disease with an increased risk of experiencing poor vision, peripheral neuropathy, chronic gait and/or balance impairments and subsequently falls. Not unexpectedly, patients treated with insulin are more likely to have hypoglycaemic events that increase the risk of falls than those not treated with insulin. The Health ABC (HABC) study found that poor neuronal function, high levels of cystatin C (an index of impaired renal function) and poor contrast sensitivity each increased the risk of falls in patients with T2DM³³. In particular, a linear correlation between renal function and falls has been reported³³. Impaired renal function might interfere with vitamin D metabolism, which results in reduced muscle strength and neuropathy. Factors leading to postural

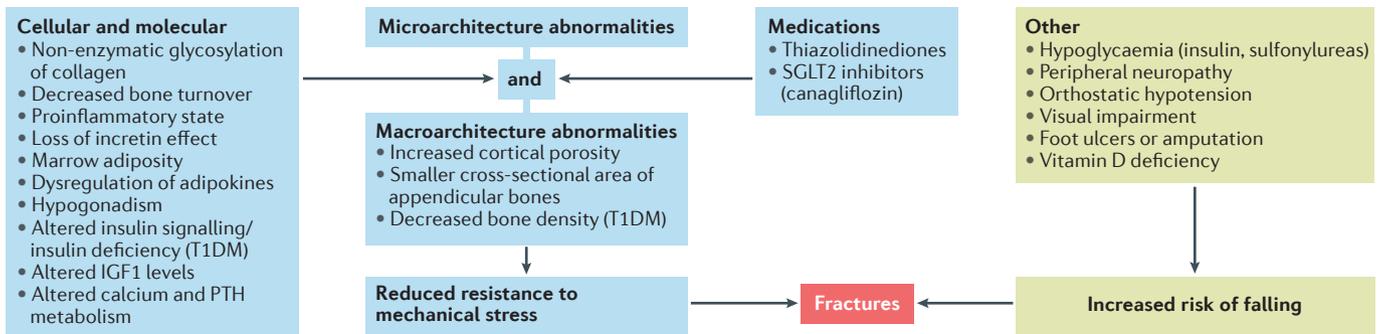


Figure 1 | Mechanisms underlying bone loss and fractures in type 2 diabetes mellitus. Multiple mechanisms can contribute to the increased fracture risk observed in diabetes mellitus. Non-enzymatic glycosylation of collagen, decreased bone turnover, a pro-inflammatory state and microvascular disease determine both micro and macro bone architecture abnormalities that cause reduced resistance to mechanical stress. Several studies have shown a different trend in terms of BMD, which is generally decreased in type 1 diabetes (T1DM) and normal or increased in type 2 diabetes mellitus (T2DM). Alterations in bone structure in T2DM include increased cortical porosity and reduced cortical density. Insulin treatment is an additional risk factor for falls and fractures, probably because of the increased rate of hypoglycaemic episodes in patients treated with insulin. The negative effect of thiazolidinediones on bone health is well known. In patients with T2DM, recent evidence suggest a potential negative effect also for some sodium/glucose cotransporter 2 (SGLT2) inhibitors. In this clinical scenario characterized by increased bone fragility, typical diabetic complications such as poor balance, diabetic retinopathy, impaired renal function and neuropathy have been associated with an increased risk of falls and fractures. All these complications have even a greater effect in patients with T1DM. IGF1, insulin-like growth factor 1; PTH, parathyroid hormone.

instability and falls³⁴, and thus contributing to fractures in patients with diabetes mellitus are shown in FIG. 1. As the focus of this Review is on bone fragility, the reader is directed elsewhere for a discussion of the association between diabetes mellitus and falls^{35,36}.

Bone fragility

Determinants of reduced bone strength

Individuals with T1DM have decreased BMD^{37–40}. The decrease in BMD is generally in the range of 22 to 37%²⁰. An association between the decreased BMD observed in patients with T1DM and the presence of a microvascular complication (retinopathy, neuropathy or nephropathy) has been documented²⁰. However no association was noted between BMD and HbA_{1c} levels in this study²⁰. Some studies have suggested that decreased BMD occurs more frequently in patients with long-term T1DM than in patients with short-term disease^{41,42}, whereas other studies have reported the presence of osteopenia at the time of diagnosis of diabetes mellitus⁴³.

Many studies have found BMD in patients with T2DM to be increased, in the range of 5 to 10% above an age-matched nondiabetic population²³; however, significant and pronounced statistical heterogeneity exists between the results of these studies⁴⁴. The increase in BMD was more pronounced in young men, in the presence of high BMI and, perhaps surprisingly, high HbA_{1c} levels. The increase in BMD is predominantly a feature of the weight-bearing skeleton but not of non-weight-bearing bone such as the forearm. However, some caveats exist regarding the increased spine BMD in patients with diabetes mellitus, as diffuse idiopathic skeletal hyperostosis is common among patients with diabetes mellitus and is found in 15% of women and 25% of men >50 years⁴⁵. By contrast, the trabecular bone score at the lumbar spine

is somewhat decreased in patients with T2DM^{46–48}. Importantly, BMD remains a significant predictor of fracture risk in T2DM, that is, independent of trabecular bone score and diabetes mellitus itself⁴⁷. Fracture risk in T2DM is, therefore, higher for a given BMD T-score and age or for a given FRAX score (a diagnostic tool for estimating the 10-year probability of bone fracture risk)²⁶. Consequently, FRAX score is only partially effective at predicting the probability of hip and non-spine fracture risk in patients with T2DM and should be adjusted accordingly. By use of quantitative ultrasound, speed of sound measurements at the radius were found to be significantly decreased in patients with T2DM compared with controls⁴⁹. Conversely, calcaneal speed of sound measurements were unchanged in patients with T2DM and prevalent vertebral fractures compared with those without vertebral fractures⁵⁰.

Bone fragility results not only from decreased bone mineral mass, but also from alterations in bone microstructure and, eventually, in the intrinsic properties of the bone material itself. A decrease in either trabecular and/or cortical volumetric BMD at the distal radius or tibia has been documented in some studies that compared patients with T1DM to nondiabetic controls^{51–56}. A smaller cross-sectional radial or tibial bone area in T1DM has been documented^{51,56,57}, together with an association between these alterations and glycaemic control^{52,54}. Using MRI, greater cortical porosity, or at least larger holes, have been found in patients with T2DM than in nondiabetic controls^{58,59}. Similarly, in small cohorts of postmenopausal women with or without T2DM, high-resolution, peripheral, quantitative CT (Xtreme CT) of the distal radius and/or tibia revealed a trend or increase in cortical porosity in those with T2DM compared with controls, particularly in those

with fractures and/or microvascular complications^{60–63}. By contrast, trabecular bone volume might be preserved or even increased in these patients⁶⁰, as this parameter could result from trabecularization of the cortex⁶⁴.

In African-American women with diabetes mellitus, cortical porosity has been reported to be 26% greater, and cortical volumetric BMD 3% lower than nondiabetic controls⁶⁵. Bone strength estimated by micro finite element analysis has been shown to be impaired in T2DM compared with controls and occurs in association with increased cortical porosity at the distal radius⁶⁰. Furthermore, in patients with T2DM and fractures, stiffness, failure load and cortical load fraction were significantly decreased at the ultradistal and distal tibia compared with patients who have T2DM without fractures; this deficit was related to the increased porosity⁶². Moreover, bone material strength at the cortical surface of the tibia (assessed by *in vivo* microindentation) was lower in patients with T2DM than in nondiabetic controls⁶¹. Although still preliminary, this observation is consistent with the alterations in collagen structure induced by diabetes mellitus⁶⁶.

Cellular and molecular mechanisms

The mechanisms underlying bone fragility in diabetes mellitus are complex and result from the interaction of several factors that only, in part, are common between T1DM and T2DM. Patients with T1DM are affected by almost complete β -cell failure and low levels of IGF1, which negatively affect the function of osteoblasts (bone-forming cells) during growth and lead to low peak bone mass at a young age⁶⁷. Conversely, T2DM impairs bone health in the later stages of the disease when lack of insulin, glucose toxicity, advanced glycation endproducts (AGEs), fat-derived factors including pro-inflammatory cytokines and adipokines, Wnt pathway inhibition and, possibly, bone microvascular disease all concur to impair the mechanostatic function of osteocytes, bone turnover and collagen properties⁶⁸.

Low bone turnover. Most published studies have suggested that bone turnover is reduced in patients with diabetes mellitus. Osteocalcin is produced by osteoblasts and is a marker of bone formation. In children with T1DM, osteocalcin levels were found to be low and negatively correlated with HbA_{1c} levels⁶⁹. Similar negative correlations between levels of HbA_{1c} and osteocalcin, but also C-terminal telopeptide of type I collagen (CTX), a marker of bone resorption, were found in a large cohort of patients with diabetes mellitus from Italy⁷⁰. Serum concentrations of both uncarboxylated and carboxylated osteocalcin were also found to be lower in patients with T2DM than in individually matched controls⁷¹. In turn, the osteocalcin to bone alkaline phosphatase (ALP; also known as TNSALP) ratio is inversely associated with the presence of vertebral fractures in men with T2DM⁷². This association was still significant after additional adjustment for lumbar or femoral neck BMD⁷². In a meta-analysis assessing levels of bone turnover markers in patients with T1DM and T2DM, osteocalcin and CTX were decreased

and ALP was increased compared with controls⁷³. Procollagen type 1 amino-terminal propeptide (P1NP), N-terminal telopeptide of type I collagen (NTX) and deoxypyridinoline also tended to be lower in patients with diabetes mellitus than in nondiabetic controls²⁰, although heterogeneity existed between the studies. Looking separately at T1DM and T2DM, osteocalcin levels have been reported to be decreased in T1DM and borderline significantly decreased in T2DM compared with nondiabetic controls⁷³. Most of the recent studies (after 2014) have confirmed decreased levels of bone turnover markers in patients with diabetic mellitus²⁰, although these results are in conflict with other evidence⁷⁴. These discrepancies might be due to differences in disease duration, metabolic status, glucose control, timing of serum collection, age, ethnicity and several other differences among study participants. Whether levels of bone markers can be used to predict BMD loss or fractures in patients with diabetes mellitus remains uncertain.

At the tissue level, decreased numbers of osteoblasts and diminished quantities of osteoid have been documented by histomorphometry in patients with T2DM⁷⁵. Decreases in mineralizing surfaces and bone formation rate have also been reported on cancellous, intracortical and endocortical surfaces in bone biopsies from patients with T2DM⁷⁶ but not from those with T1DM⁷⁷. However, a detailed analysis in 2015 of the latter bone biopsies indicated that the activation frequency of the bone remodelling units was decreased whereas the degree of bone mineralization and of non-enzymatic collagen crosslinking by pentosidine was increased and positively correlated with HbA_{1c} levels⁷⁸; this finding is consistent with a relatively low bone turnover state⁷⁸.

A few studies have suggested that a state of relative (moderate or subclinical) hypoparathyroidism could contribute to low bone turnover in patients with diabetes mellitus. Reduced serum levels of CTX and tartrate resistant acid phosphatase 5b (TRAP5b) have been found to correlate with low levels of PTH⁷⁹. Low levels of osteocalcin might be due to the low levels of PTH found in patients with diabetes mellitus as the two measurements correlate⁸⁰. Impaired PTH secretion caused by a calcium-sensing defect or secondary to chronic hypomagnesaemia has also been described in T2DM⁸¹. Furthermore, osmotic diuresis induced by glucosuria causes renal calcium leakage that can result in a negative calcium balance. Improvement of blood glucose control is associated with a reduction in urinary levels of calcium in both T1DM and T2DM⁸².

The association between microvascular disease and bone microstructure as well as with fracture risk observed in some studies suggests that an altered vascular supply to the skeleton, in particular cortical bone, could have a role in compromising bone formation.

Adipokines. The alterations in bone turnover that have been found in patients with T2DM could partly be secondary to dysregulation of adipokine levels. Adiponectin is exclusively produced by adipose tissue and low levels of adiponectin are found in patients with

T2DM⁸³. Adiponectin seems to have an anabolic effect on osteoblasts and an inhibitory effect on osteoclasts *in vitro*⁸⁴. The clinical evidence linking adiponectin to bone mass is conflicting with some studies favouring an inverse relationship^{85,86} and others not, with serum adiponectin levels positively associated with BMD at the distal radius in Japanese individuals with T2DM⁸⁷. Levels of leptin, another adipokine produced by white adipose tissue as well as by bone marrow adipocytes and osteoblastic cells, have been shown to be lower in patients with diabetes mellitus than in nondiabetic controls. A significant negative correlation between serum levels of leptin and urinary NTX (a marker of bone resorption) has been found in Japanese individuals with T2DM; a significant positive correlation between serum levels of leptin and Z-scores at the distal radius but not at the femoral neck or the lumbar spine was noted in these patients⁸⁷. These results suggest a differential effect of this adipokine on cancellous versus cortical bone⁸⁸. Further research is needed to confirm these associations.

Sclerostin. One of the key, yet unresolved questions about the low bone formation rate and potentially decreased bone quality in patients with diabetes mellitus, is if osteocytes, the most abundant bone cell type orchestrating bone modelling and remodelling, have altered functions and/or survival in diabetes mellitus. If so, then both the bone biomechanical response to loading, which is normally elevated in overweight individuals such as many of those with T2DM, and the capacity to repair microcracks (that is, the initiators of fractures) would be impaired. Indeed, osteocyte alterations in diabetes mellitus have been suggested by some investigators. In a rat model of T2DM, expression of sclerostin (encoded by *SOST*)⁷⁸ and dickkopf-related protein 1 (DKK1), two major inhibitors of bone formation via inhibition of Wnt- β -catenin signalling, were increased in bone⁸⁹. Sclerostin levels were also found to be higher in patients with T2DM than in healthy individuals⁹⁰ and this increase was associated with a decrease in levels of other markers of bone formation such as β -catenin⁹¹, further suggesting that the notion of sclerostin inhibiting bone turnover in diabetic states is plausible.

The usual transcriptional suppression of sclerostin production by PTH observed in nondiabetic individuals might be impaired in patients with either T1DM or T2DM. This postulation is substantiated by the usual negative association between sclerostin and PTH levels observed in nondiabetic individuals but not in those with diabetes mellitus⁹⁰. The increased circulating levels of sclerostin found in patients with T2DM have been shown to be associated with vertebral fractures in postmenopausal women with T2DM⁹². These women with prior fractures have significantly thinner bone cortices, a trend towards larger volumetric bone density on quantitative CT and higher serum levels of sclerostin than diabetic women without fractures and nondiabetic controls with fractures (increases of 31.4% and 25.2%, respectively)⁹³. This finding suggests that volumetric

bone parameters measured by quantitative CT as well as serum levels of sclerostin can identify individuals with T2DM at high risk of fracture. These markers might, thus, be promising clinical tools for fracture risk assessment in patients with T2DM.

AGEs and hyperglycaemia. Levels of AGEs are increased in patients with diabetes mellitus as a result of hyperglycaemia and increased levels of oxidative stress⁹⁴, and might have a pivotal role in the development of bone fragility in these individuals. Activation of the receptor for AGEs (RAGE) expressed in human bone-derived cells can enhance inflammatory cytokine and reactive oxygen species (ROS) production, which results in a vicious cycle of chronic inflammation and bone resorption⁹⁵. Accumulation of AGEs in bone is also negatively associated with bone material properties and abnormal biomechanical properties of both cortical and cancellous bone⁹⁶. In contrast to normal enzymatic crosslinking in collagen, AGE crosslinking leads to more brittle bones that are less able to deform before fracturing⁹⁷. Pentosidine is the best studied AGEs to date. Bones of diabetic rats with a high content of pentosidine show impaired biomechanical properties on three point bending compared with nondiabetic control rats⁹⁸. Higher serum levels of pentosidine, AGEs and soluble RAGE have been found in patients with diabetes mellitus than in nondiabetic controls⁹⁹. The pentosidine content of cortical and trabecular bone derived from patients with a femoral neck fracture is higher than those of age-matched controls¹⁰⁰. Pentosidine, measured in urine, is associated with an increase in clinical and vertebral fracture risk in patients with T2DM¹⁰¹ and, when measured in serum, with an increase in the prevalence of vertebral fractures^{101,102}. AGEs might also contribute to reduced bone formation by inhibiting the synthesis of type I collagen and osteocalcin, mature nodule formation in osteoblasts and mineralization of osteoblasts^{66,103–105}. AGEs might also interfere with osteoblast development¹⁰⁶, function¹⁰⁷ and attachment of osteoblasts to the collagen matrix¹⁰⁸. Endogenous secretory RAGE (esRAGE) acts as a decoy receptor that binds and neutralizes AGEs¹⁰⁹. The esRAGE to pentosidine ratio in men and women with T2DM and vertebral fractures is lower than that in those without vertebral fractures¹¹⁰.

In vitro studies have shown a direct negative effect of hyperglycaemia on osteoblasts¹¹¹. Acute hyperglycaemia and its associated hyperosmolality suppress expression of osteocalcin¹¹² and other genes involved in osteoblast maturation¹¹³; chronic hyperglycaemia downregulates expression of the osteocalcin gene (*BGLAP*)¹¹⁴ and uptake of calcium by osteoblasts in culture¹¹⁵. Hyperglycaemia-induced acidosis might also enhance bone resorption¹¹⁶. Hyperglycaemia and oxidative stress might influence mesenchymal stem cell differentiation with adipogenesis being favoured over bone formation. This shift to an adipogenic lineage is mediated through the production of ROS¹¹⁷. Although these results imply that hyperglycaemia has a deleterious effect on bone either directly or indirectly through the production of AGEs, the clinical effect of poor glycaemic control

on the incidence of fractures in patients with diabetes mellitus is still being debated; so far, only observational studies have explored this possibility. Poor glycaemic control was associated with an increased risk of fractures in individuals with diabetes mellitus in the Rotterdam cohort¹¹⁸, in the Atherosclerosis Risk in Communities (ARC) study and in a study conducted in Taiwan¹⁸. These observational studies, in general, suggest that a target HbA_{1c} level of <8% could reduce fracture risk in patients with diabetes mellitus.

Insulin, IGF1 and amylin. Evidence from *in vivo* and *in vitro* studies have shown that insulin exerts a bone anabolic effect¹¹⁹. The detrimental effect of insulin deficiency on bone homeostasis has been substantiated by studies using animal models of T1DM. Diabetic rodents were found to have impaired bone formation following bone injury compared with nondiabetic controls¹²⁰. Infusion of insulin into the distraction gap normalized bone formation in these rodents¹²⁰. Elegant studies have clarified a complex mechanism of action through which insulin regulates bone turnover. Conditional deletion of the gene encoding insulin-like growth factor 1 receptor (IGF1R) in osteoblasts demonstrated that insulin exerts direct anabolic actions in osteoblasts by activation of its cognate receptor and that the strength of insulin-generated signals is tempered through interactions with IGF1R¹²¹.

Insulin-deficient conditions such as T1DM are typically characterized by low levels and/or action of IGF1. Dysregulation of IGFs is possibly linked to the pathogenesis of diabetes mellitus-related bone fragility. Several *in vivo* studies have shown that the stimulatory actions of IGF1 on osteoblasts are blunted by high concentrations of AGEs and that high glucose concentrations or AGEs might induce osteoblast resistance to the actions of IGF1 (REFS 122, 123). Serum levels of IGF1 were found to be inversely associated with the presence of vertebral fractures in postmenopausal women with T2DM independent of age, diabetes mellitus control, renal function, insulin secretion or lumbar spine BMD, and with the number of prevalent vertebral fractures in these women independent of lumbar spine BMD¹²⁴. Co-secreted with insulin, amylin is deficient in T1DM⁶⁸. In the skeleton, amylin might stimulate osteoblast proliferation and high serum levels of this factor have been shown to correlate with high bone mass¹²⁵. Conflicting results have been obtained from studies exploring the osteogenic effect of amylin in experimental models of diabetes mellitus⁶⁸. Further studies are, therefore, needed to confirm the role of amylin in bone metabolism in diabetes mellitus.

Although relative insulin deficiency occurs in the later stages of T2DM, the predominant defect in this condition is insulin resistance. How insulin resistance affects bone is unclear. Skeletal loading might be compromised due to decreased muscle strength secondary to decreased glucose uptake by muscles; however, this postulate remains to be confirmed.

Pro-inflammatory cytokines. Diabetes mellitus is often referred to as a state of accelerated ageing and pro-inflammatory cytokines have been implicated in the

development of both T1DM and T2DM and also in the development of microvascular and macrovascular complications of both disease types. Pro-inflammatory cytokines could also have a role in diabetic bone disease. Elevated cytokine levels can activate osteoclastogenesis and suppress osteoblast differentiation^{126,127}. Levels of TNF and IL-6 have been shown to be increased in patients with obesity and diabetes mellitus. TNF has also been shown to stimulate osteoclastogenesis¹²⁷ and inhibit osteoblastogenesis¹²⁶. Exposure of tissues to inflammatory cytokines such as IL-1, IL-6 and TNF, which are released in hyperglycaemic states, results in the production of ROS that directly affect differentiation and survival of osteoclasts, osteoblasts and osteocytes¹²⁸. Whether the bone loss and increased fracture risk observed in diabetes mellitus has a firm inflammatory basis needs to be determined through further studies.

Marrow adiposity. Adipogenesis is under the master control of PPAR γ ⁶⁸. Accumulation of lipids in bone marrow and increases in PPAR γ 2 expression has been found in ageing bone¹²⁹. Free fatty acids released by adipocytes in bone marrow generate ROS, which inhibit osteoblast proliferation and function, and induce osteoblast apoptosis¹³⁰. An inverse association between marrow adipose tissue (MAT) and BMD has been noted in overweight, postmenopausal women with T2DM¹³¹. Women with diabetes mellitus and HbA_{1c} levels >7% have significantly higher levels of MAT than those with levels \leq 7%, which suggests that in T2DM, MAT might influence or be influenced by glycaemic control¹³². The functional significance of MAT and its implications for the structural integrity of the skeleton in diabetes mellitus remains to be elucidated. The relationship between MAT and other fat depots, including subcutaneous and visceral fat stores, as well as the hormonal determinants of MAT also need to be studied.

Brown/beige fat. The presence of thermogenically active brown adipose tissue has been found to be inversely associated with obesity and T2DM¹³³. Brown adipose tissue secretes factors such as insulin-like growth factor-binding protein 2 and Wnt10b, which are anabolic to bone and induce osteoblast activity¹³⁴. The finding of promotion of browning of adipocytes via inactivation of TGF β -SMAD3-myostatin signalling¹³⁵ might contribute to the development of a novel class of TGF β -myostatin antagonists that could be used to treat obesity and, potentially, the low bone turnover associated with diabetes mellitus.

Loss of incretin effect. Gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP1) are two hormones (called incretins) secreted by the gut (GIP in the jejunum and GLP1 in distal ileum) that are responsible for the 'incretin effect'. Patients with T2DM have a reduced incretin effect with impaired GLP1 production after a meal¹³⁶. Receptors for GLP1 are expressed on bone marrow stromal cells and immature osteoblasts¹³⁷. GLP1 has been shown to stimulate proliferation of

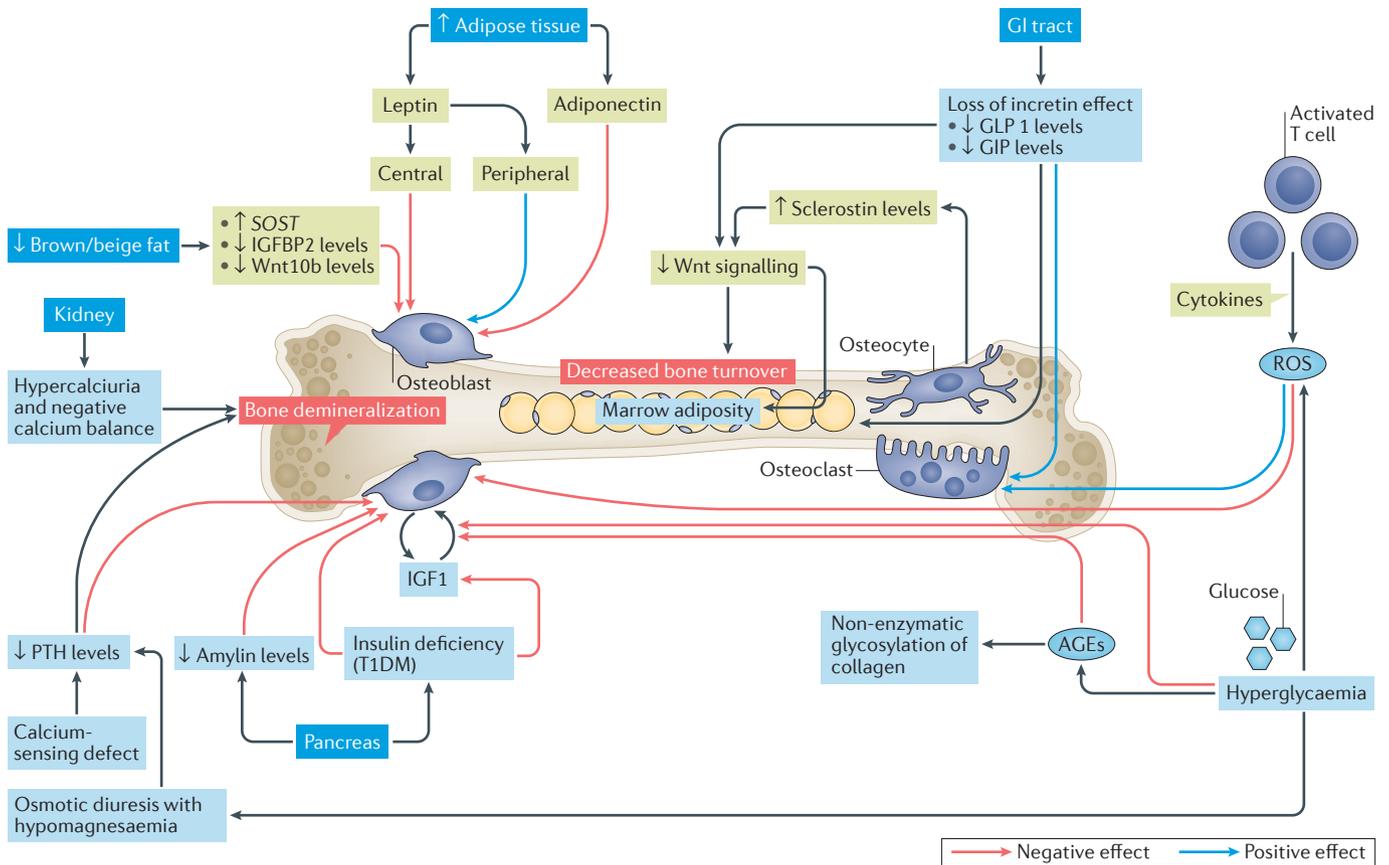


Figure 2 | Cellular and molecular mechanisms of bone diseases in diabetes mellitus. Although several reports consistently indicate an increased risk of fractures in patients with diabetes mellitus, the underlying mechanisms are unclear and there is not enough evidence for a conclusive model of bone fragility in diabetes mellitus; however, some factors should be highly considered. With the decline of β -cell function, chronic hyperglycaemia causes oxidative stress, inflammation, the production of reactive oxygen species (ROS) and advanced glycation end products (AGEs), causing organ damage and reduced bone strength. In particular, accumulation of reactive bone collagen determines reduced material properties and increased susceptibility to fracture. AGEs and hyperglycaemia also directly inhibit bone formation via suppression of osteoblast function. Low bone formation is also caused by disturbances to the WNT signalling pathway, with increased *SOST* expression, higher sclerostin levels and decreased levels of insulin-like growth factor-binding protein 2 (IGFBP2) and protein Wnt10b (Wnt10b). In type 1 diabetes mellitus (T1DM) and in the late stages of type 2 diabetes mellitus (T2DM), bone formation is also decreased by insulin deficiency through an inhibitory effect on osteoblasts, either directly or through alterations in insulin-like growth factor 1 (IGF1) levels. Other factors typically linked to T2DM and obesity interfere with bone health. Dysregulation of adipokines like adiponectin and leptin have a negative effect through complex central and peripheral mechanisms. New evidence also indicates a negative effect on bone health by loss of the incretin effect, with reduced bone formation and increased osteoclastogenesis. Finally, alterations of the calcium–parathyroid hormone (PTH) axis result in a negative calcium balance, thereby contributing to bone demineralization in diabetes mellitus. GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP1, glucagon-like peptide 1.

mesenchymal stem cells and inhibit their differentiation into adipocytes¹³⁸. Indirect evidence of the osteogenic effect of GLP1 comes from use of GLP1 analogues in animal models. This effect seems to be mediated through a positive interaction with the Wnt pathway¹³⁷ and suppression of *SOST* expression¹³⁹. Increasing doses of exendin-4, a GLP1 mimetic, have been tested in rodents, showing a proportional increase in BMD, bone strength and bone formation¹⁴⁰. The role of endogenous incretins in diabetic bone health merits further study. The cellular and molecular mechanisms underlying bone fragility in diabetes mellitus are shown in FIG. 2.

Effectors of bone metabolism

Antidiabetic drugs and glucose control

Achieving good glucose control is the target of any anti-diabetic treatment and is crucial to reduce the risk of complications. Data from the UKPDS study¹⁴¹ showed that increasing HbA_{1c} levels are associated with a higher risk of microvascular complications: a 37% reduction in microvascular endpoints per 1% reduction in HbA_{1c} levels has been described¹⁴¹. Considering the relationship between HbA_{1c} levels, microvascular disease and bone fragility, optimal glucose control should, logically, also decrease fracture risk. Observational studies have found that patients with poor glycaemic control

have an increased risk of fractures^{18,118,142}. For example, the Rotterdam study reported a 62% higher risk of fracture in patients with T2DM and HbA_{1c} ≥7.5% than in those with HbA_{1c} levels <7.5%¹¹⁸. The ACCORD trial showed that patients receiving intensive glucose control (median HbA_{1c} level 6.4%) did not have a higher risk of fractures or falls than those receiving standard treatment (median HbA_{1c} level 7.5%), which suggests that lowering HbA_{1c} levels below ~7.5% does not contribute substantially to fracture prevention¹⁴³.

The most recent guidelines from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD)¹⁴⁴ indicate that lifestyle modification is the first-line treatment for patients with diabetes mellitus. Data from elderly individuals with obesity show that when weight loss is associated with physical activity, improvements in muscle strength, balance and gait are observed¹⁴⁵. During weight loss, exercise is also crucial to prevent bone loss and the increases in bone resorption¹⁴⁶ and sclerostin levels¹⁴⁷ that are observed in those treated with diet alone. The effects of antidiabetic medications on bone metabolism have been reviewed in detail elsewhere¹⁴⁸. We now briefly describe the available evidence on the effects of antidiabetic medications on bone health (TABLES 1,2).

Insulin. Several studies have reported an increase in the number of fractures among patients with T2DM who were treated with insulin¹⁴⁹. However, these data should be interpreted with caution, as patients on insulin usually have long-term disease and suffer from complications (microvascular disease and/or peripheral neuropathy) that might impair both bone quality and individual balance, and increase the risk of falling. Findings from the HABC study showed an increased risk of falls in insulin-treated patients if their HbA_{1c} levels were ≤6%³³. A more aggressive therapeutic approach in elderly individuals might increase the rate of hypoglycaemic events and in turn the risk of falls and fractures³³.

Metformin. Metformin is a first-line agent used to treat diabetes mellitus. Preclinical data suggest a positive¹⁵⁰ or a neutral¹⁴⁸ effect on bone metabolism. Similarly,

most clinical evidence has shown a positive or neutral effect of metformin on BMD and fracture risk in different, large cohorts^{8,17,151}.

Sulfonylureas. These medications are characterized by a substantially neutral effect on levels of markers of bone metabolism; however, their clinical effect has not been clearly established, as longitudinal studies on fracture risk during sulfonylurea treatment have yielded contrasting findings¹⁷. Considering the high rate of hypoglycaemic events associated with these medications¹⁵², their use should generally be avoided in patients at risk of bone fragility.

Thiazolidinediones. Thiazolidinediones (commonly know as TZDs) activate peroxisome proliferator-activated receptors (PPARs), with greatest specificity for PPAR γ . Several studies have investigated the effect of thiazolidinediones on bone metabolism, both *in vivo* and *in vitro*, identifying increased adipogenesis and impaired osteoblastogenesis¹⁵³. A comprehensive meta-analysis of 10 randomized controlled trials (total 13,715 participants) and two observational studies (total 31,679 participants) confirmed an increased risk of fractures (OR 2.23, 95% CI 1.65–3.01) in women treated with pioglitazone or rosiglitazone¹⁵⁴. According to this meta-analysis, men with diabetes mellitus are not at increased risk of fragility fractures with thiazolidinedione use (OR 1.0, 95% CI 0.73–1.39)¹⁵⁴. Subgroup analysis of the same data confirmed the negative effect of rosiglitazone on bone health (HR 1.64, 95% CI 1.24–2.17), whereas pioglitazone-treated patients were not at increased fracture risk (OR 1.26, 95% CI 0.92–1.71)¹⁵⁵. However, a subsequent meta-analysis, including 22 randomized clinical trials, found that both pioglitazone and rosiglitazone were associated with increased fracture risk in women¹⁵⁶. Use of these medications should, therefore, be avoided in postmenopausal women.

Incretin-based treatments. A 2013 study found a favourable effect of the GLP1 analogue exendin on different bone parameters in ovariectomized rats¹⁴⁰. However,

Table 1 | Effects of hypoglycaemic agents on bone metabolism

Agent	Animal <i>In vitro</i>		Animal <i>In vivo</i>		Human <i>In vitro</i>	
	Bone formation	Bone resorption	Bone formation	Bone resorption	Bone formation	Bone resorption
Metformin	↑↑/=	↓	↑	↓	=/↓	=/↓
Sulfonylureas	↑	ND	ND	ND	ND	ND
Thiazolidinediones	↓↓↓	↑↑	↓↓↓	↑↑	↓	↑
Incretin (GLP1 analogue)	↑	↓	↑	↓	↑	ND
Incretin (DPP4 inhibitor)	↓/=	=	↓/=↑	=	↓/=	ND
SGLT2 inhibitor	ND	ND	=	=	ND	ND
Insulin	↑	=	↑	=	ND	ND

↑ Increased. ↓Decreased. = Unchanged. DPP4, dipeptidyl peptidase inhibitor 4; GLP1, glucagon-like peptide 1; ND, not determined; SGLT2, sodium/glucose cotransporter 2. Adapted with permission of Springer © Palermo, A. et al. *Osteoporos. Int.* 26, 2073–2089 (2015).

Table 2 | Effects of hypoglycaemic agents on fracture risk in T2DM

Agent	Bone biomarkers		BMD	Fracture
	Bone formation	Bone resorption		
Metformin	↓/=	↓/=	=/↑	↓/=
Sulfonylureas	↑/=	↓/=	ND	↓/=↑
Thiazolidinediones	↓↓/=↑	↑↑/=	↓↓/=	↑↑/=
Incretin (GLP1 analogue)	=	↓↓*	↑/=	=
Incretin (DPP4 inhibitor)	↓/=	=	--	↓/=
SGLT2 inhibitor	=	=/↑	=	=/↑
Insulin	=	=	=	↑

↑ Increased. ↓ Decreased. = Unchanged. DPP4, dipeptidyl peptidase inhibitor 4; GLP1, glucagon-like peptide 1; GLP2, glucagon-like peptide 2; ND, not determined; SGLT2, sodium/glucose cotransporter 2; T2DM, type 2 diabetes mellitus. *GLP2 administration. Adapted with permission of Springer © Palermo, A. et al. *Osteoporos. Int.* 26, 2073–2089 (2015).

these findings have not yet been confirmed in humans and available data are inconclusive. A meta-analysis of clinical trials, with fractures reported as serious adverse events, found no effect of treatment but confidence intervals were wide¹⁵⁷. A later meta-analysis (2015), also using adverse event reports from clinical trials, found differing effects of GLP1 analogues on fracture risk, identifying a protective effect of liraglutide and a negative effect of exenatide¹⁵⁸. Considering that none of the considered studies were designed for bone outcomes and that the studies differed in power and design, the clinical relevance of these meta-analyses is limited. Similarly, clinical evidence is lacking for DPP4 inhibitors. Although a meta-analysis from has shown a protective effect of these medications on fracture prevention¹⁵⁹, an analysis of the SAVOR-TIMI trial of saxagliptin, with fractures reported as ‘adverse events of interest’, found no effect of treatment on fracture risk¹⁶⁰. Further studies are needed to confirm the potential favourable effect of these agents shown in preclinical studies and clinical trials.

SGLT2 inhibitors. Sodium/glucose co-transporter 2 (SGLT2) inhibitors are new generation antidiabetic medications that inhibit the reabsorption of glucose in the proximal tubule of the kidney¹⁶¹. Dapagliflozin and empagliflozin seem to have a neutral effect on bone metabolism, with no significant changes in bone turnover or BMD parameters¹⁶². Concerns have been raised for canagliflozin, which might cause bone loss at the hip^{163,164} and increase the risk of hip fractures¹⁶⁴. More studies are needed to identify a possible class effect and the reasons for the discrepancies in safety profile among these medications.

Conclusions

Peripheral, and to a lesser extent vertebral, fracture risk is now well-acknowledged to be increased in patients with diabetes mellitus, although much more prominently in those with T1DM than in those with T2DM. Patients with T2DM have a higher risk of fractures for a given BMD than the nondiabetic population, and an

increased fracture rate compared with their estimated probability (by tools such as FRAX), which pertains to their relatively increased BMD and BMI. In addition, levels of bone turnover markers seem to be relatively low in patients with diabetes mellitus. These features present clinical challenges on how to identify patients with T2DM at high fracture risk. By contrast, T1DM is characterized throughout its history by low levels of endogenous insulin and IGF1, which might largely explain the low BMD and much higher hip fracture risk in these patients.

Data from UKPDS show that the longer the duration of diabetes mellitus, the higher the risk of diabetic complications¹⁶⁵⁻¹⁶⁷. This is also probably true for bone health in this population. As reported in large cohort studies, after diagnosis, β-cell function declines progressively¹⁶⁶ and glucose control deteriorates^{167,168}, which results in oxidative stress, inflammation and the production of ROS and AGEs, which causes organ damage and increases the risk of complications¹⁶⁹. Bone collagen and mineralization, microstructure and, ultimately, bone strength also become compromised by these processes. Obesity¹⁷⁰, bone marrow fat¹⁷¹, and altered production of other metabolic modulators^{172,173} contribute as well to impaired bone health in these patients. To compensate for the advanced β-cell loss, patients usually receive combined treatments starting with insulin. However, insulin use has also been associated with an increased risk of fractures¹⁷; whether insulin use is a marker of the severity and/or duration of the disease, or possibly the occurrence of hypoglycaemic events that precipitate falls, is uncertain. For this reason, a careful therapeutic approach is recommended in patients with diabetes mellitus and bone fragility, as has been advised for other complications. Consequently, lifestyle intervention in patients with diabetes mellitus should always include physical exercise programs to balance the negative effects of weight loss on bone mass. Medications with a neutral or favourable effect on bone metabolism, such as metformin and incretin-based treatments, should be the preferred treatment. By contrast, medications like thiazolidinediones should be used with caution; further studies are needed on SGLT2 inhibitors.

Currently, no guidelines exist on how and at which stage of the disease to initiate anti-osteoporotic medication in patients with diabetes mellitus. Current evidence, based on BMD responses in subgroups of patients with osteoporosis and diabetes mellitus enrolled in osteoporosis fracture trials, support the use of both anti-resorptive and anabolic agents such as teriparatide in these patients. By contrast, no evidence exists, so far, that any osteoporosis drug has anti-fracture efficacy in patients with diabetes mellitus who are at high risk of fractures despite having non-osteoporotic BMD levels. The ongoing development of new osteoporosis drugs, such as sclerostin antibodies, that specifically improve osteocyte functions, cortical bone microstructure and bone stiffness, might provide new opportunities to test their ability to also improve bone strength specifically in patients in diabetes mellitus.

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Acknowledgements

The authors acknowledge the support of the other members of the CSA IOF Bone and Diabetes Working Group: K. Akesson, M. S. M. Ardawi, C. Cooper, R. Eastell, G. El Hajj Fuleihan, S. Hough, R. Josse, D. Kendler, M. Kraenzlin, W. Leslie, M. Massi Benedetti, A. Mithal and A. Suzuki.

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N.N. and D.D.P. researched data for the article. N.N., M.C., B.A., A.V.S. and S.L.F. made substantial contributions to discussions of the content. N.N., M.C., B.A., A.V.S. and S.L.F. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests statement

N.N. has served as a consultant for Amgen and Takeda. A.V.S. is a consultant for Amgen and Jansen. The other authors declare no competing interests.