Mechanisms of diabetes mellitus-induced bone fragility

Nicola Napoli[1–3], Manju Chandran[4], Dominique D. Pierroz[5], Bo Abrahamsen[6], Ann V. Schwartz[7] and Serge L. Ferrari[8]

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 systems[1]. 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 men[3]. The global effect of reduced BMD, including osteoporosis and also milder reductions in BMD, theoretically translates to >5 million DALY and 188,000 deaths annually[4]. 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 costs[5]. 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.

Corresponence to N. N.
n.napoli@unicampus.it

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

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 population[6]. This risk is increased at all ages in both male and female individuals and increases further above that of the general population with ageing[7]. In the large prospective Nurses' Health Study[6], 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 population[5]. 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 years[7]. 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].

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, GLP1analogues or DPP4 inhibitors are preferred

Author addresses

On behalf of the IOF Bone and Diabetes Working Group
[1]Unit of Endocrinology and Diabetes, Department of Medicine, Università Campus Bio-Medico di Roma, Via Alvaro di Portillo 21, 00128 Roma, Italy.
[2]Division of Bone and Mineral Diseases, Washington University in St Louis, St Louis, Missouri, USA.
[3]Diabetes and Bone Network.
[4]Osteoporosis and Bone Metabolism Unit, Department of Endocrinology, Singapore General Hospital, Outram Road, 169608 Singapore.
[5]International Osteoporosis Foundation (IOF), Rue Juste-Olivier 9, 1260 Nyon, Switzerland.
[6]University of Southern Denmark, Department of Medicine, Faculty of Health, Holbaek Hospital, Holbaek, Denmark.
[7]Department of Epidemiology and Biostatistics, University of California, 550 16th Street, San Francisco, California 94158, USA.
[8]Service of Bone Diseases, Geneva University Hospital and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland,

Several studies have reported an association between fracture risk and diabetic complications such as retinopathy[11], neuropathy[12], cerebrovascular disease[13] and nephropathy[12].

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 episodes[19]. 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 wrist[22] and the foot[14,23] also seem to be more frequent in patients with T2DM than in healthy individuals[5]. 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, respectively[26]. 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 falls[19]. 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 falls[32]. Data from the Study of Osteoporotic Fractures (S OF) 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 insulin[17].

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 T2DM[33]. In particular, a linear correlation between renal function and falls has been reported[33]. Impaired renal function might interfere with vitamin D metabolism, which results in reduced muscle strength and neuropathy. Factors leading to postural

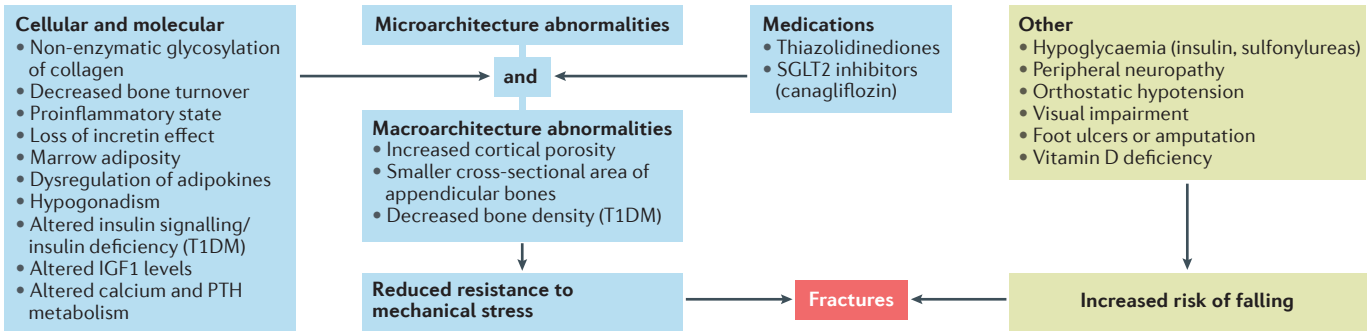

Figure 1 | **Mechanisms underlying bone loss and fractures in type 2diabetes mellitus.** Multiple mechanisms can contribute to the increased fracture risk observed in diabetes mellitus. Non-enzymatic glycosylation of collagen, decreased bone turnover, a pro-inflammatory state and microvascular disease 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 falls[34], 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 documented[20]. However no association was noted between BMD and HbA_{1c} levels in this study[20]. 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 mellitus[43].

Many studies have found BMD in patients with T2DM to be increased, in the range of 5 to 10% above an age-matched nondiabetic population[23]; however, significant and pronounced statistical heterogeneity exists between the results of these studies[44]. 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 years[45]. 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 itself[47]. 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 controls[49]. Conversely, calcaneal speed of sound measurements were unchanged in patients with T2DM and prevalent vertebral fractures compared with those without vertebral fractures[50].

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 patients[60], as this parameter could result from trabecularization of the cortex[64].

In African-American women with diabetes mellitus, cortical porosity has been reported to be 26% greater, and cortical volumetric BMD 3% lower than non-diabetic controls[65]. 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 radius[60]. 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 porosity[62]. 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 controls[61]. Although still preliminary, this observation is consistent with the alterations in collagen structure induced by diabetes mellitus[66].

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 age[67]. 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 properties[68].

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} levels[69]. 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 Italy[70]. Serum concentrations of both uncarboxylated and carboxylated osteocalcin were also found to be lower in patients with T2DM than in individually matched controls[71]. 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 T2DM[72]. This association was still significant after additional adjustment for lumbar or femoral neck BMD[72]. 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 controls[73]. 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 controls[20], 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 controls[73]. Most of the recent studies (after 2014) have confirmed decreased levels of bone turnover markers in patients with diabetic mellitus[20], although these results are in conflict with other evidence[74]. 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 T2DM[75]. Decreases in mineralizing surfaces and bone formation rate have also been reported on cancellous, intracortical and endocortical surfaces in bone biopsies from patients with T2DM[76] but not from those with T1DM[77]. 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} levels[78]; this finding is consistent with a relatively low bone turnover state[78].

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 PTH[79]. Low levels of osteocalcin might be due to the low levels of PTH found in patients with diabetes mellitus as the two measurements correlate[80]. Impaired PTH secretion caused by a calcium-sensing defect or secondary to chronic hypomagnesaemia has also been described in T2DM[81]. 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 T2DM[82].

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

T2DM[83]. 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 T2DM[87]. 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 patients[87]. These results suggest a differential effect of this adipokine on cancellous versus cortical bone[88]. 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, osteocytes 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 bone[89]. Sclerostin levels were also found to be higher in patients with T2DM than in healthy individuals[90] and this increase was associated with a decrease in levels of other markers of bone formation such as β-catenin[91], 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 mellitus[90]. The increased circulating levels of sclerostin found in patients with T2DM have been shown to be associated with vertebral fractures in postmenopausal women with T2DM[92]. 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 stress[94], 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 resorption[95]. Accumulation of AGEs in bone is also negatively associated with bone material properties and abnormal biomechanical properties of both cortical and cancellous bone[96]. In contrast to normal enzymatic crosslinking in collagen, AGE crosslinking leads to more brittle bones that are less able to deform before fracturing[97]. 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 rats[98]. Higher serum levels of pentosidine, AGEs and soluble RAGE have been found in patients with diabetes mellitus than in nondiabetic controls[99]. The pentosidine content of cortical and trabecular bone derived from patients with a femoral neck fracture is higher than those of age-matched controls[100]. Pentosidine, measured in urine, is associated with an increase in clinical and vertebral fracture risk in patients with T2DM[101] 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 1 collagen and osteocalcin, mature nodule formation in osteoblasts and mineralization of osteoblasts[66,103–105]. AGEs might also interfere with osteoblast development[106], function[107] and attachment of osteoblasts to the collagen matrix[108]. Endogenous secretory RAGE (esRAGE) acts as a decoy receptor that binds and neutralizes AGEs[109]. The esRAGE to pentosidine ratio in men and women with T2DM and vertebral fractures is lower than that in those without vertebral fratcures[110].

In vitro studies have shown a direct negative effect of hyperglycaemia on osteoblasts[111]. Acute hyperglycaemia and its associated hyperosmolality suppress expression of osteocalcin[112] and other genes involved in osteoblast maturation[113]; chronic hyperglyceamia downregulates expression of the osteocalcin gene (*BGLAP*)[114] and uptake of calcium by osteoblasts in culture[115]. Hyerglycaemia-induced acidosis might also enhance bone resorption[116]. 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 ROS[117]. 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 cohort[118], in the Atherosclerosis Risk in Communities (ARC) study and in a study conducted in Taiwan[18]. 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 effect[119]. 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 controls[120]. Infusion of insulin into the distraction gap normalized bone formation in these rodents[120]. 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 (IGFR1) 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 IGF1R[121].

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 BMD[124]. Co-secreted with insulin, amylin is deficient in T1DM[68]. In the skeleton, amylin might stimulate osteoblast proliferation and high serum levels of this factor have been shown to correlate with high bone mass[125]. Conflicting results have been obtained from studies exploring the osteogenic effect of amylin in experimental models of diabetes mellitus[68]. 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 osteoclastogenesis[127] and inhibit osteoblastogenesis[126]. 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 osteocytes[128]. 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 PPARγ[68]. Accumulation of lipids in bone marrow and increases in PPARγ2 expression has been found in ageing bone[129]. Free fatty acids released by adipocytes in bone marrow generate ROS, which inhibit osteoblast proliferation and function, and induce osteoblast apoptosis[130]. An inverse association between marrow adipose tissue (MAT) and BMD has been noted in overweight, postmenopausal women with T2DM[131]. Women with diabetes mellitus and HbA_{1c} levels >7% have significantly higher levels of MAT than those with levels ≤7%, which suggests that in T2DM, MAT might influence or be influenced by glycaemic control[132]. 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 T2DM[133]. Brown adipose tissue secretes factors such as insulin-like growth factor-binding protein 2 and Wnt10b, which are anabolic to bone and induce osteoblast activity[134]. The finding of promotion of browning of adipocytes via inactivation of TGFβ–SMAD3–myostatin signalling[135] might contribute to the development of a novel class of TGFβ–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 meal[136]. Receptors for GLP1 are expressed on bone marrow stromal cells and immature osteoblasts[137]. GLP1 has been shown to stimulate proliferation of

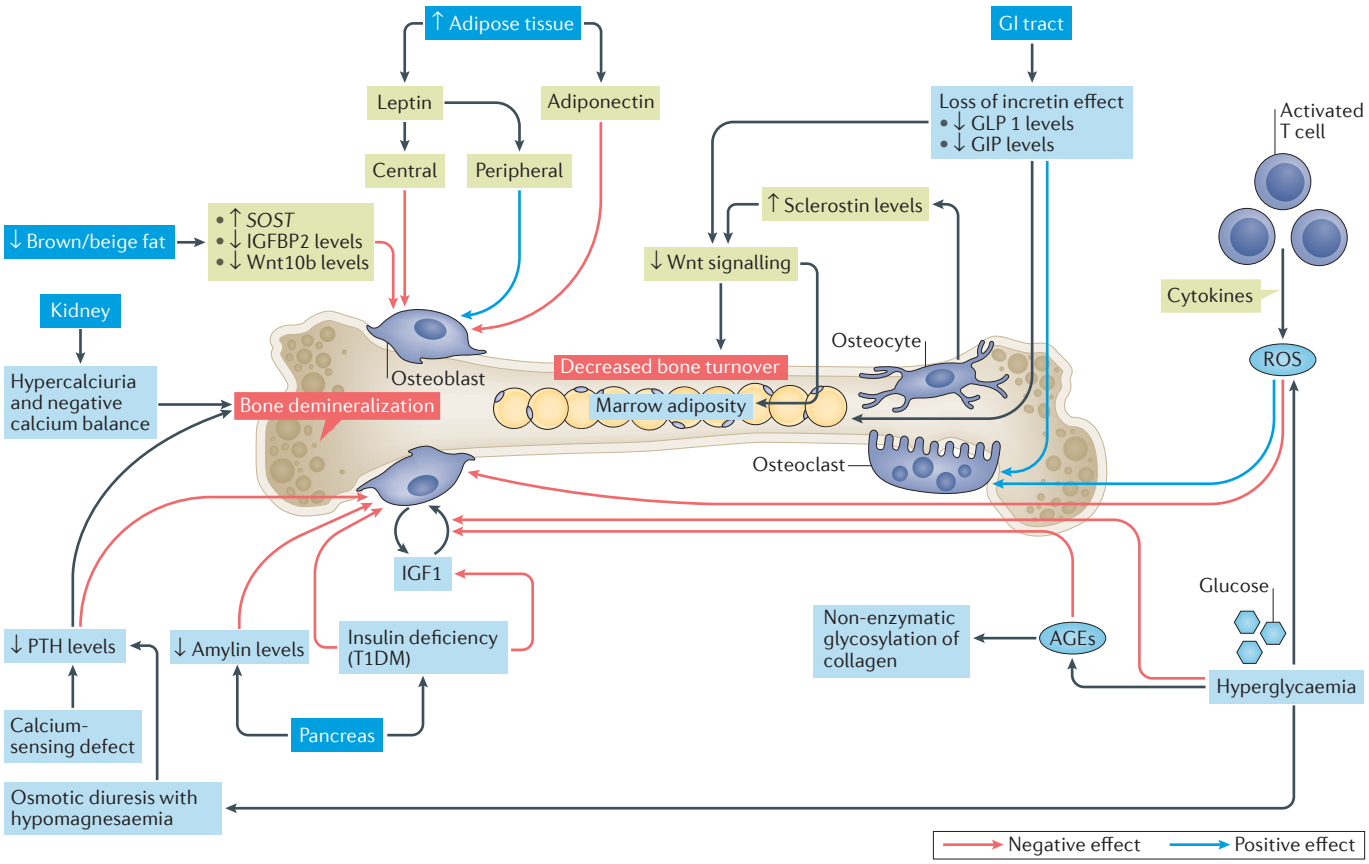

Figure 2 | **Cellular and molecular mechanisms of bone diseases in diabetes mellitus.** Although several reports consistently indicate an increased risk of fractures in patients with diabetes mellitus, the underlying mechanisms are unclear and there is not enough evidence for a conclusive model of bone 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 AGEs in diabetic 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 osteoclatogenesis. 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 adipocytes[138]. 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 pathway[137] and suppression of *SOST* expression[139]. Increasing doses of exendin-4, a GLP1 mimetic, have been tested in rodents, showing a proportional increase in BMD, bone strength and bone formation[140]. 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 antidiabetic treatment and is crucial to reduce the risk of complications. Data from the UKPDS study[141] 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 described[141]. 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 prevention[143].

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 observed[145]. During weight loss, exercise is also crucial to prevent bone loss and the increases in bone resorption[146] and sclerostin levels[147] that are observed in those treated with diet alone. The effects of antidiabetic medications on bone metabolism have been reviewed in detail elsewhere[148]. 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 insulin[149]. 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 fractures[33].

Metformin. Metformin is a first-line agent used to treat diabetes mellitus. Preclinical data suggest a positive[150] or a neutral[148] 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 findings[17]. Considering the high rate of hypoglycaemic events associated with these medications[152], 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 PPARγ. Several studies have investigated the effect of thiazolidinediones on bone metabolism, both *in vivo* and *in vitro*, identifying increased adipogenesis and impaired osteoblastogenesis[153]. 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 rosiglitazone[154]. 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 women[156]. 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 rats[140]. However,

Table 1 | **Effects of hypoglycaemic agents on bone metabolism**

Agent	Animal *In vitro*		Animal *In vivo*		Human *In vitro*	
	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 wide[157]. 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 exenatide[158]. 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 prevention[159], an analysis of the SAVOR–TIMI trial of saxagliptin, with fractures reported as 'adverse events of interest', found no effect of treatment on fracture risk[160]. 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 kidney[161]. Dapagliflozin and empagliflozin seem to have a neutral effect on bone metabolism, with no significant changes in bone turnover or BMD parameters[162]. Concerns have been raised for canagliflozin, which might cause bone loss at the hip[163,164] and increase the risk of hip fractures[164]. 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 complications[165–167]. This is also probably true for bone health in this population. As reported in large cohort studies, after diagnosis, β-cell function declines progressively[166] 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 complications[169]. Bone collagen and mineralization, microstructure and, ultimately, bone strength also become compromised by these processes. Obesity[170], bone marrow fat[171], 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 fractures[17]; 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 SGTL2 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 antiresorptive 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.

1. International Diabetes Federation. *IDF Diabetes Atlas* 6th edn (International Diabetes Federation, 2013).
2. Johnell, O. & Kanis, J. A. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos. Int.* **17**, 1726–1733 (2006).
3. Melton, L. J. 3rd, Chrischilles, E. A., Cooper, C., Lane, A. W. & Riggs, B. L. Perspective. How many women have osteoporosis? *J. Bone Miner. Res.* **7**, 1005–1010 (1992).
4. Sanchez-Riera, L. *et al.* The global burden attributable to low bone mineral density. *Ann. Rheum. Dis.* **73**, 1635–1645 (2014).
5. Janghorbani, M., Van Dam, R. M., Willett, W. C. & Hu, F. B. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am. J. Epidemiol.* **166**, 495–505 (2007).
6. Janghorbani, M., Feskanich, D., Willett, W. C. & Hu, F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. *Diabetes Care* **29**, 1573–1578 (2006).
7. Weber, D. R., Haynes, K., Leonard, M. B., Willi, S. M. & Denburg, M. R. Type 1 diabetes is associated with an increased risk of fracture across the life span: a population-based cohort study using the Health Improvement Network (THIN). *Diabetes Care* **38**, 1913–1920 (2015).
8. Vestergaard, P., Rejnmark, L. & Mosekilde, L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. *Diabetologia* **48**, 1292–1299 (2005).
9. Kelsey, J. L., Browner, W. S., Seeley, D. G., Nevitt, M. C. & Cummings, S. R. Risk factors for fractures of the distal forearm and proximal humerus. The Study of Osteoporotic Fractures Research Group. *Am. J. Epidemiol.* **135**, 477–489 (1992).
10. Zhukouskaya, V. V. *et al.* Prevalence of morphometric vertebral fractures in patients with type 1 diabetes. *Diabetes Care* **36**, 1635–1640 (2013).
11. Ivers, R. Q., Cumming, R. G., Mitchell, P. & Peduto, A. J. Diabetes and risk of fracture: the Blue Mountains Eye Study. *Diabetes Care* **24**, 1198–1203 (2001).
12. Miao, J., Brismar, K., Nyren, O., Ugarph-Morawski, A. & Ye, W. Elevated hip fracture risk in type 1 diabetic patients: a population-based cohort study in Sweden. *Diabetes Care* **28**, 2850–2855 (2005).
13. Strotmeyer, E. S. *et al.* Nontraumatic fracture risk with diabetes mellitus and impaired fasting glucose in older white and black adults: the health, aging, and body composition study. *Arch. Intern. Med.* **165**, 1612–1617 (2005).
14. Schwartz, A. V. *et al.* Older women with diabetes have an increased risk of fracture: a prospective study. *J. Clin. Endocrinol. Metab.* **86**, 32–38 (2001).
15. Forsen, L., Meyer, H. E., Midthjell, K. & Edna, T. H. Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trondelag Health Survey. *Diabetologia* **42**, 920–925 (1999).
16. Ahmed, L. A., Joakimsen, R. M., Berntsen, G. K., Fonnebo, V. & Schirmer, H. Diabetes mellitus and the risk of non-vertebral fractures: the Tromso study. *Osteoporos. Int.* **17**, 495–500 (2006).
17. Napoli, N. *et al.* Fracture risk in diabetic elderly men: the MrOS study. *Diabetologia* **57**, 2057–2065 (2014).
18. Li, C. I. *et al.* Glycated hemoglobin level and risk of hip fracture in older people with type 2 diabetes: a competing risk analysis of Taiwan Diabetes Cohort Study. *J. Bone Miner. Res.* **30**, 1338–1346 (2015).
19. Johnston, S. S., Conner, C., Aagren, M., Ruiz, K. & Bouchard, J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. *Diabetes Obes. Metab.* **14**, 634–643 (2012).
20. Vestergaard, P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes — a meta-analysis. *Osteoporos. Int.* **18**, 427–444 (2007).
21. Napoli, N. *et al.* Risk factors for subtrochanteric and diaphyseal fractures: the study of osteoporotic fractures. *J. Clin. Endocrinol. Metab.* **98**, 659–667 (2013).
22. de Liefde, I. I. *et al.* Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Osteoporos. Int.* **16**, 1713–1720 (2005).
23. Bonds, D. E. *et al.* Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study. *J. Clin. Endocrinol. Metab.* **91**, 3404–3410 (2006).
24. Yamamoto, M., Yamaguchi, T., Yamauchi, M., Kaji, H. & Sugimoto, T. Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications. *J. Bone Miner. Res.* **24**, 702–709 (2009).
25. Lipscombe, L. L., Jamal, S. A., Booth, G. L. & Hawker, G. A. The risk of hip fractures in older individuals with diabetes: a population-based study. *Diabetes Care* **30**, 835–841 (2007).
26. Schwartz, A. V. *et al.* Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. *JAMA* **305**, 2184–2192 (2011).
27. Dubey, A., Aharonoff, G. B., Zuckerman, J. D. & Koval, K. J. The effects of diabetes on outcome after hip fracture. *Bull. Hosp. Jt Dis.* **59**, 94–98 (2000).
28. Huang, Y. F. *et al.* Diabetes and health outcomes among older Taiwanese with hip fracture. *Rejuvenation Res.* **15**, 476–482 (2012).
29. Muraki, S., Yamamoto, S., Ishibashi, H. & Nakamura, K. Factors associated with mortality following hip fracture in Japan. *J. Bone Miner. Metab.* **24**, 100–104 (2006).
30. Schwartz, A. V. *et al.* Older women with diabetes have a higher risk of falls: a prospective study. *Diabetes Care* **25**, 1749–1754 (2002).
31. Maurer, M. S., Burcham, J. & Cheng, H. Diabetes mellitus is associated with an increased risk of falls in elderly residents of a long-term care facility. *J. Gerontol. A Biol. Sci. Med. Sci.* **60**, 1157–1162 (2005).
32. Gregg, E. W., Pereira, M. A. & Caspersen, C. J. Physical activity, falls, and fractures among older adults: a review of the epidemiologic evidence. *J. Am. Geriatr. Soc.* **48**, 883–893 (2000).
33. Schwartz, A. V. *et al.* Diabetes-related complications, glycemic control, and falls in older adults. *Diabetes Care* **31**, 391–396 (2008).
34. Hewston, P. & Deshpande, N. Falls and balance impairments in older adults with type 2 diabetes: thinking beyond diabetic peripheral neuropathy. *Can. J. Diabetes* **40**, 6–9 (2016).
35. Berlie, H. D. & Garwood, C. L. Diabetes medications related to an increased risk of falls and fall-related morbidity in the elderly. *Ann. Pharmacother.* **44**, 712–717 (2010).
36. Vinik, A. I., Vinik, E. J., Colberg, S. R. & Morrison, S. Falls risk in older adults with type 2 diabetes. *Clin. Geriatr. Med.* **31**, 89–99 (2015).
37. Campos Pastor, M. M., Lopez-Ibarra, P. J., Escobar-Jimenez, F., Serrano Pardo, M. D. & Garcia-Cervigon, A. G. Intensive insulin therapy and bone mineral density in type 1 diabetes mellitus: a prospective study. *Osteoporos. Int.* **11**, 455–459 (2000).
38. Eller-Vainicher, C. *et al.* Low bone mineral density and its predictors in type 1 diabetic patients evaluated by the classic statistics and artificial neural network analysis. *Diabetes Care* **34**, 2186–2191 (2011).
39. Joshi, A., Varthakavi, P., Chadha, M. & Bhagwat, N. A study of bone mineral density and its determinants in type 1 diabetes mellitus. *J. Osteoporos.* **2013**, 397814 (2013).
40. Soto, N. *et al.* Bone mass and sex steroids in postmenarcheal adolescents and adult women with type 1 diabetes mellitus. *J. Diabetes Comp.* **25**, 19–24 (2011).
41. Hampson, G. *et al.* Bone mineral density, collagen type 1 α 1 genotypes and bone turnover in premenopausal women with diabetes mellitus. *Diabetologia* **41**, 1314–1320 (1998).
42. Mastrandrea, L. D. *et al.* Young women with type 1 diabetes have lower bone mineral density that persists over time. *Diabetes Care* **31**, 1729–1735 (2008).
43. Lopez-Ibarra, P. J. *et al.* Bone mineral density at time of clinical diagnosis of adult-onset type 1 diabetes mellitus. *Endocr. Pract.* **7**, 346–351 (2001).
44. Ma, L. *et al.* Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studies. *Eur. J. Epidemiol.* **27**, 319–332 (2012).
45. Weinfeld, R. M., Olson, P. N., Maki, D. D. & Griffiths, H. J. The prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in two large American Midwest metropolitan hospital populations. *Skeletal Radiol.* **26**, 222–225 (1997).
46. Dhaliwal, R., Cibula, D., Ghosh, C., Weinstock, R. S. & Moses, A. M. Bone quality assessment in type 2 diabetes mellitus. *Osteoporos. Int.* **25**, 1969–1973 (2014).
47. Leslie, W. D., Aubry-Rozier, B., Lamy, O., Hans, D. & Manitoba Bone Density Program. TBS (trabecular bone score) and diabetes-related fracture risk. *J. Clin. Endocrinol. Metab.* **98**, 602–609 (2013).
48. Rubin, J. *et al.* Trabecular bone assessment in type 2 diabetes mellitus. *J. Bone Miner. Res.* **28**, S398 (2013).
49. Tao, B. *et al.* Differences between measurements of bone mineral densities by quantitative ultrasound and dual-energy X-ray absorptiometry in type 2 diabetic postmenopausal women. *J. Clin. Endocrinol. Metab.* **93**, 1670–1675 (2008).
50. Yamaguchi, T. *et al.* Quantitative ultrasound and vertebral fractures in patients with type 2 diabetes. *J. Bone Miner. Metab.* **29**, 626–632 (2011).
51. Bechtold, S. *et al.* Early manifestation of type 1 diabetes in children is a risk factor for changed bone geometry: data using peripheral quantitative computed tomography. *Pediatrics* **118**, e627–e634 (2006).
52. Danielson, K. K., Elliott, M. E., LeCaire, T., Binkley, N. & Palta, M. Poor glycemic control is associated with low BMD detected in premenopausal women with type 1 diabetes. *Osteoporos. Int.* **20**, 923–933 (2009).
53. Forst, T. *et al.* Peripheral osteopenia in adult patients with insulin-dependent diabetes mellitus. *Diabet. Med.* **12**, 874–879 (1995).
54. Heap, J., Murray, M. A., Miller, S. C., Jalili, T. & Moyer-Mileur, L. J. Alterations in bone characteristics associated with glycemic control in adolescents with type 1 diabetes mellitus. *J. Pediatr.* **144**, 56–62 (2004).
55. Lettgen, B., Hauffa, B., Mohlmann, C., Jeken, C. & Reiners, C. Bone mineral density in children and adolescents with juvenile diabetes: selective measurement of bone mineral density of trabecular and cortical bone using peripheral quantitative computed tomography. *Hormone Res.* **43**, 173–175 (1995).
56. Saha, M. T., Sievanen, H., Salo, M. K., Tulokas, S. & Saha, H. H. Bone mass and structure in adolescents with type 1 diabetes compared to healthy peers. *Osteoporos. Ont.* **20**, 1401–1406 (2009).
57. Roggen, I., Gies, I., Vanbesien, J., Louis, O. & De Schepper, J. Trabecular bone mineral density and bone geometry of the distal radius at completion of pubertal growth in childhood type 1 diabetes. *Hormone Res. Paediatr.* **79**, 68–74 (2013).
58. Pritchard, J. M. *et al.* Changes in trabecular bone microarchitecture in postmenopausal women with and without type 2 diabetes: a two year longitudinal study. *BMC Musculoskelet. Disord.* **14**, 114 (2013).
59. Pritchard, J. M. *e al.* Association of larger holes in the trabecular bone at the distal radius in postmenopausal women with type 2 diabetes mellitus compared to controls. *Arthritis Care Res.* **64**, 83–91 (2012).
60. Burghardt, A. J. *et al.* High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **95**, 5045–5055 (2010).
61. Farr, J. N. *et al. In vivo* assessment of bone quality in postmenopausal women with type 2 diabetes. *J. Bone Miner. Res.* **29**, 787–795 (2014).
62. Patsch, J. M. *et al.* Increased cortical porosity in type 2 diabetic postmenopausal women with fragility fractures. *J. Bone Miner. Res.* **28**, 313–324 (2013).
63. Shanbhogue, V. V. *et al.* Compromised cortical bone compartment in type 2 diabetes mellitus patients with microvascular disease. *Eur. J. Endocrinol.* **174**, 115–124 (2016).
64. Bala, Y. *et al.* Trabecular and cortical microstructure and fragility of the distal radius in women. *J. Bone Miner. Res.* **30**, 621–629 (2015).
65. Yu, E. W. *et al.* Defects in cortical microarchitecture among African-American women with type 2 diabetes. *Osteoporos. Int.* **26**, 673–679 (2015).
66. Ogawa, N. *et al.* The combination of high glucose and advanced glycation end-products (AGEs) inhibits the mineralization of osteoblastic MC3T3-E1 cells through glucose-induced increase in the receptor for AGEs. *Horm. Metab. Res.* **39**, 871–875 (2007).
67. Hough, F. S. *et al.* Mechanisms in endocrinology: mechanisms and evaluation of bone fragility in type 1 diabetes mellitus. *Eur. J. Endocrinol.* **174**, R127–138 (2016).
68. Napoli, N. *et al.* The alliance of mesenchymal stem cells, bone, and diabetes. *Int. J. Endocrinol.* **2014**, 690783 (2014).

69. Maggio, A. B. *et al.* Decreased bone turnover in children and adolescents with well controlled type 1 diabetes. *J. Pediatr. Endocrinol. Metab.* **23**, 697–707 (2010).
70. Adami, S. Bone health in diabetes: considerations for clinical management. *Curr. Med. Res. Opin.* **25**, 1057–1072 (2009).
71. Diaz-Lopez, A. *et al.* Reduced serum concentrations of carboxylated and undercarboxylated osteocalcin are associated with risk of developing type 2 diabetes mellitus in a high cardiovascular risk population: a nested case-control study. *J. Clin. Endocrinol. Metab.* **98**, 4524–4531 (2013).
72. Kanazawa, I. *et al.* Serum osteocalcin level is associated with glucose metabolism and atherosclerosis parameters in type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **94**, 45–49 (2009).
73. Starup-Linde, J., Eriksen, S. A., Lykkeboe, S., Handberg, A. & Vestergaard, P. Biochemical markers of bone turnover in diabetes patients — a meta-analysis, and a methodological study on the effects of glucose on bone markers. *Osteoporos. Int.* **25**, 1697–1708 (2014).
74. Starup-Linde, J. & Vestergaard, P. Biochemical bone turnover markers in diabetes mellitus — a systematic review. *Bone* **82**, 69–78 (2016).
75. Leite Duarte, M. E. & da Silva, R. D. [Histomorphometric analysis of the bone tissue in patients with non-insulin-dependent diabetes (DMNID)]. *Rev. Hosp. Clin. Fac. Med. Sao Paulo* **51**, 7–11 (in Portuguese) (1996).
76. Manavalan, J. S. *et al.* Circulating osteogenic precursor cells in type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **97**, 3240–3250 (2012).
77. Armas, L. A., Akhter, M. P., Drincic, A. & Recker, R. R. Trabecular bone histomorphometry in humans with type 1 diabetes mellitus. *Bone* **50**, 91–96 (2012).
78. Farlay, D. *et al.* Nonenzymatic glycation and degree of mineralization are higher in bone from fractured patients with type 1 diabetes mellitus. *J. Bone Miner. Res.* **31**, 190–195 (2016).
79. Reyes-Garcia, R. *et al.* Serum levels of bone resorption markers are decreased in patients with type 2 diabetes. *Acta Diabetol.* **50**, 47–52 (2013).
80. Yamamoto, M., Yamaguchi, T., Nawata, K., Yamauchi, M. & Sugimoto, T. Decreased PTH levels accompanied by low bone formation are associated with vertebral fractures in postmenopausal women with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **97**, 1277–1284 (2012).
81. McNair, P., Christensen, M. S., Madsbad, S., Christiansen, C. & Transbol, I. Hypoparathyroidism in diabetes mellitus. *Acta Endocrinol.* **96**, 81–86 (1981).
82. Thalassinos, N. C., Hadjiyanni, P., Tzanela, M., Alevizaki, C. & Philokiprou, D. Calcium metabolism in diabetes mellitus: effect of improved blood glucose control. *Diabet. Med.* **10**, 341–344 (1993).
83. Weyer, C. *et al.* Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. *J. Clin. Endocrinol. Metab.* **86**, 1930–1935 (2001).
84. Williams, G. A. *et al. In vitro* and *in vivo* effects of adiponectin on bone. *Endocrinology* **150**, 3603–3610 (2009).
85. Lenchik, L. *et al.* Adiponectin as a novel determinant of bone mineral density and visceral fat. *Bone* **33**, 646–651 (2003).
86. Napoli, N. *et al.* Adiponectin and bone mass density: The InCHIANTI study. *Bone* **47**, 1001–1005 (2010).
87. Tamura, T. *et al.* Serum leptin and adiponectin are positively associated with bone mineral density at the distal radius in patients with type 2 diabetes mellitus. *Metabolism* **56**, 623–628 (2007).
88. Hamrick, M. W. & Ferrari, S. L. Leptin and the sympathetic connection of fat to bone. *Osteoporos. Int.* **19**, 905–912 (2008).
89. Nuche-Berenguer, B. *et al.* Exendin-4 exerts osteogenic actions in insulin-resistant and type 2 diabetic states. *Regul. Pept.* **159**, 61–66 (2010).
90. Gennari, L. *et al.* Circulating sclerostin levels and bone turnover in type 1 and type 2 diabetes. *J. Clin. Endocrinol. Metab.* **97**, 1737–1744 (2012).
91. Gaudio, A. *et al.* Sclero stin levels associated with inhibition of the Wnt/β-catenin signaling and reduced bone turnover in type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **97**, 3744–3750 (2012).
92. Yamamoto, M., Yamauchi, M. & Sugimoto, T. Elevated sclerostin levels are associated with vertebral fractures in patients with type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **98**, 4030–4037 (2013).
93. Heilmeier, U. *et al.* Volumetric femoral BMD, bone geometry, and serum sclerostin levels differ between type 2 diabetic postmenopausal women with and without fragility fractures. *Osteoporos. Int.* **26**, 1283–1293 (2015).
94. Bucala, R. & Vlassara, H. Advanced glycosylation end products in diabetic renal and vascular disease. *Am. J. Kidney Dis.* **26**, 875–888 (1995).
95. Hein, G. E. Glycation endproducts in osteoporosis — is there a pathophysiologic importance? *Clin. Chim. Acta* **371**, 32–36 (2006).
96. Leslie, W. D., Rubin, M. R., Schwartz, A. V. & Kanis, J. A. Type 2 diabetes and bone. *J. Bone Miner. Res.* **27**, 2231–2237 (2012).
97. Vashishth, D. *et al.* Influence of nonenzymatic glycation on biomechanical properties of cortical bone. *Bone* **28**, 195–201 (2001).
98. Saito, M., Fujii, K., Mori, Y. & Marumo, K. Role of collagen enzymatic and glycation induced cross-links as a determinant of bone quality in spontaneously diabetic WBN/Kob rats. *Osteoporos. Int.* **17**, 1514–1523 (2006).
99. Kerkeni, M., Saidi, A., Bouzidi, H., Ben Yahya, S. & Hammami, M. Elevated serum levels of AGEs, sRAGE, and pentosidine in Tunisian patients with severity of diabetic retinopathy. *Microvasc. Res.* **84**, 378–383 (2012).
100. Saito, M., Fujii, K. & Marumo, K. Degree of mineralization-related collagen crosslinking in the femoral neck cancellous bone in cases of hip fracture and controls. *Calcif. Tissue Int.* **79**, 160–168 (2006).
101. Schwartz, A. V. *et al.* Pentosidine and increased fracture risk in older adults with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **94**, 2380–2386 (2009).
102. Yamamoto, M., Yamaguchi, T., Yamauchi, M., Yano, S. & Sugimoto, T. Serum pentosidine levels are positively associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **93**, 1013–1019 (2008).
103. Takagi, M. *et al.* Advanced glycation endproducts stimulate interleukin-6 production by human bone-derived cells. *J. Bone Miner. Res.* **12**, 439–446 (1997).
104. Yamamoto, T. *et al.* Role of advanced glycation end products in adynamic bone disease in patients with diabetic nephropathy. *Am. J. Kidney Dis.* **38**, S161–S164 (2001).
105. Katayama, Y., Akatsu, T., Yamamoto, M., Kugai, N. & Nagata, N. Role of nonenzymatic glycosylation of type I collagen in diabetic osteopenia. *J. Bone Miner. Res.* **11**, 931–937 (1996).
106. Kume, S. *et al.* Advanced glycation end-products attenuate human mesenchymal stem cells and prevent cognate differentiation into adipose tissue, cartilage, and bone. *J. Bone Miner. Res.* **20**, 1647–1658 (2005).
107. Sanguineti, R., Storace, D., Monacelli, F., Federici, A. & Odetti, P. Pentosidine effects on human osteoblasts *in vitro*. *Ann. NY Acad. Sci.* **1126**, 166–172 (2008).
108. McCarthy, A. D., Uemura, T., Etcheverry, S. B. & Cortizo, A. M. Advanced glycation endproducts interefere with integrin-mediated osteoblastic attachment to a type-I collagen matrix. *Int. J. Biochem. Cell Biol.* **36**, 840–848 (2004).
109. Yonekura, H. *et al.* Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury. *Biochem. J.* **370**, 1097–1109 (2003).
110. Yamamoto, M., Yamaguchi, T., Yamauchi, M. & Sugimoto, T. Low serum level of the endogenous secretory receptor for advanced glycation end products (esRAGE) is a risk factor for prevalent vertebral fractures independent of bone mineral density in patients with type 2 diabetes. *Diabetes Care* **32**, 2263–2268 (2009).
111. Cunha, J. S., Ferreira, V. M., Maquigussa, E., Naves, M. A. & Boim, M. A. Effects of high glucose and high insulin concentrations on osteoblast function *in vitro*. *Cell Tissue Res.* **358**, 249–256 (2014).
112. Zayzafoon, M., Stell, C., Irwin, R. & McCabe, L. R. Extracellular glucose influences osteoblast differentiation and c-Jun expression. *J. Cell. Biochem.* **79**, 301–310 (2000).
113. Botolin, S. & McCabe, L. R. Chronic hyperglycemia modulates osteoblast gene expression through osmotic and non-osmotic pathways. *J. Cell. Biochem.* **99**, 411–424 (2006).
114. Wei, J. *et al.* Bone-specific insulin resistance disrupts whole-body glucose homeostasis via decreased osteocalcin activation. *J. Clin. Invest.* **124**, 1–13 (2014).
115. Balint, E., Szabo, P., Marshall, C. F. & Sprague, S. M. Glucose-induced inhibition of *in vitro* bone mineralization. *Bone* **28**, 21–28 (2001).
116. Frassetto, L. A. & Sebastian, A. How metabolic acidosis and oxidative stress alone and interacting may increase the risk of fracture in diabetic subjects. *Med. Hypotheses* **79**, 189–192 (2012).
117. Aguiari, P. *et al.* High glucose induces adipogenic differentiation of muscle-derived stem cells. *Proc. Natl Acad. Sci. USA* **105**, 1226–1231 (2008).
118. Oei, L. *et al.* High bone mineral density and fracture risk in type 2 diabetes as skeletal complications of inadequate glucose control: the Rotterdam Study. *Diabetes Care* **36**, 1619–1628 (2013).
119. Yang, J., Zhang, X., Wang, W. & Liu, J. Insulin stimulates osteoblast proliferation and differentiation through ERK and PI3K in MG-63 cells. *Cell Biochem. Funct.* **28**, 334–341 (2010).
120. Gandhi, A., Beam, H. A., O'Connor, J. P., Parsons, J. R. & Lin, S. S. The effects of local insulin delivery on diabetic fracture healing. *Bone* **37**, 482–490 (2005).
121. Fulzele, K. *et al.* Disruption of the insulin-like growth factor type 1 receptor in osteoblasts enhances insulin signaling and action. *J. Biol. Chem.* **282**, 25649–25658 (2007).
122. McCarthy, A. D., Etcheverry, S. B. & Cortizo, A. M. Effect of advanced glycation endproducts on the secretion of insulin-like growth factor-I and its binding proteins: role in osteoblast development. *Acta Diabetol.* **38**, 113–122 (2001).
123. Terada, M. *et al.* Growth-inhibitory effect of a high glucose concentration on osteoblast-like cells. *Bone* **22**, 17–23 (1998).
124. Kanazawa, I., Yamaguchi, T. & Sugimoto, T. Serum insulin-like growth factor-I is a marker for assessing the severity of vertebral fractures in postmenopausal women with type 2 diabetes mellitus. *Osteoporos. Int.* **22**, 1191–1198 (2011).
125. Cornish, J. & Naot, D. Amylin and adrenomedullin: novel regulators of bone growth. *Curr. Pharm. Design* **8**, 2009–2021 (2002).
126. Gilbert, L. *et al.* Inhibition of osteoblast differentiation by tumor necrosis factor-α. *Endocrinology* **141**, 3956–3964 (2000).
127. Glantschnig, H., Fisher, J. E., Wesolowski, G., Rodan, G. A. & Reszka, A. A. M-CSF TNFα and RANK ligand promote osteoclast survival by signaling through mTOR/S6 kinase. *Cell Death Differ.* **10**, 1165–1177 (2003).
128. Manolagas, S. C. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. *Endocr. Rev.* **31**, 266–300 (2010).
129. Hotta, K. *et al.* Age-related adipose tissue mRNA expression of ADD1/SREBP1, PPARγ, lipoprotein lipase, and GLUT4 glucose transporter in rhesus monkeys. *J. Gerontol. A Biol. Sci. Med. Sci.* **54**, B183–B188 (1999).
130. Dong, X. *et al.* FFAs–ROS–ERK/P38 pathway plays a key role in adipocyte lipotoxicity on osteoblasts in co-culture. *Biochimie* **101**, 123–131 (2014).
131. Blonde, L. *et al.* Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. *Diabetes Obes. Metab.* **8**, 436–447 (2006).
132. Fazeli, P. K. *et al.* Marrow fat and bone — new perspectives. *J. Clin. Endocrinol. Metab.* **98**, 935–945 (2013).
133. Giralt, M. & Villarroya, F. White, brown, beige/brite: different adipose cells for different functions? *Endocrinology* **154**, 2992–3000 (2013).
134. Rahman, S. *et al.* Inducible brown adipose tissue, or beige fat, is anabolic for the skeleton. *Endocrinology* **154**, 2687–2701 (2013).
135. Singh, R., Braga, M. & Pervin, S. Regulation of brown adipocyte metabolism by myostatin/follistatin signaling. *Front. Cell Dev. Biol.* **2**, 60 (2014).
136. Knop, F. K. *et al.* Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state? *Diabetes* **56**, 1951–1959 (2007).
137. Nuche-Berenguer, B. *et al.* Presence of a functional receptor for GLP-1 in osteoblastic cells, independent of the cAMP-linked GLP-1 receptor. *J. Cell. Physiol.* **225**, 585–592 (2010).
138. Sanz, C. *et al.* Signaling and biological effects of glucagon-like peptide 1 on the differentiation of mesenchymal stem cells from human bone marrow. *Am. J. Physiol. Endocrinol. Metab.* **298**, E634–E643 (2010).

139. Kim, J. Y. *et al.* Exendin-4 increases bone mineral density in type 2 diabetic OLETF rats potentially through the down-regulation of *SOST*/sclerostin in osteocytes. *Life Sci.* **92**, 533–540 (2013).
140. Ma, X. *et al.* Exendin-4, a glucagon-like peptide-1 receptor agonist, prevents osteopenia by promoting bone formation and suppressing bone resorption in aged ovariectomized rats. *J. Bone Miner. Res.* **28**, 1641–1652 (2013).
141. Stratton, I. M. *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* **321**, 405–412 (2000).
142. Schneider, A. L. *et al.* Diabetes and risk of fracture-related hospitalization: the Atherosclerosis Risk in Communities Study. *Diabetes Care* **36**, 1153–1158 (2013).
143. Schwartz, A. V. *et al.* Intensive glycemic control is not associated with fractures or falls in the ACCORD randomized trial. *Diabetes Care* **35**, 1525–1531 (2012).
144. Inzucchi, S. E. *et al.* Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **38**, 140–149 (2015).
145. Villareal, D. T. *et al.* Weight loss, exercise, or both and physical function in obese older adults. *N. Engl. J. Med.* **364**, 1218–1229 (2011).
146. Shah, K. *et al.* Exercise training in obese older adults prevents increase in bone turnover and attenuates decrease in hip bone mineral density induced by weight loss despite decline in bone-active hormones. *J. Bone Miner. Res.* **26**, 2851–2859 (2011).
147. Armamento-Villareal, R. *et al.* Weight loss in obese older adults increases serum sclerostin and impairs hip geometry but both are prevented by exercise training. *J. Bone Miner. Res.* **27**, 1215–1221 (2012).
148. Palermo, A. *et al.* Oral anti-diabetic drugs and fracture risk, cut to the bone: safe or dangerous? A narrative review. *Osteoporos. Int.* **26**, 2073–2089 (2015).
149. Monami, M. *et al.* Bone fractures and hypoglycemic treatment in type 2 diabetic patients: a case-control study. *Diabetes Care* **31**, 199–203 (2008).
150. Kanazawa, I., Yamaguchi, T., Yano, S., Yamauchi, M. & Sugimoto, T. Metformin enhances the differentiation and mineralization of osteoblastic MC3T3-E1 cells via AMP kinase activation as well as eNOS and BMP-2 expression. *Biochem. Biophys. Res. Commun.* **375**, 414–419 (2008).
151. Solomon, D. H. *et al.* A cohort study of thiazolidinediones and fractures in older adults with diabetes. *J. Clin. Endocrinol. Metab.* **94**, 2792–2798 (2009).
152. Del Prato, S., Camisasca, R., Wilson, C. & Fleck, P. Durability of the efficacy and safety of alogliptin compared with glipizide in type 2 diabetes mellitus: a 2-year study. *Diabetes Obes. Metab.* **16**, 1239–1246 (2014).
153. Kawai, M. & Rosen, C. J. PPARγ: a circadian transcription factor in adipogenesis and osteogenesis. *Nat. Rev. Endocrinol.* **6**, 629–636 (2010).
154. Loke, Y. K., Singh, S. & Furberg, C. D. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* **180**, 32–39 (2009).
155. Toulis, K. A., Goulis, D. G. & Anastasilakis, A. D. Thiazolidinedione use and the risk of fractures. *CMAJ* **180**, 841–842; author reply 842–843 (2009).
156. Zhu, Z. N., Jiang, Y. F. & Ding, T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. *Bone* **68**, 115–123 (2014).
157. Mabilleau, G., Mieczkowska, A. & Chappard, D. Use of glucagon-like peptide-1 receptor agonists and bone fractures: a meta-analysis of randomized clinical trials. *J. Diabetes* **6**, 260–266 (2014).
158. Su, B. *et al.* Risk of bone fractures associated with glucagon-like peptide-1 receptor agonists' treatment: a meta-analysis of randomized controlled trials. *Endocrine* **48**, 107–115 (2015).
159. Monami, M., Dicembrini, I., Antenore, A. & Mannucci, E. Dipeptidyl peptidase-4 inhibitors and bone fractures: a meta-analysis of randomized clinical trials. *Diabetes Care* **34**, 2474–2476 (2011).
160. Mosenzon, O. *et al.* Incidence of fractures in patients with type 2 diabetes in the SAVOR-TIMI 53 trial. *Diabetes Care* **38**, 2142–2150 (2015).
161. DeFronzo, R. A., Davidson, J. A. & Del Prato, S. The role of the kidneys in glucose homeostasis: a new path towards normalizing glycaemia. *Diabetes Obes. Metab.* **14**, 5–14 (2012).
162. Ljunggren, O. *et al.* Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. *Diabetes Obes. Metab.* **14**, 990–999 (2012).
163. Bilezikian, J. P. *et al.* Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. *J. Clin. Endocrinol. Metab.* **101**, 44–51 (2016).
164. Watts, N. B. *et al.* Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **101**, 157–166 (2016).
165. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**, 837–853 (1998).
166. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* **44**, 1249–1258 (1995).
167. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**, 854–865 (1998).
168. Kahn, S. E. *et al.* Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N. Engl. J. Med.* **355**, 2427–2443 (2006).
169. Lebovitz, H. E. Insulin secretagogues: old and new. *Diabetes Rev.* **7**, 139–153 (1999).
170. Aguirre, L. *et al.* Increasing adiposity is associated with higher adipokine levels and lower bone mineral density in obese older adults. *J. Clin. Endocrinol. Metab.* **99**, 3290–3297 (2014).
171. Ma, Y. H. *et al.* Circulating sclerostin associated with vertebral bone marrow fat in older men but not women. *J. Clin. Endocrinol. Metab.* **99**, E2584–E2590 (2014).
172. Napoli, N. *et al.* Effect of ghrelin on bone mass density: The InChianti study. *Bone.* **49**, 257–263 (2011).
173. Iacobellis, G. *et al.* Relation of adiponectin, visfatin and bone mineral density in patients with metabolic syndrome. *J. Endocrinol. Invest.* **34**, e12–e15 (2011).

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.

Author contributions
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.