# Update on the pathogenesis and treatment of skeletal fragility in type 2 diabetes mellitus

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## Abstract

Fracture risk is increased in patients with type 2 diabetes mellitus (T2DM). In addition, these patients sustain fractures despite having higher levels of areal bone mineral density, as measured by dual-energy X-ray absorptiometry, than individuals without T2DM. Thus, additional factors such as alterations in bone quality could have important roles in mediating skeletal fragility in patients with T2DM. Although the pathogenesis of increased fracture risk in T2DM is multifactorial, impairments in bone material properties and increases in cortical porosity have emerged as two key skeletal abnormalities that contribute to skeletal fragility in patients with T2DM. In addition, indices of bone formation are uniformly reduced in patients with T2DM, with evidence from mouse studies published over the past few years linking this abnormality to accelerated skeletal ageing, specifically cellular senescence. In this Review, we highlight the latest advances in our understanding of the mechanisms of skeletal fragility in patients with T2DM and suggest potential novel therapeutic approaches to address this problem.

Type 2 diabetes mellitus (T2DM) is increasing in incidence and prevalence around the world[1]. Although considerable attention has been appropriately focused on the well-recognized complications of T2DM, including retinopathy, nephropathy, neuropathy and vascular disease, data are now accumulating that warrant skeletal fragility being added to the list of known diabetic complications. Fracture risk is clearly increased in patients with T2DM[2]. However, numerous studies have demonstrated that areal bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA) is preserved, or even elevated, in patients with T2DM relative to individuals without T2DM[2–4]. In addition to elevated fracture risk, patients with T2DM have increased morbidity following a fracture compared with patients with a fracture but without T2DM[5]. Further complicating the issue is the observation that the most widely used fracture risk assessment tool (FRAX)[6] underestimates fracture risk in patients with T2DM[4]. This observation indicates that additional factors beyond BMD and the risk factors for fracture included in FRAX (prior fragility fracture, parental history of hip fracture, smoking, glucocorticoid use, rheumatoid

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arthritis and alcohol consumption) probably contribute to increased skeletal fragility in patients with T2DM.

The topic of diabetic skeletal fragility in type 1 diabetes mellitus and T2DM was extensively reviewed in *Nature Reviews Endocrinology* in 2017 by Napoli and colleagues[2]. As such, the goal of this article is to provide an update with new information that has been published since that review. Furthermore, we focus on specific areas emerging as key to the pathogenesis of skeletal fragility in these patients and potential therapeutic approaches to manage increased fracture risk in patients with T2DM. In addition, we summarize the evidence that skeletal fragility should now be included in the list of well-recognized diabetic complications, given shared mechanisms across the different complications of T2DM. For this Review, we selected published papers based on the authors' knowledge of the literature as well as PubMed searches using 'diabetes' and 'bone' as search keywords, focusing largely on papers published since the review by Napoli and colleagues[2].

## Epidemiology of fracture risk in T2DM

### Evidence for increased fracture risk in T2DM.

The clinical importance of fragility fractures in patients with T2DM has considerably increased worldwide, as increasing life expectancy in people with T2DM has led to rapid growth in the number of ageing patients with T2DM[7]. In 2008, we reported a population-based study of 700 residents with T2DM in Olmsted County, Minnesota, USA, with 23,236 person-years of follow-up, who experienced 1,369 fractures[8]. Fracture risk was elevated (standardized incidence ratio (SIR) 1.3, 95% CI 1.2–1.4) compared with residents without T2DM. Moreover, fractures were increased among patients with neuropathy (HR 1.3, 95% CI 1.1–1.6) and those on insulin (HR 1.3, 95% CI 1.1–1.5), but the risk was reduced among users of biguanides (HR 0.7, 95% CI 0.6–0.96)[8]. These findings are consistent with a meta-analysis published in 2020 that reported data from 17,571,738 participants with 319,652 hip fractures and 2,978,487 participants with 181,228 non-vertebral fractures[9]. Patients with T2DM had an elevated risk of fracture at the hip (relative risk (RR) 1.33, 95% CI 1.19–1.49) and non-vertebral sites (RR 1.19, 95% CI 1.11–1.28) compared with participants without T2DM. In addition, a long duration of T2DM and insulin use were independently associated with an increased risk of hip fracture[9].

Out of all fracture sites, the risk of hip fractures has been most consistently increased in T2DM[3,10,11]. Interestingly, a large-scale, retrospective, longitudinal, nationwide population-based cohort study of 5,761,785 individuals in the Republic of Korea confirmed that the hazard ratios of hip fractures were slightly increased in people with prediabetes compared with people without T2DM (HR 1.032, 95% CI 1.009–1.056)[12]. Further progressive increases in hip fracture risk were observed in those with newly diagnosed T2DM (meaning individuals diagnosed at the time of the initial clinic visit for the study and without a prior history of T2DM) (HR 1.168, 95% CI 1.113–1.225), T2DM of less than 5 years' duration (HR 1.543, 95% CI 1.495–1.592) and T2DM of greater than 5 years' duration (HR 2.105, 95% CI 2.054–2.157). The secular trend of risk of hip fracture increasing according to the duration of T2DM was consistent in both sexes and all age groups. Moreover, a meta-analysis evaluating fractures in patients with diabetes mellitus showed an increased

risk of total, hip, upper arm and ankle fractures: patients who had type 1 diabetes mellitus had a greater risk than those with T2DM[13]. Another meta-analysis focusing on peripheral fractures found an increased risk of ankle fractures (RR 1.30, 95% CI 1.15–1.48) but a decreased risk of wrist fractures (RR 0.85, 95% CI 0.77–0.95) in patients with T2DM[14].

The most recent meta-analysis from 2020 indicated a decrease in prevalence (OR 0.84, 95% CI 0.70–0.95) but an increase in incidence (OR 1.35, 95% CI 1.27–1.44)[5] of vertebral fracture in patients with T2DM compared with control individuals without diabetes mellitus. Furthermore, individuals with both T2DM and vertebral fracture have increased mortality compared with individuals without T2DM or vertebral fracture (HR 2.11, 95% CI 1.72– 2.59) or with vertebral fracture alone (HR 1.84, 95% CI 1.49–2.28), and a borderline increased risk compared with individuals with T2DM alone (HR 1.23, 95% CI 0.99–1.52). In addition, a paper published in 2020 reported an Italian nationwide study of 59,950 women of whom 5.2% had diabetes mellitus (predominantly T2DM) and noted an association between diabetes mellitus and any fracture (OR 1.3, 95% CI 1.1–1.4, and OR 1.3, 95% CI 1.2–1.5, for vertebral or hip fractures and non-vertebral, non-hip fractures, respectively)[15]. Interestingly, the prevalence of vertebral or hip fracture was higher in participants with diabetes mellitus but without obesity (OR 1.9, 95% CI 1.7–2.1) than in patients with obesity and diabetes mellitus (OR 1.5, 95% CI 1.3–1.8), suggesting that obesity might be partially protective against vertebral or hip fractures in T2DM[15].

However, data from the Osteoporotic Fractures in Men Study, which enrolled men aged 65 years and older with T2DM ($n = 875$) and men without diabetes mellitus ($n = 4,679$), showed that the prevalence (7.0% versus 7.7%, respectively) and incidence (4.4% versus 4.5%, respectively) of vertebral fracture were not higher in men with T2DM than in men without diabetes mellitus[16]. The risk of prevalent (OR, 1.05, 95% CI 0.78–1.40) or incident (OR, 1.28, 95% CI 0.81–2.00) vertebral fracture was also not higher in men with T2DM than in men without diabetes mellitus in models adjusted for age, clinic site, race, BMI and BMD. Nevertheless, the results revealed a trend for an increased risk of incident vertebral fractures by 30% in BMD-adjusted models[16]. Collectively, these findings raise the possibility that increased vertebral fracture risk might be more consistently present in older women with T2DM than in older men with T2DM.

### The impact of glycaemic control on fracture risk in T2DM.

The association between glycaemic control and fracture risk is best described as a J-shaped relationship, as observational studies have found that both poor glycaemic control and very strict glycaemic control are associated with increased fracture risk[17–20] This relationship is probably best explained by hypoglycaemia resulting from very strict glycaemic control[21–23]. For example, in a study published in 2020, 4,706 Japanese patients with T2DM (2,755 men and 1,951 postmenopausal women; mean age 66 years) were followed prospectively (median of 5.3 years; follow-up rate 97.6%) and stratified by severe hypoglycaemia status and glycaemic control[24]. Fractures occurred in 662 participants (249 men and 413 women). FIGURE 1 shows the age-adjusted and sex-adjusted incidence rates (expressed per 1,000 person-years) based on multiple or single episodes of hypoglycaemia as well as $HbA_{1c}$ measurements. Having multiple episodes of hypoglycaemia was associated with a marked

increase in fracture risk, and even a history of a single episode of hypoglycaemia led to an increase in fracture risk. In the absence of hypoglycaemia, fracture risk was similar in those with $HbA_{1c}$ values of <7%, 7% to <8%, and 8% to <9%, but increased statistically significantly in patients with $HbA_{1c}$ values of 9%[24].

Another study published in 2020 confirmed the relationship between poor glycaemic control and increased fracture risk. Here, Chinese individuals aged 60 years with T2DM were identified from electronic health records in Hong Kong between 2008 and 2012 and observed for incident hip fractures[25]. A total of 83,282 participants were included, with a mean age of 71.3 ± 7.5 years, duration of diabetes mellitus of 11.7 ± 7.7 years, baseline $HbA_{1c}$ of 7.33 ± 1.23%, and median follow-up of 6.8 years. A mean $HbA_{1c}$ of 8.0% was associated with a 25% increase in incident hip fractures compared with a mean $HbA_{1c}$ of <7.0%. In addition, all $HbA_{1c}$ variability indices were independent predictors of incident hip fractures, with an adjusted hazard ratio of up to 1.29 (all $P < 0.001$) and persisted as independent predictors across groups of different intensities of glycaemic control. Thus, both poor glycaemic control and $HbA_{1c}$ variability across the spectrum of glycaemic control are independent positive predictors of hip fractures in patients with T2DM[25].

## Pathogenesis of skeletal fragility in T2DM

### Clinical studies on skeletal fragility pathogenesis in T2DM.

Despite the increase in fracture risk, most studies have found that patients with T2DM have preserved, or even increased, BMD compared with control individuals without diabetes mellitus. For example, in a subset ($n = 6,384$) of postmenopausal women from the Women's Health Initiative, women with T2DM consistently had higher spine and hip BMD values than women without diabetes mellitus both at baseline and over 9 years of follow-up (TABLE 1)[26]. A meta-analysis that included studies of women and men with T2DM showed similar findings, with high $Z$-scores (standard deviations from the mean) of 0.41 at the spine and 0.27 at the hip in patients with T2DM[3]. These findings have been subsequently confirmed and extended by perhaps the most comprehensive meta-analysis to date on the association between BMD and T2DM, which included 15 observational studies (3,437 patients with T2DM and 19,139 control individuals)[27]. This analysis showed that BMD in patients with T2DM was significantly higher than in participants without diabetes mellitus, with pooled mean differences of 0.04 $g/cm^2$ (95% CI 0.02–0.05) at the femoral neck, 0.06 $g/cm^2$ (95% CI 0.04–0.08) at the hip and 0.06 $g/cm^2$ (95% CI 0.04–0.07) at the spine. These differences were equivalent to about a 25–50% higher standard deviation for BMD in patients with T2DM than in control individuals, depending on the skeletal site. The differences between patients with T2DM and participants without diabetes mellitus for forearm BMD were not significant, perhaps due to reduced statistical power as forearm BMD was included in fewer studies.

Because T2DM is associated with obesity, this meta-analysis[27] also evaluated the effects of BMI and found that in general, the association between T2DM and BMD remained despite correction for BMI. The authors postulated that additional factors, including altered adipokine levels (for example, increased leptin and reduced adiponectin) and

hyperinsulinaemia might potentially have mediated the effects of obesity on BMD in T2DM[27].

Along with increased BMD, several studies have noted reduced bone turnover in patients with T2DM[28–30]. As shown in FIG. 2 from a previous study from our group[29], patients with T2DM have reduced markers of bone formation (serum levels of procollagen type 1 amino-terminal propeptide (P1NP); FIG. 2a) and resorption (carboxy-terminal telopeptide of type 1 collagen (CTx); FIG. 2b). The mechanisms underlying the reduced bone turnover in patients with T2DM are unclear. However, one study[30] found that bone formation and resorption markers were not reduced in participants with obesity who were insulin sensitive, but were reduced in participants with obesity who were insulin resistant and in patients with T2DM, indicating that insulin resistance contributed to the reduced bone turnover in T2DM. In addition, these investigators found that visceral adipose tissue (assessed by CT) was negatively correlated with both serum levels of P1NP (FIG. 2c) and serum levels of CTx (FIG. 2d). Thus, both insulin resistance and increased visceral adipose tissue contribute to the reduced bone formation and resorption indices in patients with T2DM, although there are probably also other factors involved.

Importantly, BMD still predicts fracture risk in patients with T2DM; however, the FRAX algorithm generally underestimates fracture risk in patients with T2DM[4]. Although this underestimation is related, at least in part, to an increased risk of falls[31], additional factors are probably also involved, leading to the search for indices of 'bone quality' that might be impaired in patients with T2DM. The spine trabecular bone score, which is derived from the texture of the spine DXA image, is reduced in patients with T2DM and predicts fracture risk independent of BMD[32]. In addition, a number of studies have utilized high-resolution peripheral quantitative CT (HR-pQCT) to evaluate the effects of T2DM on bone microarchitecture in the peripheral skeleton (radius and tibia). These studies have generally found preserved, or even improved, trabecular bone microarchitecture in patients with T2DM compared with control individuals without diabetes mellitus[33–38]. However some[35,36,38–40], but not all[29,37,41], studies have found increased cortical porosity in patients with T2DM, which independently predicts fracture risk, at least in postmenopausal women without diabetes mellitus[42,43].

### Impairments in bone material properties and increased cortical porosity in T2DM.

Another aspect of bone quality that might be impaired in patients with T2DM is the material property of bone. Using in vivo microindentation, our group initially reported that postmenopausal women with longstanding (>10 years) T2DM had a reduced bone material strength index (BMSi) compared with age-matched control women who did not have diabetes mellitus[29]. Other groups subsequently reported similar findings[44,45]. Of note, one study found reductions in BMSi in Black patients with T2DM, but not in white patients with T2DM as compared with race-matched subjects without T2DM[46]. However, in a larger cohort of patients with T2DM, we were unable to find a statistically significant difference in BMSi between patients with T2DM and control participants[37].

These data suggest that although patients with T2DM might have alterations in bone quality, specifically increased cortical porosity and impaired bone material properties (that

is, BMSi), heterogeneity could exist within these patients leading to the conflicting findings noted in this section. We reasoned that these skeletal abnormalities could be related to underlying diabetic complications, which might vary from cohort to cohort. Thus, we performed a comprehensive assessment of diabetic complications in a fairly large ($n =$ 171) cohort of men   50 years of age and postmenopausal women with T2DM, as well as 108 control individuals without diabetes mellitus. This assessment included evaluation of urine microalbuminuria, retinopathy, detailed neuropathy testing and vascular testing[37]. The vascular testing included transcutaneous oxygen tension (a non-invasive measure of microvascular blood flow assessed on the dorsum of the foot) and the ankle brachial index (a measure of macrovascular blood flow). These measures, as well as skin advanced glycation end products (AGEs) assessed non-invasively using skin autofluorescence[47] were then related to bone microarchitectural parameters by HR-pQCT and BMSi. AGEs are the products of irreversible, non-enzymatic reactions between proteins and sugars[48,49]. The long-lived and slowly turned-over proteins in bone, most notably collagens[50], are particularly susceptible to these modifications, which negatively affect bone material properties.

In terms of the HR-pQCT parameters, we found that the patients with T2DM had statistically significantly higher bone volume fraction and trabecular thickness at the tibia but not the radius than the control participants, even following adjustment for age, sex and BMI[37]. Overall, cortical porosity was not statistically significantly different between the groups, but we found that patients with T2DM and clinically relevant microvascular disease (defined as a transcutaneous oxygen tension of   40 mm Hg[51,52]) had increased cortical porosity (+21%, $P = 0.031$) at the distal tibia compared with the control participants without diabetes mellitus[37]. As noted already, in this cohort, BMSi did not differ significantly between the groups, but skin AGEs were significantly higher (+17%, $P < 0.001$) in the T2DM patients than in the control participants. Interestingly, significant negative correlations were observed between BMSi and skin AGEs in both the T2DM patients ($r = -0.30$, $P < 0.001$) and the control participants ($r = -0.23$, $P < 0.001$)[37].

Based on these data and previous work[29,44–46], we have proposed a working model for the pathogenesis of skeletal abnormalities and increased fracture risk in patients with T2DM (FIG. 3)[37]. These patients generally have preserved, or even increased, BMD and trabecular bone volume fraction, which is probably related to obesity and/or hyperinsulinaemia (see section on "Mechanisms of skeletal fragility in T2DM")[53,54]. However, these beneficial trabecular bone changes are negated by impaired bone quality, specifically increased accumulation of AGEs that probably contributes to impaired bone material properties, and microvascular disease that could be responsible for increased cortical porosity. The low bone turnover associated with T2DM[28–30] might also contribute to reduced bone quality due to impaired microfracture repair. Collectively, the impaired bone material properties and increased cortical porosity, along with impaired microfracture repair secondary to the low bone turnover lead to skeletal fragility, which, in the setting of peripheral neuropathy and an increased propensity for falls[31], results in the increased fracture risk observed in these patients despite a relative preservation of BMD. Of note, weight loss, which can be crucial in the management of T2DM, might also increase fracture risk. For example, in the Look AHEAD trial, an intensive lifestyle intervention (   7% weight loss) in individuals with

T2DM and obesity or overweight increased the risk of fragility fractures (composite of hip, pelvis or upper arm and/or shoulder) (HR 1.39, 95% CI 1.02–1.89)[55]. Clearly, additional human and animal studies are needed to further test and refine this model, but the model (FIG. 3) does provide a potentially useful framework for such studies.

## Mechanisms of skeletal fragility in T2DM

### Overview of potential mechanisms.

A complex network of hormones, neurotransmitters and other factors are necessary to regulate bone metabolism and energy homeostasis. Mounting evidence has established that the skeleton not only regulates itself via remodelling of bone, but also has far-reaching systemic influences, for example, on whole-body energy metabolism[56–58]. Conversely, basic mechanisms central to energy metabolism have important roles in regulating skeletal homeostasis[59,60]. Precisely how these remarkable functions go awry in T2DM is still unclear and the complexity of the process is becoming increasingly apparent. As reviewed previously[2,61], several multifactorial cellular and molecular mechanisms probably interact to either protect against or contribute to skeletal fragility in T2DM at various stages of the natural course of the disease. These mechanisms include, but are not limited to, effects of hyperinsulinaemia, obesity and increased bone marrow adiposity, long-term hyperglycaemia and accumulation of AGEs, inflammation, reactive oxygen species, oxidative stress, accumulation of senescent cells and the presence of diabetic complications such as microvascular disease[2,62].

In the early stages of T2DM, hyperinsulinaemia is probably responsible for the preserved, or improved, BMD and trabecular bone microarchitectural parameters observed in patients with T2DM[35,54,63], as insulin is osteoanabolic[53,64]. The benefit of hyperinsulinaemia to bone is independent of adipose tissue mass[65]. This early stage advantage in trabecular bone microarchitecture is not maintained at the later stages of T2DM[63], when hyperinsulinaemia subsides due to β-cell failure.

The increased BMI and percentage body adiposity that is common in patients with T2DM might have beneficial effects on the skeleton due to the protective effects of greater mechanical loading. These effects are perhaps either potentiated or offset by the complex actions of adipokines (for example, adiponectin and leptin) and by the pathophysiological effects of adipose-derived pro-inflammatory cytokines[61]. The skeletal effects of obesity could also be dependent on adipose distribution, as depots associated with insulin resistance and the metabolic syndrome, such as visceral adipose tissue and bone marrow adipose tissue (BMAT), have been linked to increased chronic inflammation[60,61]. Examples of pro-inflammatory cytokines associated with increased visceral adipose tissue mass include TNF and IL-6 (REF.[66]). Along with other factors, these cytokines promote bone resorption by stimulating production of the osteoclastogenic cytokine RANKL[67], which could have a causal role in the development of cortical porosity in uncontrolled T2DM.

Obesity in the setting of T2DM is also associated with increased BMAT in both rodents[68] and humans[69]; however, the functional roles of this adipose depot remain incompletely understood. Although some evidence suggests that BMAT is negatively correlated with

BMD in postmenopausal women with T2DM and obesity, and that women with poorly controlled diabetes mellitus have increased levels of BMAT[70,71], the mechanism underlying these observations are unknown. Clearly, a better understanding of the roles of BMAT in potentially mediating skeletal fragility in T2DM is needed. Some evidence from the past few years suggests that high levels of BMAT-derived lipids both locally in the bone marrow and in the circulation generate reactive oxygen species and oxidative stress that are detrimental to the functions of stem and progenitor cells as well as to cells of the osteoblast lineage[60]. Furthermore, studies in rodents[72] and humans[73,74] have found that levels of sclerostin, a potent soluble antagonist of the bone-anabolic canonical WNT–β-catenin signalling pathway[75], are increased in T2DM and correlate with BMAT accumulation[76]. Taken together, these mechanisms might, at least in part, explain the low bone formation rates observed in T2DM.

**The role of cellular senescence in mediating skeletal fragility in T2DM.**

Diverse forms of age-related stress or metabolic insults, including DNA breaks, reactive oxygen species, proteotoxic aggregates and inflammation, converge to cause a cell to enter an essentially irreversible permanent growth arrest, termed senescence[77]. The senescence programme is activated by cyclin-dependent kinase inhibitors, most notably p16$^{Ink4a}$ and p21$^{Cip1}$, that antagonize the actions of cyclin-dependent kinases to halt cell proliferation and malignant transformation[78,79]. Senescent cells develop an altered gene expression profile that includes upregulation of senescent cell anti-apoptotic pathways[80] and a senescence-associated secretory phenotype (SASP), typically consisting of pro-inflammatory cytokines, chemokines and matrix remodelling proteins[81,82]. Accumulation of senescent cells increases with ageing, obesity and T2DM[77,83,84]. In these contexts, the accumulation of senescent cells is presumably due to metabolic dysfunction, inefficient immune system removal and resistance to apoptosis[85,86]. The biological relevance and consequences of senescent cells are becoming evident in several models of ageing and disease[77], including models of T2DM.

Obesity and T2DM are associated with the premature increased burden of senescent cells in adipose tissue[87,88], pancreatic β-cells[89], liver[90], brain[91] and bone[62], which contributes to metabolic dysfunction and several accelerated ageing phenotypes[77]. Mechanistically, the SASP of senescent cells, characterized by increased levels of pro-inflammatory cytokines (for example, IL-6, TNF and activin A), contributes to insulin resistance in T2DM by disrupting insulin signalling, attracting macrophages that exacerbate inflammation and spreading senescence to neighbouring cells and tissues[88,92–95]. In addition, the consequences of T2DM (for example, glucotoxicity and lipotoxicity) can amplify the accumulation of senescent cells in multiple tissues, resulting in a pathogenic positive feedback loop[83]. This systemic increase in senescent cell burden contributes to the development of metabolic dysfunction and several other diabetic complications, such as cardiovascular disease, neurodegeneration, renal disease and hepatic steatosis[77]. These effects are exacerbated in patients with poorly controlled T2DM.

With regard to skeletal fragility, work from our group published in 2020 demonstrated accelerated osteocyte senescence and poor bone quality in an inducible obese mouse model of T2DM[62]. Importantly, obesity was induced in these mice during adulthood, after skeletal

maturity. After 3 months of established disease, these mice display several detrimental alterations in bone quality that closely mirror those in bones from humans with T2DM, including defective cortical bone microarchitecture, reduced biomechanical strength and impaired bone material properties[62]. In addition, bone histomorphometry revealed lower bone formation rates in mice with T2DM than in non-diabetic mice[62], again consistent with data in patients with T2DM[96].

A combination of multiple key characteristics (as encouraged by a consensus article[97]) was used to identify senescent osteocytes in mice with T2DM. First, mRNA expression of the key mediators of senescence, $p16^{Ink4a}$ and $p21^{Cip1}$, were found to be statistically significantly elevated in osteocyte-enriched bones of T2DM mice (FIG. 4a). Further, as shown in FIG. 4b, the senescence-associated distension of satellites assay[98] (that is, large-scale unravelling of peri-centromeric satellite DNA characteristic of senescent cells), revealed that the percentage of senescent osteocytes was statistically significantly higher in bone cortices of T2DM mice than in control mice (FIG. 4c). We also measured telomere-associated foci (TAF), a specific, robust marker of senescence, in osteocytes (FIG. 4d). TAF are sites of DNA damage ($\gamma$H2AX), which colocalize with telomeres[97]. As quantified (FIG. 4e), the percentage of TAF$^+$ osteocytes increased in bone cortices of T2DM mice. Finally, quantitative PCR with reverse transcription was used to measure a panel of established SASP genes[81,82,99] in the osteocyte-enriched samples of T2DM mice[62]. Interestingly, this analysis revealed a unique pro-inflammatory SASP composed predominantly of upregulated levels of matrix metalloproteinases (MMPs; that is, *Mmp3*, *Mmp9*, *Mmp12* and *Mmp13*) (FIG. 4f). In addition, the expression of *Nfkb1* (which encodes NF-$\kappa$B), a downstream target of the RAGE pathway[48,100] that is activated by AGEs[48], was also statistically significantly elevated in osteocyte-enriched bones of T2DM mice (FIG. 4f). Thus, elevated levels of MMPs and NF-$\kappa$B seem to be part of the SASP signature of senescent osteocytes unique to T2DM[62]. These findings establish that T2DM, in the context of obesity, causes the premature accumulation of senescent osteocytes during young adulthood, at least in a mouse model. Other bone-resident cell types, however, might also become senescent and additional key SASP factors specific to T2DM are likely to exist.

### Role of AGEs.

As noted above, the production and accumulation of AGEs is an important complication of hyperglycaemia observed in patients with T2DM. Based on rodent and cadaver studies, AGEs lead to impairments in the ability of collagen to dissipate energy and a reduction in the capacity of organic and mineralized matrix to creep (deform under mechanical stress), leading to bone fracture at low levels of strain[101]. In addition to their direct effects on bone material properties through collagen modification, AGEs also bind to and can signal through a transmembrane protein termed receptor for AGE (RAGE, the protein product of the *Ager* gene) in diverse cell types throughout the body, including in the osteoclastic and osteoblastic cell lineages in bone[102,103]. Indeed, $N^\varepsilon$-(1-carboxymethyl)-l-lysine is a dominant RAGE ligand in bone and has been found to accumulate in the bone and serum of mice with T2DM[62,104,105].

Of note, almost all of the data regarding the accumulation of AGEs in bone are currently derived from rodent studies, as studying this issue in humans is a challenge. However, one study has quantified serum levels of AGEs (pentosidine and total AGEs) as well as AGEs from proximal femur specimens from participants with and without T2DM[106]. Serum levels of pentosidine or total AGEs did not differ between groups, but cortical bone levels of AGEs tended to be higher in the participants with T2DM than in those without T2DM (+21.3%, $P$ = 0.08), whereas trabecular bone levels of AGEs were similar between the groups. Cortical or trabecular bone levels of AGEs were only weakly correlated ($r$ = 0.28–0.39) with serum levels of AGEs. Additional human studies are needed to evaluate the accumulation of AGEs in bone in patients with T2DM and the relationship of these to AGEs in serum, urine or skin. In terms of fracture risk, a study found an association between urinary levels of pentosidine and vertebral fracture risk in patients with T2DM[107]. Collectively, these data demonstrate that AGEs accumulate in patients with T2DM and provide the basis for future studies of accumulated AGEs in the context of T2DM and its effects on bone material properties.

A number of intracellular signalling pathways are potentially activated through RAGE signalling (including PKC, JAK–STAT, PI3K and MAPK), many of which converge on the activation of NF-κB signalling, thereby generating an inflammatory response that contributes to T2DM[48,100]. This observation suggests that specific blockade of RAGE signalling might alleviate the increased inflammatory response seen in bone in patients with T2DM. Indeed, it has been demonstrated that the soluble RAGE molecule (sRAGE) inhibits HMGB1-induced inflammation[108]. In addition, sRAGE slowed the rate of alveolar bone loss in a diabetic model of periodontal disease[109]. Small-molecule inhibitors have also been shown to inhibit RAGE signalling and have anti-inflammatory effects in Alzheimer disease, neuroinflammation and cancer[110,111]. Some of these RAGE inhibitors have also been shown to prevent bone loss through RAGE-dependent inhibition of osteoblast and/or osteocyte apoptosis[112,113]. Whether blockade of RAGE signalling in bone improves bone material properties in the context of T2DM is a subject of ongoing research.

### Links between the vasculature and bone.

In addition to the accumulation of AGEs and senescent cells in bone, another potential contributor to skeletal fragility in T2DM is macrovascular and microvascular disease. Histological examination of bone remodelling units, the clusters of cells responsible for the active processes of bone resorption and formation, has revealed the presence of a capillary system that provides the bone remodelling unit access to the bloodstream, nutrients and other cells involved in bone homeostasis[114]. The crosstalk between the vasculature and bone remodelling compartments is essential for proper bone development, normal functioning and repair following bone injury[115]. Disruptions in this interface can lead to impaired bone homeostasis, as is often seen in diseases such as T2DM[115]. This crosstalk occurs between vascular endothelial cells and other neighbouring cells that assist in the control of bone metabolism. Mesenchymal stem cells for example, have intrinsic osteogenic capacity and promote vascularization through communication with vascular endothelial cells, which occurs via pro-angiogenic factors such as vascular endothelial growth factors, insulin-like growth factors, platelet-derived growth factors and fibroblast growth factors[116,117]. Crosstalk of vascular endothelial cells also exists with other cell

types, such as periosteum-derived progenitors[118], adipose-derived progenitors[119], stromal cells[120], macrophages[121] and pericytes[122]. The interactions between endothelial cells and these auxiliary cells promote angiogenesis and bone mineralization, leading to normal and healthy bone metabolism.

The appearance of vascular disease in patients with T2DM is a common diabetic complication, due to hyperglycaemia damaging blood vessels[123]. Another common feature in diabetic bone disease is increased cortical porosity, which has been found in patients with T2DM in several studies[35,36,39,40]. In our 2020 study[37], we found that our cohort of patients with T2DM and clinically relevant microvascular disease (defined as exhibiting a lowered oxygen tension, as described previously) had increased cortical porosity at the distal tibia. The causal link between lowered oxygen tension and cortical porosity in T2DM is unknown, but impaired crosstalk between the bone vasculature (for example, vascular endothelial cells) and osteogenic cell precursors could be a potential mechanism. In this model, the decreased vascularization, and therefore the decreased number of vascular endothelial cells, would lead to reduced signalling for the recruitment and differentiation of osteogenic precursor cells. This reduced signalling would inhibit the restoration of bone formation at sites of intracortical remodelling, leading to the appearance of a cortical pore that cannot be filled. However, further studies are clearly needed to fully understand the link between the vasculature and cortical porosity.

FIGURE 5 builds on FIG. 3 and presents a working model of the cellular and molecular changes leading to impaired bone quality and skeletal fragility in patients with T2DM, focusing specifically on AGEs, cellular senescence and microvascular disease. Multiple key mechanisms and effects, stemming from the accumulation of AGEs and senescent cells, converge to cause accelerated ageing of several tissues, including bone. Over long periods, these mechanisms (and probably additional mechanisms) contribute to established skeletal complications in T2DM, such as low bone turnover and abnormal collagen and mineralization, which leads to impaired bone material properties. In addition, the microvascular disease associated with T2DM probably contributes to compromised cortical bone microarchitecture, ultimately increasing fracture risk[124]. Given that these mechanisms are linked and overlap, interventions that target one could in theory ameliorate others and have beneficial influences on multiple systems and physiological functions in T2DM. Therefore, basic mechanisms central to energy metabolism and accelerated ageing, such as cellular senescence and the RAGE pathway, are potential therapeutic targets for interventions that could alleviate or partially treat T2DM and its complications, including skeletal fragility.

## Treatment of skeletal fragility in T2DM

Currently, limited evidence exists for therapeutic interventions to prevent or treat skeletal fragility in patients with T2DM. However, similar to individuals without T2DM, lifestyle measures, including appropriate physical activity, smoking cessation, avoidance of alcohol abuse and assuring adequate dietary calcium and vitamin D intake, should be implemented as the mainstay of osteoporosis prevention and treatment in patients with T2DM[125]. As noted already, evidence from the Look AHEAD trial shows that intensive lifestyle

intervention leading to considerable weight loss in individuals with T2DM and obesity or overweight increases the risk of fragility fractures[55]. Thus, a fracture prevention programme, especially weight-bearing exercise, to balance the potential negative effects of weight loss in patients with T2DM should be considered.

Patients with T2DM have an increased risk of falls[126,127], so risk factors for falls, including visual impairment due to diabetic retinopathy, peripheral neuropathy, poor balance, sarcopenia, cardiovascular diseases, sequalae of stroke (neurological and cognitive impairment) and hypoglycaemic events, should be included in the evaluation of fracture risk in patients with T2DM[23,127]. Fall risk should be rigorously assessed and, where appropriate, preventive measures instituted. A systematic review demonstrated that fall prevention programmes in patients with T2DM[128] and peripheral neuropathy[129] improved balance without the risk of adverse effects in older adults ( 60 years of age) with T2DM.

### Impact of diabetes mellitus medications on fracture risk.

As discussed already, maintenance of good glycaemic control and avoidance of hypoglycaemia should reduce fracture risk. Although no prospective trials have been performed on the effects of diabetes mellitus medications on bone fragility, evidence from epidemiological studies and adverse effects surveillance in clinical trials in diabetes mellitus have provided important insights into the potentially beneficial or adverse effects of diabetes mellitus medications on fracture risk (TABLE 2)[2,61]. Insulin use has also been associated with an increased risk of fractures[130]; however, whether insulin use is a marker of the severity and/or duration of the disease or the occurrence of hypoglycaemic events that precipitate falls is uncertain. The choice of insulin formulation might affect fracture risk, as long-standing therapy with insulin glargine was associated with a lower fracture risk than treatment with NPH insulin[131]; whether this difference was related to a reduced frequency of hypoglycaemia with insulin glargine remains to be determined. However, another study found no differences between types of insulin and risk of fractures[132].

Medications with a neutral or favourable effect on bone metabolism, such as metformin and incretin-based treatments, should be the preferred treatment in patients with T2DM at increased fracture risk based on BMD testing and/or FRAX scores[133]. Interestingly, the latest meta-analysis of GLP1 receptor antagonists, which included 38 studies with 39,795 patients (241 incident fractures, 107 in the GLP1 receptor antagonist group and 134 in the control group), found that when compared with placebo and other antidiabetic drugs, liraglutide and lixisenatide were associated with a statistically significant reduction in the risk of fractures and the beneficial effects were dependent on the duration of treatment[134]. By contrast, use of thiazolidinediones should be avoided as these drugs are associated with an increase in fracture risk[135]. SGLT2 inhibitors, specifically canagliflozin, should also probably be used with caution in patients with T2DM as this drug has also been associated with increased fracture risk[136] However, the most recent meta-analysis (from 2019) which included 27 eligible randomized controlled trials with 20,895 participants with T2DM, with an average study duration of 64.22 weeks, did not find an increased risk of fracture in patients with T2DM treated with SGLT2 inhibitors[137]. More long-term follow-up data are needed to clarify the impact of SGLT2 inhibitors on fracture risk.

In addition, concomitant medications related to comorbidities should also be carefully considered for their possible effects on fracture risk in patients with T2DM; note that much of the data cited in this section has come from studies largely in patients without diabetes mellitus. In terms of antihypertensive medications, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial, thiazide diuretic users had a lower risk of fracture in adjusted analyses (HR 0.79, 95% CI 0.63–0.98) than users of calcium channel blockers or angiotensin-converting enzyme inhibitors[138]. In a large Swedish cohort study published in 2020, loop diuretics were associated with an increased risk of hip fracture (HR 1.23, 95% CI 1.11–1.35). No statistically significant associations were found between the risk of hip fracture and current exposure to β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or aldosterone receptor blockers[139]. An updated meta-analysis of randomized controlled trials revealed no significant effect of statin treatment on the risk of fractures (RR 1.00, 95% CI 0.87–1.15)[140]. However, antidepressants and drugs for treatment of diabetic neuropathy should be prescribed cautiously because meta-analyses of observational studies have shown increased risk of fractures among users of selective serotonin reuptake inhibitors[141] and tricyclic antidepressants[142] compared with participants not using these medications.

**Impact of osteoporosis medications on fracture risk in T2DM.**

Studies evaluating the antifracture efficacy of current osteoporosis drugs in patients with T2DM have not been widely published. As osteoporosis in T2DM is a condition with a low bone turnover, antiresorptive medications, which further reduce bone turnover, might not be the preferred option[28–30]. However, a meta-analysis evaluating osteoporosis drugs, including bisphosphonates (which are potent antiresorptive drugs), found an efficacy similar to that achieved in patients with osteoporosis but without diabetes mellitus[143]. Nonetheless, randomized control trials are needed to assess the antifracture efficacy of osteoporosis drugs in patients with T2DM. In the absence of further evidence, bisphosphonates remain the first choice for osteoporosis treatment in patients with T2DM. However, the possibility that the RANKL antagonist, denosumab could have favourable effects on glucose metabolism could make that a more attractive antiresorptive option for patients with T2DM than bisphosphonates. Thus, although a post hoc analysis of the FREEDOM trial showed no overall effect of denosumab on fasting glucose levels in postmenopausal women with diabetes mellitus or prediabetes, a statistically significant decrease in fasting serum levels of glucose was observed in women with diabetes mellitus not using antidiabetic medications[144]. Interestingly, as, in animal studies, denosumab induced human β-cell proliferation both in vitro and in vivo[145], the possibility of using it in the future as a treatment for T2DM itself has been raised[146]. Indeed, in 2020, our group reported that denosumab-treated patients showed a statistically significant improvement in $HbA_{1c}$ of a magnitude similar to that seen with commonly used antidiabetic medications, relative to no treatment or bisphosphonate use[147].

Finally, post hoc analysis of patients with T2DM from the Abaloparatide Comparator Trial In Vertebral Endpoints (ACTIVE), a phase III, double-blind, randomized, placebo-controlled and active-controlled trial, showed that in women with postmenopausal osteoporosis and

T2DM, abaloparatide treatment led to statistically significant improvements in BMD compared with placebo, similar to the improvements in the overall ACTIVE population[148].

### Future directions.

Future directions for treatment of T2DM-related skeletal fragility will be driven by mechanistic insights into the factors that cause compromised bone quality (for example, RAGE inhibitors and senolytic drugs). Based on the pathogenesis of T2DM-related skeletal fragility, RAGE inhibitors are potential agents that might help alleviate fracture risk in patients with T2DM. Several studies have demonstrated beneficial effects with RAGE inhibitors in various age-related pathologies, including T2DM, cardiovascular disease, neurodegeneration and cancer[149]. Moreover, downregulation of RAGE signalling has been shown to protect against disease-induced bone and muscle loss[150,151]. Notably, in bone, genetic RAGE deficiency protects against ovariectomy-induced bone loss in mice[150]. However, studies have shown that short-term pharmacological RAGE inhibition does not protect against early ageing-induced bone loss[152]. Further studies of RAGE inhibitors are needed to evaluate their role in preventing or treating T2DM-related skeletal fragility. As described already, senescent cells accumulate in the bone microenvironment in a T2DM mouse model[62] and these cells could lead to a reduction in bone formation and a relative increase in bone resorption[153]. Intermittent senolytic therapy reduces senescent cell burden, which simultaneously suppresses bone resorption with either an increase (in cortical bone) or maintenance (in trabecular bone) of bone formation, leading to higher levels of bone formation relative to bone resorption[153]. However, further research is needed to better understand whether the clearance of the senescent cells would be beneficial for skeletal fragility in the setting of T2DM.

## Conclusions

The evidence is now clear that skeletal fragility should be included among known, established diabetic complications such as retinopathy, nephropathy, neuropathy and vascular disease. Patients with T2DM tend to sustain fragility fractures despite higher levels of BMD than individuals who do not have diabetes mellitus, with impaired bone material properties seeming to most consistently contribute to skeletal frailty in patients with T2DM. Alterations in bone material properties are related, at least in part, to AGE accumulation. In addition, patients with T2DM also have increased cortical porosity, which is linked to microvascular disease. The underlying cellular and molecular mechanisms leading to skeletal fragility in T2DM are complex, but probably involve AGE effects not only on bone material properties, but also on bone cell function through RAGE signalling. Additionally, premature accumulation of senescent cells could possibly lead to an accelerated skeletal ageing phenotype in T2DM, as seems to be present in other tissues. Although standard osteoporosis drugs remain the mainstay in preventing fractures in patients with T2DM, future research should focus on targeting the underlying mechanisms (for example, RAGE signalling and senescence) that mediate the skeletal fragility in patients with T2DM.

## Acknowledgements

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**Key points**

- Fracture risk is increased in patients with type 2 diabetes mellitus (T2Dm) despite normal, or even increased, bone mineral density.

- Clinical studies have revealed that the two most consistent alterations in bone quality in patients with T2Dm are impaired bone material properties and increased cortical porosity.

- These abnormalities seem to be linked, at least in part, to accumulation of advanced glycation end products (leading to impaired bone material properties) and microvascular disease (leading to increased cortical porosity).

- evidence from the past few years also indicates that T2Dm, at least in mice, is associated with accelerated skeletal ageing and increased accumulation of senescent cells, in bone as well as in other tissues.

- Current strategies for fracture prevention in patients with T2Dm include minimizing exposure to diabetes mellitus drugs that increase fracture risk and use of osteoporosis medications shown to be effective in patients without diabetes mellitus.

- Further studies are needed to evaluate the efficacy of osteoporosis medications specifically in patients with T2Dm and to develop new drugs targeting the mechanisms potentially driving skeletal fragility in patients with T2Dm.
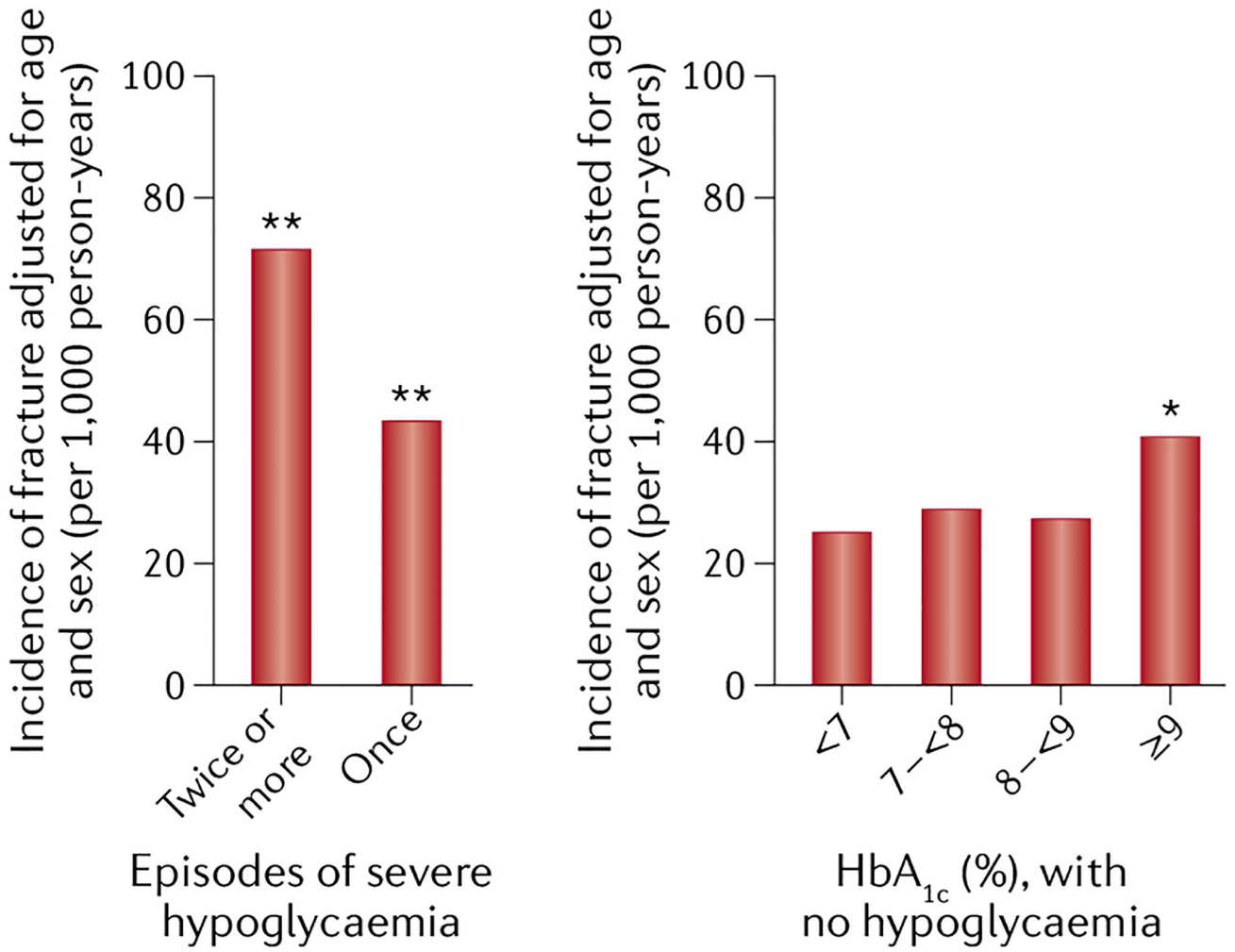
**Fig. 1 |. Age-adjusted and sex-adjusted incidence of fractures based on the number of hypoglycaemic episodes and baseline HbA$_{1c}$ in a cohort of Japanese patients with T2DM.**
Multiple episodes of hypoglycaemia are associated with a marked increase in fracture risk, and even a history of a single episode of hypoglycaemia results in an increase in fracture risk. In the absence of hypoglycaemia, fracture risk is increased significantly in patients with HbA$_{1c}$ values 9%. *$P < 0.01$, **$P < 0.001$ versus the reference group (HbA$_{1c}$ <7% without severe hypoglycaemia). Adapted with permission from Komorita et al. 2020[24].
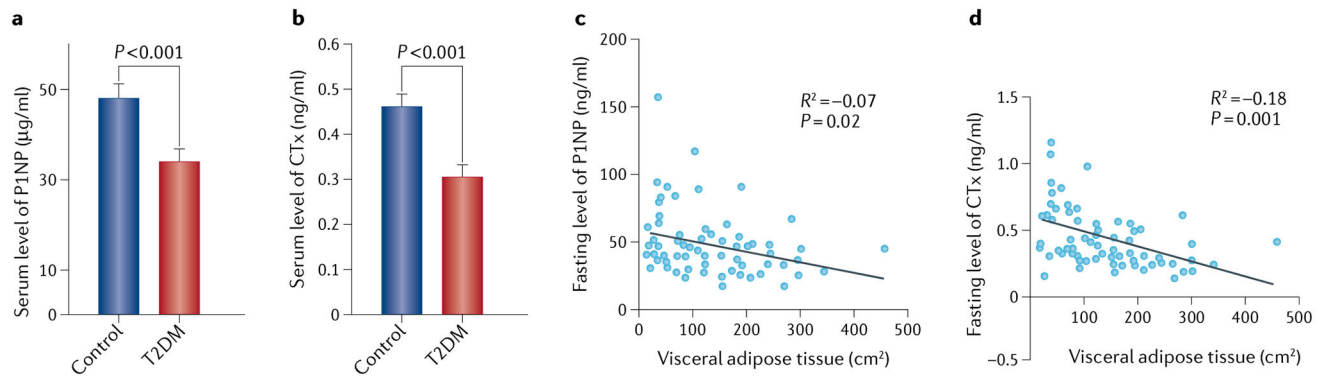
**Fig. 2 |. Bone turnover is reduced in patients with T2DM.**
Serum levels of procollagen type 1 amino-terminal propeptide (P1NP) (part **a**) and of carboxy-terminal telopeptide of type 1 collagen (CTx) (part **b**) in a cohort of patients with type 2 diabetes mellitus (T2DM) compared with a cohort without diabetes mellitus, demonstrating the reduction in bone turnover observed across studies in patients with T2DM[29]. Correlation between visceral adipose tissue area (assessed by CT) and serum levels of P1NP (part **c**) and of CTx (part **d**) in a combined cohort of people without diabetes mellitus (including those who were lean and those with obesity) and patients with T2DM. Parts **c** and **d** adapted with permission from Tonks et al.[30].
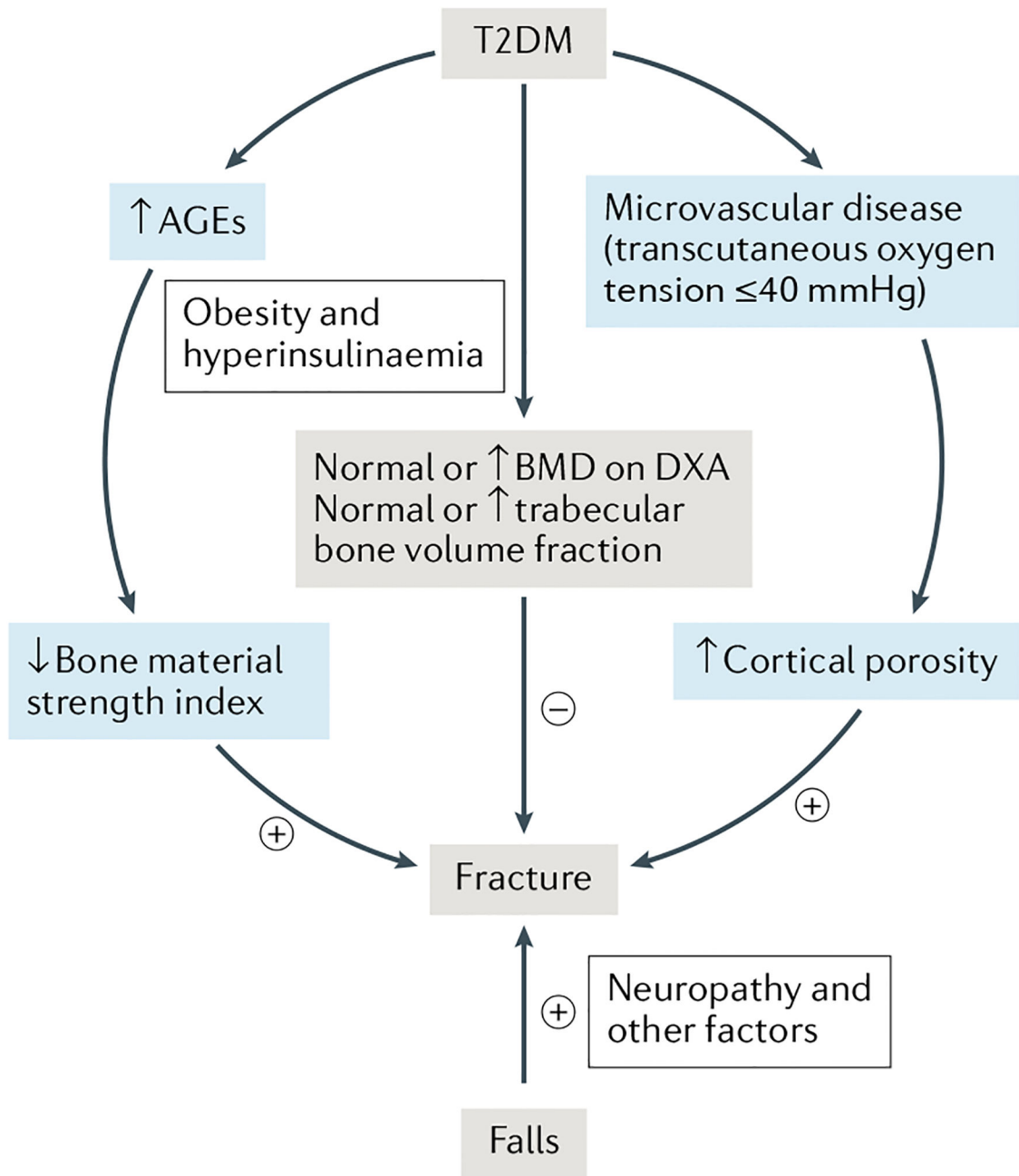
**Fig. 3 |. A working model for the pathogenesis of skeletal fragility and increased fracture risk in patients with T2DM.**
Patients with type 2 diabetes mellitus (T2DM) generally have preserved or increased bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DXA) and trabecular bone fraction as measured by high-resolution peripheral quantitative CT (HR-pQCT), which is probably related to obesity and/or hyperinsulinaemia. However, these patients have impaired bone quality, including increased accumulation of advanced glycation end products (AGEs) in bone that leads to impaired bone material properties and microvascular disease that contributes to increased cortical porosity. Patients with T2DM also have an increased propensity for falls, which further contributes to fracture risk. +,

increases fracture risk; −, decreases fracture risk. FIGURE 3 reproduced with permission from Samakkarnthai et al.[37].
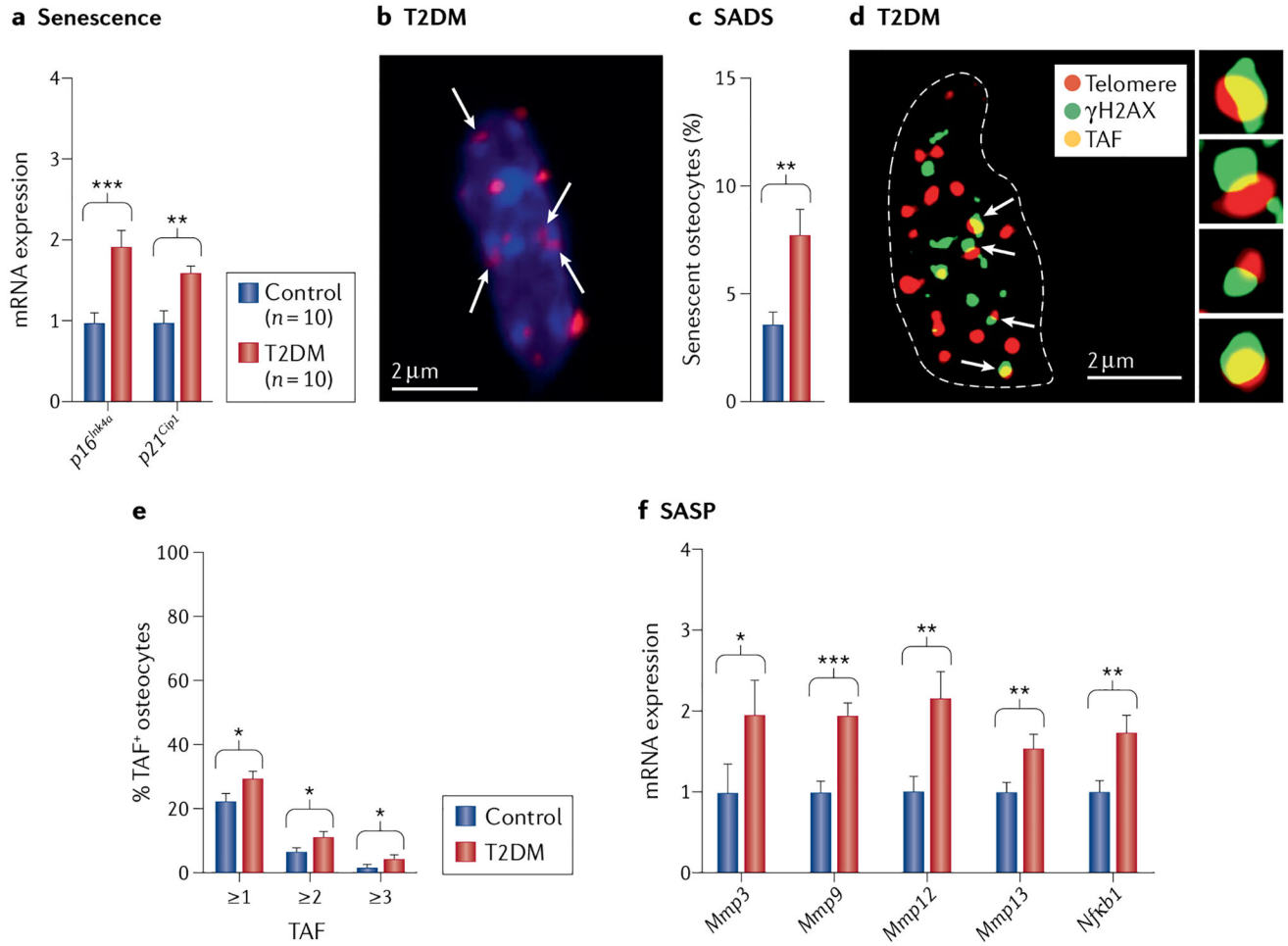
**Fig. 4 |. Accelerated osteocyte senescence in T2DM.**
mRNA expression of $p16^{Ink4a}$ and $p21^{Cip1}$ in osteocyte-enriched bones (part **a**). Senescence-associated distension of satellites (SADS)$^+$ osteocytes in control mice versus mice with type 2 diabetes mellitus (T2DM) (parts **b**, **c**). Arrows in part **b** indicate SADS (unravelling of peri-centromeric satellite DNA) in the osteocyte nucleus. Telomere-associated foci (TAF)$^+$ osteocytes in control mice versus mice with T2DM (parts **d**, **e**). Arrows in part **d** indicate TAFs (yellow) and sites of DNA damage (γH2AX, green), which colocalize with telomeres (red) in the osteocyte nucleus. mRNA expression of senescence-associated secretory phenotype (SASP) markers in control mice versus mice with T2DM (part **f**). Collectively, these data demonstrate that T2DM, at least in a mouse model, is associated with accelerated osteocyte senescence and the secretion of a SASP that might have deleterious skeletal effects. Data are means ± standard error of the mean. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. Adapted with permission from Eckhardt et al.[62].
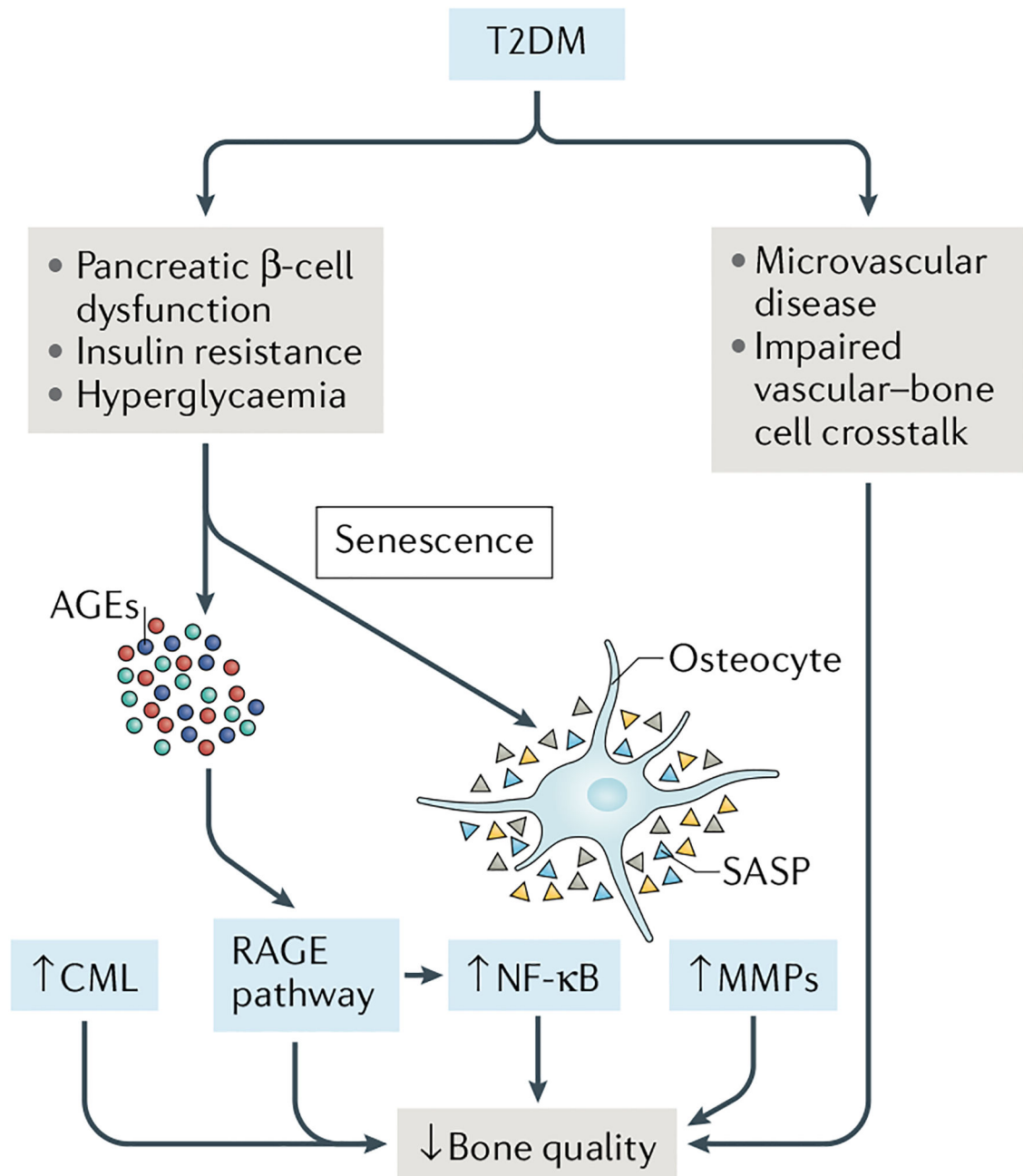
**Fig. 5 |. Emerging pathophysiological mechanisms at the nexus of complications related to T2DM, including skeletal fragility.**

Microvascular disease, including impaired vascular–bone crosstalk contributes to increased cortical porosity and reduced bone quality. Accumulation of advanced glycation end products (AGEs) and cellular senescence activate the senescence-associated secretory phenotype (SASP), which contributes to reduced bone formation and further impairments in bone quality. Coloured circles represent AGEs and coloured triangles represent the SASP. CML, $N^{\varepsilon}$-(carboxymethyl)lysine; MMPs, matrix metalloproteinases. Adapted with permission from Eckhardt et al. 2020[62].

**Table 1 |**

BMD values in women with and without T2DM

| Timepoint | Spine BMD (g/cm²) | | Hip BMD (g/cm²) | |
|---|---|---|---|---|
| | Women with T2DM (*n*) | Women without T2DM (*n*) | Women with T2DM (*n*) | Women without T2DM (*n*) |
| Baseline | 1.04 ± 0.19 (472) | 0.97 ± 0.17 (5,922) | 0.90 ± 0.16 (469) | 0.84 ± 0.14 (5,915) |
| Year 3 | 1.06 ± 0.20 (331) | 0.99 ± 0.17 (4,839) | 0.89 ± 0.16 (331) | 0.84 ± 0.13 (4,831) |
| Year 6 | 1.07 ± 0.21 (253) | 1.00 ± 0.18 (4,203) | 0.87 ± 0.16 (261) | 0.84 ± 0.13 (4,262) |
| Year 9 | 1.12 ± 0.24 (91) | 1.02 ± 0.18 (1,608) | 0.88 ± 0.17 (92) | 0.82 ± 0.13 (1,606) |

Women were recruited from the Women's Health initiative; all comparisons of women with versus without T2DM were *P* < 0.01. BMD, bone mineral density; T2DM, type 2 diabetes mellitus. TABLE 1 adapted with permission from Bonds et al.[26].

**Table 2 |**

Effects of hypoglycaemic agents on fracture risk in T2DM

| Medication | Risk of fracture | Remarks |
|---|---|---|
| Metformin | No effect[154], decrease[8,155–157] | Sub-analysis of the TECOS study (testing the cardiovascular safety of sitagliptin) showed that patients treated with metformin have a reduced fracture risk[157] |
| Thiazolidinedione | Increase[135,156] | Sub-analysis of data from the ACCORD trial indicated that risk of fractures decreases with time after thiazolidinedione discontinuation[158] |
| Sulfonylurea | Decrease[155], no effect[154], increase[156] | Sulfonylureas seem not to directly increase fracture risk in patients with T2DM; however, fracture risk might increase due to increased risk of falls secondary to hypoglycaemia[156,159] |
| Glucagon-like peptide 1 agonist | No effect[160], decrease[134] | Liraglutide and lixisenatide were associated with decreased fracture events[134] |
| Dipeptidyl peptidase 4 inhibitor | No effect[160], decrease[161] | Results of the cardiovascular outcome trials with saxagliptin (SAVOR-TIMI 54)[162] and sitagliptin (TECOS)[157] show the safety (but also lack of benefit) of dipeptidyl peptidase 4 inhibitor treatment regarding the risk of fractures |
| Sodium–glucose cotransporter 2 inhibitor | No effect[137,160], increase[136,163] | Canagliflozin increases the risk of hip fractures[136]; dapagliflozin increases fractures in patients with T2DM who have moderate renal failure[163] |
| Insulin | Increase[132,156] | Insulin use might increase fracture risk due to hypoglycaemia-induced falls[156] |

T2DM, type 2 diabetes mellitus.