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REVIEW

Pathophysiology of Bone Fragility in Type 2 Diabetes Mellitus

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Abstract

Purpose of Review Individuals with type 2 diabetes mellitus (T2DM) are at greater risk of fragility fractures compared to those without diabetes despite comparable or higher bone mineral density (BMD). T2DM may increase skeletal fragility by altering aspects of bone quality including bone geometry, microstructure, tissue properties and remodeling independently of BMD, a parameter of bone quantity. The objective of this review is to synthesize recent work involving aspects of bone quantity and quality that may contribute to fragility in T2DM.

Recent Findings Compared to those without diabetes, women with T2DM have less structurally robust hip geometries despite greater BMD after covariate adjustment. A growing body of evidence indicates that cancellous microarchitecture may be maintained in T2DM; however, cortical bone microarchitecture may be impacted by dysglycemia. Bone material properties – inclusive of tissue and/or compositional properties – and mechanical properties are influenced by T2DM. These include greater concentrations of advanced glycation end-products (AGEs) and increased tissue mineral content, changes associated with greater modulus and hardness, as well as reduced ductility and ability to mitigate damage accumulation. T2DM bone and serum markers indicate reduced bone remodeling compared to controls.

Summary Recent work bolsters prior observations reporting greater AGE and tissue mineral content in T2DM bone and reinforces findings of reduced remodeling. While some evidence indicates that these differences may adversely affect mechanical properties and result in stiffer, stronger – but more brittle – bone, this finding is not universal. Future studies require consideration of the multifactorial underpinnings of bone fragility in T2DM to guide screening, prevention strategies and fracture treatment in this at-risk population.

Keywords Type 2 diabetes · Material properties · Advanced glycation end-products · Remodeling

Introduction

Individuals with type 2 diabetes mellitus (T2DM) have a greater risk of fragility fracture compared to non-diabetic individuals (Relative Risk [RR] = 1.4, 1.7 in representative meta-analyses) [1, 2]. Paradoxically, women and men with T2DM have normal or greater bone mineral density (BMD) as assessed by dual-energy X-ray absorptiometry (DXA) compared to age-matched, non-diabetic controls [1]. The greater fracture risk observed in individuals with T2DM appears to persist even following adjustment for BMD, BMI and falls as well as confounders including renal function and diabetes medication use in larger, observational studies not specifically designed to query diabetes and bone [3, 4]. Collectively, these observations suggest that T2DM may increase skeletal fragility by altering aspects of bone quality (such as bone geometry, microstructure, and tissue properties) independently of bone quantity (BMD).

The pathophysiology of the greater fracture risk observed in T2DM is incompletely understood and is an active area of investigation in the field of metabolic bone disease. Although T2DM may be associated with increased fall risk due to neuropathy, hypoglycemia, low vision, and/or sarcopenia, falls alone do not entirely explain the increased fracture risk, calling into question increased skeletal fragility

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in this at-risk population [5], as characterized in multiple reviews [6–8]. Furthermore, T2DM may have both beneficial and adverse effects on the skeleton, and its net effect on skeletal health may change with disease progression [6]. Beneficial factors, including hyperinsulinemia and large body size, may have favorable effects on bone health by increasing bone mass and size. In contrast, many adverse factors, including hyperglycemia; oxidative stress; fat-derived inflammatory cytokines and adipokines; and AGEs, collectively inhibit osteoblast function, alter bone turnover, and degrade collagen properties [8]. Identification of the individual and combined effects on bone fragility of these competing factors represents a major challenge in characterizing the pathophysiology of bone fragility in T2DM (Fig. 1).

The objective of this review is to synthesize and evaluate recent work that identifies the aspects of bone quantity and quality that may contribute to fragility in T2DM. As reviewed previously, earlier publications have established how BMD assessed by DXA differs in individuals with T2DM [1, 2, 9]. We focus here on key new findings from investigations that have evaluated changes in bone geometry, microarchitecture, and tissue-level compositional and mechanical properties associated with T2DM.

Bone Quantity

Despite normal to elevated BMD as measured by DXA, women and men with T2DM are at increased risk for fracture. BMD is a gold-standard parameter of bone quantity that should correlate with bone strength and predict fragility fracture. Unfortunately, low-trauma, or fragility fracture, is often the first sign of metabolic bone disease in individuals not previously diagnosed with osteoporosis or in those with deceptively normal BMD.

The recognition that women and men with T2DM have an increased risk of fracture compared to those without diabetes emerged over the last few decades thanks, in part, to large prospective cohort studies characterizing changes in health parameters with age. In 1999, Forsen and colleagues published one of the earliest reports quantifying hip fracture risk in women and men with T2DM as a disease state distinct from type 1 disease [10]. Using questionnaire data from the Nord-Trøndelag Health Survey and hospital records of hip fracture, the investigators showed increased fracture risk in both sexes with self-reported type 2 diabetes by up to two-fold compared to those without the disease.

From this early report of skeletal complications arising from T2DM, additional studies emerged confirming

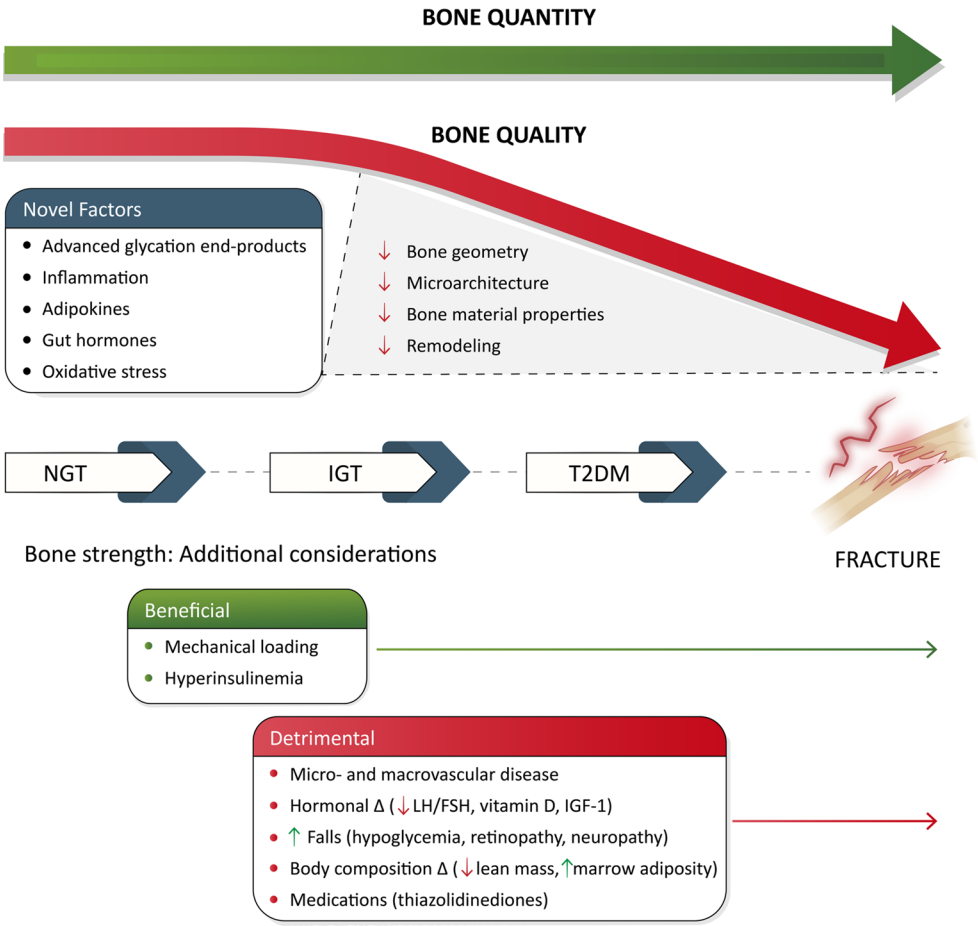

Fig. 1 Pathophysiology of bone fragility in type 2 diabetes mellitus (T2DM) Normal glucose tolerance (NGT); impaired glucose tolerance (IGT)

increased fracture risk at multiple sites in both women and men with T2DM. In 2001, Schwartz and colleagues analyzed data from 6956 older women in the Study of Osteoporotic Fractures and found that non-insulin-requiring women with T2DM were at increased risk for fractures of the hip (relative risk (RR), 1.82; 95% confidence interval (CI), 1.24–2.69) and of the proximal humerus (RR, 1.94; 95% CI, 1.24–3.02) compared to non-diabetic, age and weight-match controls [11]. In this study, insulin-requiring T2DM participants also were found to be at increased risk for foot fracture (RR, 2.66; 95% CI, 1.18–6.02). The prospective Osteoporotic Fractures in Men (MrOS) research study demonstrated that insulin-requiring men with T2DM are at increased risk for non-vertebral fracture (HR 1.74, 95% CI 1.13, 2.69) [12], though not necessarily for fractures at vertebral locations [13]. To date, additional studies and meta-analyses have summarized the site-specific impact of T2DM on fracture risk. Most show that both men and women with T2DM fall into high-risk categories compared to age-, weight-, and sex-matched controls, though the sites of fracture have been less consistent. There is consensus that fracture of the hip, as well as peripheral and nonvertebral sites, are more common in T2DM, with more recent meta-analyses showing that incident and prevalent vertebral fractures are also of concern [14–19].

Bone Loss with Age

To explore the discrepancy between total bone density measured in two dimensions and bone strength, researchers have investigated the rate of bone loss with age in men and women with T2DM as compared to those without diabetes. Schwartz and colleagues found that, despite higher baseline BMD, white women with T2MD had a greater velocity of bone loss at the femoral neck compared to normoglycemic white women (−0.32%/year; 95% CI: −0.61, −0.02), possibly due to greater weight loss with age [20]. In the MrOS study, bone loss in men over 65 was significantly higher for men with T2DM than for those with normal glucose tolerance over a 4.5-year period (T2DM −2.23%; 95% CI: −2.54 to −1.91; $p < 0.001$ vs. −1.57%; 95% CI −1.73 to −1.41) [21]. Note that there may be additional causes of increased bone loss with age in T2DM including microvascular damage, progressive renal failure and decreases in insulin production with longstanding disease and pancreatic insufficiency [22], though these more nuanced contributors were not queried in the epidemiological studies described here.

VBMD by QCT

Though not used routinely in the clinical setting, volumetric bone density (vBMD) assessed by quantitative computed tomography (QCT) can be used as a three-dimensional characterization of bone quantity. A recent review [23] confirms that vBMD assessed by QCT at the lumbar spine and femoral neck is generally but not uniformly greater in individuals with T2DM vs. non-diabetic controls. Differences in vBMD between T2DM patients vs. non-diabetic controls tend to be more pronounced with male sex, older age, and obesity [23–25]. We report first on the largest studies, which focused on the lumbar spine.

In the Health, Aging, and Body Composition Study (Health ABC), which included white and black men and women ($N = 2979$ total, $N = 566$ with T2DM, mean age 74 y), vBMD at the L3 vertebra was 15% greater in patients with T2DM vs. non-diabetic controls and remained greater (7%) after adjustment for gender, race, age, anatomic site, lean mass, fat mass, and abdominal visceral fat [26]. In contrast, vBMD at the lumbar spine was similar across a younger cohort of age-matched diabetic and non-diabetic men and women from the China Biobank project ($N = 10309$ total, $N = 897$ with T2DM, mean age 53 y) [27]. In addition, when vBMD data were stratified by sex and weight (normal, overweight, obese) in a recent study of another Chinese cohort ($N = 1967$ total, $N = 424$ with T2DM, mean age 59 y), vBMD was generally greater in men with T2DM vs. non-diabetic controls, but the differences were statistically significant only in the overweight and obese subgroups [28]. Studies of smaller cohorts showed parallel trends at the femoral neck site to those observed at the lumbar spine in Health ABC [29, 30]. The variability in the QCT data points to potential effects of additional variables such as sex, age, and weight, which may modulate the effects of T2DM on vBMD.

Bone Quality

The limitations of using bone quantity to predict bone fracture risk in T2DM have motivated research into the role of bone quality. Though there are differing opinions as to the definition and components of bone quality, this review will focus on the contributions of bone geometry, microarchitecture, tissue material properties, and bone remodeling to fracture susceptibility in T2DM.

Geometry

Recent review also finds that after accounting for differences in age, race, BMI, and other potential confounders, women with T2DM generally have less structurally robust hip geometries, despite having greater BMD, vs. non-diabetic controls as estimated from DXA images via hip structural analysis (HSA) [23]. Women with T2DM had smaller cross-sectional areas, smaller metrics of resistance to

compression and bending, and higher stresses at the femoral neck vs. non-diabetic controls in analyses of large observational studies and in smaller case-control studies [31–34]. Other data have demonstrated that these differences in hip geometry may be in.

T2DM women managed on insulin rather than oral agents alone [35]. The majority of those studies examined postmenopausal women (mean ages 61–68 y) [32, 33, 35] and were adjusted for age, race, BMI, and other potential confounders. One study examined premenopausal and early perimenopausal women (mean age: 46 y), and the results were adjusted for menopause stage, as well as age, race, and BMI [31]. The small number of studies that included men found no differences in cortical and trabecular parameters in T2DM vs. control groups in models adjusted for age, race, and BMI [32, 36, 37]. Collectively, these results suggest an impaired skeletal adaptive response to load at the hip in women with T2DM and minimal differences in hip geometry in men with T2DM vs. non-diabetic controls.

Microarchitecture

Bone microarchitecture is another important consideration for predicting bone strength and fracture resistance, as a traditional DXA scan cannot wholly capture the structural organization of bone, inclusive of its trabecular and cortical compartments. Differences in the bone microarchitecture of men and women with T2DM compared to those with normoglycemia have been considered as a mechanism to explain variation in fracture risk. Clinically, the use of trabecular bone score (TBS) has been an important complement to DXA scanning using software that quantifies and qualifies pixel variations in bone texture [38]. These variations are thought to represent trabecular connectivity, thickness and structure, with lower TBS scores indicating degraded microarchitecture and higher scores signaling more normal bone. Indeed, Ho-Pham et al. conducted a meta-analysis of TBS data from over 40 K men and women to ascertain differences in bone quality scores depending on diabetes status [39]. In this analysis, women, and to a lesser extent men, with T2DM and undetermined fracture status had significantly lower standardized mean difference in TBS (mean diabetes TBS – mean non-diabetes TBS divided by common standard deviation) compared to those without disease (women, −0.50; 95% CI, −0.69 to −0.32; men, −0.04; 95% CI, −0.17 to 0.10). The utility of fracture prediction using TBS in people with diabetes is similar to that of patients without disease. In The Manitoba Study, a cohort consisting of over 29,000 women, the lumbar spine TBS was a BMD-independent predictor of fracture in both diabetic ($n=2356$) and non-diabetic participants (diabetes, adjusted hazard ratio 1.27, 95% CI 1.10–1.46; without diabetes, HR 1.31, 95% CI 1.24–1.38) [40]. TBS was lower in women with diabetes, despite higher bone density at all sites measured, than non-diabetic participants in models adjusted for age, BMI and other pertinent covariates.

TBS is a surrogate measure of bone quality at the level of the lumbar spine, a site of trabecular microarchitecture. However, data from other imaging modalities including high-resolution peripheral quantitative CT (HRpQCT) scans at peripheral sites indicate that the cortical compartment of diabetic bone may be compromised, whereas the trabecular compartment is generally maintained. In a small study conducted by Burghardt and colleagues, older women with and without T2DM ($n=19$ per group) underwent HRpQCT of the tibia and distal radius [41] distal radius in older women with diabetes. The study was subsequently followed by another comparing the bone microarchitecture of postmenopausal women in four groups – T2DM, T2DM with fracture, no T2DM, and no T2DM with fracture – using HRpQCT. When those with T2DM and fracture were compared to those with diabetes without fracture, women sustaining a fracture had 4.7x increased cortical porosity at the distal radius, 36.8% higher intracortical pore volume at the ultradistal radius and lower total and cortical BMD at the ultradistal tibia [42]. In studies published since these initial investigations, there have been several other analyses quantifying bone microarchitecture at the radius and tibia in T2DM patients. A 2022 meta-analysis of bone microarchitecture in diabetes ($n=516$) vs. healthy controls ($n=3067$) indicated significantly higher cortical porosity at the distal radius, increased cortical thickness at the tibia and distal radius, and improved trabecular microarchitecture as measured by trabecular number and trabecular BMD [43]. These observations of generally-robust trabecular compartments with greater compromise to the cortical compartments were reinforced in two recent narrative reviews [23, 44]. Moreover, the adverse effects of T2DM on cortical bone were more pronounced at the radius than at the load-bearing tibia [43], which suggests that mechanical loading may partially compensate for adverse changes in cortical microarchitecture.

The mechanical consequences of the divergent effects of T2DM on the cortical and trabecular compartments are also evident in the estimates of radial or tibial failure load from finite element analyses of HRpQCT scans. In the same recent meta-analysis [43], failure load at the distal radius and distal tibia were maintained in individuals with T2DM. This suggests that the robust trabecular microarchitecture at these peripheral sites, in contrast to the hip geometry mentioned above, may compensate for the greater cortical porosity.

Tissue Material Properties

Perhaps some of the greatest advancements in understanding bone fragility in the context of bone quality have been in the domain of tissue material properties of the bone itself in T2DM compared to women and men without diabetes (Table 1). Tissue material properties can be further subdivided into the interrelated compositional and mechanical subcategories. Important limitations of all studies to date of tissue material properties in humans with T2DM include cross-sectional, observational study designs, which cannot demonstrate causal links between groupwise differences in bone composition and mechanical properties; generally opportunistic sample collection from heterogeneous populations with underlying skeletal disease, including individuals with osteoarthritis and/or osteoporosis, which may amplify or mask differences in bone properties associated with T2DM; and small sample sizes, which may limit power to detect differences between T2DM and control groups. Nevertheless, these studies point to novel differences in compositional and mechanical properties that can be targeted for future prospective studies.

Compositional Properties

Alterations in bone tissue composition with T2DM may arise from disease-induced changes in remodeling, as well as from accumulation of advanced glycation end products (AGEs). AGEs form diverse structures through oxidation or glycation reactions of sugars with free amino groups in protein [45]. These structures include crosslinking AGEs, such as pentosidine (PEN), and non-crosslinking AGEs, such as carboxymethyl-lysine (CML) [46].

Most studies on human tissue show greater concentrations of AGEs in bone in T2D vs. non-DM control groups as reviewed by Moseley and colleagues [47] and outlined in Table 1. A recent study comparing iliac crest biopsies in postmenopausal women with T2DM, impaired glucose tolerance (IGT), and normoglycemic tolerance (NGT) showed that bone tissue from the T2DM group had greater concentrations of the AGE pentosidine (PEN) in cortical and trabecular bone when compared to the IGT and NGT groups [48]. Bone PEN content in the IGT group was lower than in the T2DM group and did not differ from the NGT group, indicating that the greater AGE content observed in T2DM occurred with progressive diabetes. Similarly, cancellous bone from individuals with T2DM undergoing total hip arthroplasty for osteoarthritis (OA) had greater PEN at the femoral neck in men [49] and postmenopausal women [50] as well as at the proximal tibia in men [51]. No differences were observed at the femoral neck in one study of men and women [52]. Greater AGEs were also observed in cancellous bone at the femoral head and cortical bone at the femoral neck in osteoporotic men and women with T2DM and fragility fractures [53, 54]. In cortical bone, individuals with T2DM had greater CML and fluorescent AGEs (fAGEs) at the femoral mid-diaphysis in male and female cadaveric donors [55], and fAGEs trended higher at the femoral neck in men and women with OA [52]. Thus, most existing studies demonstrate greater AGE accumulation in bone tissue from individuals with T2D.

As previously reviewed, alterations in bone mineral properties have also been observed in T2DM [56]. Bone tissue from individuals with T2DM was more mineralized in cortical bone at the iliac crest [57], and in trabecular bone at the femoral neck [49, 58] in subjects with T2DM vs. nondiabetic controls. Furthermore, the distributions of tissue mineral content and acid phosphate, an indicator of new mineral, were narrower in cortical and trabecular bone from individuals with T2DM vs. nondiabetic controls [57, 58]. These differences were consistent with the lower degree of bone formation and resorption observed in T2DM [57], which enables progression of secondary mineralization and results in a more mineralized tissue with less new mineral and a more homogeneous mineral distribution. Together, compositional studies indicate greater AGE concentrations and altered mineralization in patients with T2DM, which may contribute to the greater fragility observed clinically.

Mechanical Properties

Alterations in bone composition can directly affect bone mechanical behavior [45]. Crosslinking AGEs, such as pentosidine (PEN), are implicated in embrittlement of the collagen matrix by impairing energy dissipation mechanisms, such as matrix stiffening [59] and alterations in microdamage morphology [60] and uncracked ligament bridging [61]. Non-crosslinking AGEs, such as carboxymethyl-lysine (CML), may indirectly degrade bone through interactions with the receptor for AGEs (RAGE), and lead to oxidative stress, inflammation, and reduced osteoblast activity [62, 63]. AGEs may also influence osteoclast function and bone resorption [64], although the reported effects are more variable, as reviewed in [45, 65]. Although the exact cellular mediators of RAGE signaling are uncertain [45, 65, 66], current evidence suggests that the indirect, downstream effects of AGE–RAGE interactions may add to direct effects of AGE accumulation on the collagen matrix in T2DM and alter tissue mechanical performance.

Multiple lines of evidence indicate that AGEs embrittle bone, although this finding is not universal [67], and direct measurements of deformation mechanisms that could confirm a causative role of AGEs cannot currently be performed in vivo. Nevertheless, in population-based studies, high

Table 1 Summary of the results of studies of bone quality in clinical specimens from individuals with T2DM vs. non-diabetic controls, for studies published since 2020 (a summary of studies published prior to 2020 can be found in [47]). Studies with similar cohorts or analytical approaches are shown grouped by shading. Abbreviations: aBMD = areal bone mineral density, bmsi = bone material strength index, bv/tv = bone volume fraction, cml = carboxymethyllysine, fAGEs = fluorescent advanced glycation endproducts, gags = glycosaminoglycans, igt = impaired glucose tolerance, ngt = normal glucose tolerance, mmc = mineral maturity/crystallinity, oa = osteoarthritis, pen = pentosidine, tha = total hip arthroplasty, tmd = tissue mineral density, T2DM = type 2 diabetes

First author (year)		Study cohort	Sample size	Anatomic site	Compartments	Metrics	Findings
Sammakarnthai (2020)	(85)	Postmenopausal women > 55y and men > 50y	171 T2DM, 108 control	Radius, tibia; DXA at standard sites	Cortical, cancellous	aBMD, microarchitecture, BMSi	• Bone quality parameters, including BMSi, were similar in T2DM vs. control
Holloway-Kew (2021)	(86)	349 male participants aged 33–96 of the Geelong Osteoporosis Study	47 T2DM, 59 IGT, 234 NGT	Tibia; DXA at femoral neck, lumbar spine	Cortical	aBMD, BMSi, Skin fAGEs	• Men with T2DM had lower mean BMSi (−3.8%) and lower TBS (−4.8%) compared to those without T2DM (NGT and IGT combined)
Rokidi (2020)	(112)	Premenopausal women	26 T2DM, 32 control	Iliac crest	Cortical, cancellous	Compositional properties from Raman imaging	• Compositional properties were similar in T2DM and control groups • At actively forming trabecular surfaces, MMC and GAGs were greater in T2DM vs. control
Hunt (2021)	(57)	Postmenopausal women with T2DM on insulin, IGT, and NGT controls	35 NGT, 26 IGT, 25 T2DM	Iliac crest	Cortical, cancellous	Compositional properties assessed by FTIR imaging, serum PEN, bone turnover markers	• The distributions of cortical bone mineral content had greater mean values (+7%) and were narrower (−10%) in T2DM vs. NGT • The distributions of acid phosphate, an indicator of new mineral, were narrower in T2DM vs. NGT (−14% cortical, −11% trabecular) and IGT (−14% cortical, −10% trabecular) • Bone turnover was lower in T2DM versus NGT groups (P1NP: −25%, CTx: −30%, ucOC: −24%)
Lekkala (2023)	(48)	Postmenopausal women with T2DM on insulin, IGT, and NGT controls	35 NGT, 26 IGT, 25 T2DM	Iliac crest	Cortical, cancellous	Bone AGEs, nanomechanical properties	• Bone tissue from the T2DM group had greater concentrations of (i) pentosidine vs. IGT (cortical + 24%, trabecular + 35%) and vs. NGT (cortical + 40%; trabecular + 35%) and (ii) fAGE cross-link density versus NGT (cortical + 71%; trabecular + 44%). Bone pentosidine content in the IGT group was lower vs. T2DM and did not differ from NGT • Cortical bone from the T2DM group was stiffer (+9%, $p = 0.021$) and harder (+8%, $p = 0.039$) versus the NGT group • Bone tissue AGEs increased with worsening glycemic control assessed by HbA1c
Sacher (2022)	(81)	Men who underwent THA for OA	22 T2DM, 25 control	Femoral neck	Cancellous	Damage accumulation	• Rod-like trabeculae accumulated more damage proportional to their volume than platelike trabeculae in controls, and this difference was absent in T2DM cancellous bone
Sihota (2021)	(53)	Men and women with osteoporosis who underwent THA following fragility fracture	30 T2DM, 40 control	Femoral head	Cancellous	Trabecular microarchitecture, AGEs, compositional properties (ATR-FTIR), mechanical properties	• The diabetic group had lower BV/TV (−14%), lower apparent-level strength (ultimate stress −25%) and toughness (−45%), and lower values of tissue-level modulus (−18%) and hardness (−33%) vs. non-diabetic controls with fragility fractures • The diabetic group had higher total fAGEs (+32%) and lower ash weight (−17%) • Cancellous fAGEs were inversely correlated with postyield energy and toughness.

Table 1 (continued)

First author (year)	Study cohort	Sample size	Anatomic site	Compartments	Metrics	Findings
Yadav (2022) (83)	Men and women with osteoporosis who underwent THA following fragility fracture	26 T2DM, 40 control	Femoral head	Cancellous	BV/TV and dynamic mechanical properties	• The time-dependent mechanical properties were similar in T2DM vs. non-diabetic controls
Sihota (2025) (54)	Men and women with osteoporosis who underwent THA following fragility fracture	10 T2DM, 25 control	Femoral neck	Cortical	Microstructure, mechanical properties, compositional properties	• In T2DM, cortical porosity was higher (+41%), and cortical bone was weaker (ultimate stress −28%), more brittle (post-yield strain −44%), and less tough (toughness −44%) • T2DM bone had higher fAGEs (+24%), higher non-enzymatic collagen maturity (+43%), and lower tissue mineral content (−11%) • Cortical fAGEs were inversely related to the yield- and ultimate strain of T2DM bone.
Britton (2024) (80)	Men and women with OA or osteoporosis who underwent THA	17 T2DM, 17 control	Femoral head	Cortical, cancellous	Microstructure, mechanical properties, compositional properties	• In T2DM, trabecular furosine (+40%), cortical furosine (+65%) and cortical CML (+97%) were higher • In T2DM, BV/TV (+22%), max stress (+47%), and toughness (+56%) were higher • In T2DM, no significant differences were observed in nanomechanical properties, energy dissipation, number of cycles to failure, or microdamage accumulation
Wolfel (2020) (55)	male and female cadaveric donors with T2DM diagnosis	11 T2DM, 16 control	Femur (diaphysis), T12	Cortical	fAGEs; CML	• CML was higher in cortical bone of individuals with T2DM vs. controls. • A subset of T2DM individuals with high cortical porosity exhibited distinct material properties.
Wolfel (2022) (89)	male and female cadaveric donors with T2DM diagnosis	15 T2DM, 15 control	Femur (diaphysis), T12	Cortical	BMSi, TMDM by uCT, Raman spectroscopy	• Properties of T2DM vs. control bone were generally similar. • The high-porosity T2DM subset, but not the T2DM group, showed reduced resistance to indentation and higher carbonate-to-amide I ratio in endocortical bone.
Wolfel (2023) (88)	male and female cadaveric donors with T2DM diagnosis	11 T2DM, 18 control	Femur (diaphysis), T12	Cortical	microstructure, composition, fracture toughness	• Cortical microstructure, composition, and fracture properties were similar in T2DM and control specimens.

levels of serum pentosidine, and other AGE markers, are associated with increased fracture risk, as summarized in a recent systemic review [68]. In animal and human cadaveric studies, bone with higher AGE levels exhibits reduced ultimate strain and energy absorption [69–71] and impaired collagen fibril deformation [72–74]. In in vitro models, AGE accumulation generally stiffens and embrittles bone [75, 76], though not all mechanical changes reach statistical significance [59, 77]. These findings are supported by in silico models that predict collagen fibril stiffening and embrittlement through inhibition of fibrillar sliding from non-enzymatic crosslinking [78, 79]. However, the specific AGEs most responsible for these effects remain an open question.

Indeed, several studies over the past decade analyzed retrieved surgical tissues at the femoral neck or head and found variable effects of T2DM on the mechanical properties of cancellous and cortical bone. In individuals undergoing total hip replacement, the apparent modulus and strength of cancellous bone from men with T2DM were greater even after adjustment for the larger bone volume fraction at the femoral neck in men with OA [49] and at the femoral head in men and women with OA or osteoporosis [80], or similar to controls in bone at the femoral head in studies of individuals with T2DM and OA [50, 52]. Mechanical properties assessed with nanoindentation were similar in trabecular bone of individuals with T2D and non-diabetic controls with OA or osteoporosis [80]. Total damage accumulation and morphology were similar in T2D and non-diabetic controls undergoing monotonic compression in femoral necks of men with OA [81] and undergoing monotonic and cyclic compression in the femoral heads of men and women with

OA or osteoporosis [80]. In the former cohort, non-diabetic control specimens showed that rod-like trabeculae accumulated more damage relative to their volume than platelike trabeculae during monotonic compression testing; this difference was absent in T2DM specimens [81]. These findings are consistent with prior work in non-diabetic bone that showed that trabecular rods accumulate more microdamage as sacrificial elements that protect the load-bearing plates, thereby preventing structural failure during cyclic loading [82]. These results suggest that T2DM bone may be less able to mitigate failure through damage accumulation in sacrificial rod-like trabeculae. However, the latter cohort is the only study to date that directly examined cyclic loading in bone from individuals with T2DM, and no differences were observed in microdamage accumulation or fatigue life [80]. Collectively, results add to the growing body of evidence that, although bone microarchitecture is robust in T2DM, and monotonic tests show greater or similar apparent mechanical properties, the effects of T2DM on matrix material properties and dynamic mechanical properties are unclear. A shortcoming of these studies is that specimens were opportunistically collected from individuals undergoing joint replacement, which represents a highly selective subset of the population of individuals with diabetes, e.g., well controlled diabetes, low HbA1c, and fewer comorbidities. In the study conducted by Britton et al., participants with OA and/or osteoporosis were included in the analyses, two very different disease states that could influence the ability to detect differences in bone microdamage or fatigue life [80]. Examining an overly-narrow or -variable segment of the diabetic population may mask the adverse impact of diabetes on bone fragility. Although it is possible that T2DM minimally affects bone tissue properties, there is enough data that suggests that further study is warranted. In particular, prospective studies are needed with a more representative population of individuals with T2DM.

In contrast, bone tissue from men and women with osteoporosis and T2DM showed impaired strength and energy absorption vs. nondiabetic controls. Specifically, strength and stiffness of cancellous bone were lower, which was largely accounted for by the reduced bone volume fraction (BV/TV) in the cohort with T2DM and osteoporosis [53], and viscoelastic properties were similar across T2DM and non-T2DM bones [83]. Tissue-level nanoindentation modulus and hardness were also lower in the T2DM group. In addition, ultimate stress and strain, post-yield strain, yield energy, total energy (toughness), and post-yield energy were lower in cortical bone; however, it is unclear whether these differences may be explained by the greater bone porosity in the diabetic cohort [54]. Note that this study population with fragility fractures represents a distinct subset of individuals with T2DM. Like studies in those with T2DM and OA, these studies of individuals with T2DM and osteoporosis involve opportunistically obtained tissues retrieved from surgical patients with underlying, known skeletal disease that may also influence tissue properties outside of T2DM factors [84]. Furthermore, individuals healthy enough to undergo joint replacement surgery may not be representative of the general population of individuals with T2DM.

The few studies to date that have investigated the mechanical behavior of bone in individuals with T2DM using approaches different from opportunistic studies of retrieved tissues have yielded somewhat variable results. In iliac crest biopsies from postmenopausal women ($n=84$), cortical bone from the T2DM group had a higher nanoindentation modulus and hardness compared to non-diabetic controls, which reflected greater tissue mineral content and AGEs in the T2DM group [48]. These results contrast with the similar [85] or modestly lower (−4 – −9% vs. control) resistance to in vivo impact indentation at the tibia, assessed by the Osteoprobe device and quantified by bone material strength index (BMSi), in individuals with T2DM relative to non-diabetic controls in larger cohort studies ($n=60$–300) T2DM [86, 87]. In recent studies comparing bones of men and women with hip fragility fractures ($n=35$) with those of cadaveric non-osteoporotic donors ($n=29$), BMSi, nanomechanical properties, and fracture toughness were similar across T2DM and non-diabetic groups [54, 88]. The modest potential impairment of resistance to impact indentation may reflect greater porosity at the tibia captured with the larger indentations of the Osteoprobe, while the greater tissue-level nanomechanical metrics (~10 nm) may capture stiffer, harder, and more highly mineralized bone tissue.

The observed differences in tissue compositional properties may compromise bone ductility and toughness in T2DM. Greater embrittlement of bone associated with increasing concentrations of AGEs has been observed across multiple studies of cadaveric human tissue from donors without known T2DM [69, 72, 73, 75] although this relationship was not observed in donors with a T2DM diagnosis [88, 89]. Here we focus on analyses of human bone tissue from individuals with T2DM which, to date, comprise cross-sectional, observational studies that cannot address whether groupwise differences in compositional properties have a causal relationship with mechanical properties. In men with T2DM, greater total fAGEs, greater mineral maturity, and lower BV/TV in cancellous bone were independently associated with reduced post-yield energy and toughness in the diabetic group, indicating reduced ability of the tissue to absorb energy prior to failure [49]. Similarly, greater AGE concentrations in cancellous bone in men and women with T2DM were associated with reduced ductility, the ability to deform before failure, and greater yield stress, which reflects resistance to permanent deformation

[52]. However, no relationships between bone AGEs and mechanical properties were observed in a similar study [50]. In cancellous bone from individuals with T2DM, greater tissue mineral content was associated with greater indentation modulus and hardness at the tissue level in postmenopausal women, with and greater modulus and strength at the apparent level in men [48, 49]. Together, these results suggest that the differences in bone tissue composition with T2DM, which include increased tissue mineral content and maturity, as well as greater concentrations of AGEs, are associated with stiffer, stronger, and more brittle tissue. These differences in tissue properties in individuals with T2DM can potentially make their bones more susceptible to failure through a single overload or cyclic loading [90]. However, one study to date that examined composition as well as static and dynamic mechanical properties in femoral heads from men and women with T2DM and OA or osteoporosis observed similar energy dissipation, number of cycles to failure, and microdamage accumulation across groups [80]. Because observations of altered mechanical behavior have not been universal throughout the literature, prospective studies are needed to address differences in compositional and mechanical properties of bone in T2DM.

Remodeling

Though not always included in discussions of bone quality, bone remodeling is an important factor in bone strength. This is perhaps most aptly highlighted in patients on longstanding antiresorptive medications (bisphosphonates, denosumab) who sustain subtrochanteric, or atypical, femur fractures. In these patients, osteoblast and osteoclast function is slowed to the point of creating adynamic bone that becomes brittle and unable to sustain loads in vivo. Similarly, studies of bone formation and resorption in individuals with T2DM also demonstrate low bone turnover. In the clinical setting, bone turnover can be measured using serum markers of bone formation (P1NP, osteocalcin, bone specific alkaline phosphatase) as well as bone resorption (C-telopeptides, TRACP). In studies reporting bone turnover markers in T2DM, both resorption and formation are low with longstanding disease [91–93].

Beyond bone turnover markers, investigators have measured levels of circulating osteogenic precursor cells in the peripheral serum of postmenopausal women with and without diabetes ($n=18$ and $n=27$, respectively) as an alternative parameter of bone remodeling. In this small study, the percentage of osteocalcin(+) cells was lower in women with diabetes than in those without (0.8 ± 0.2 vs. $1.6\pm0.4\%$; $P<0.0001$). There was also a higher percentage of immature osteogenic cells ($OCN^+/CD146^+$) in patients with diabetes, potentially consistent with low bone remodeling. In these participants, bone turnover markers were similarly decreased [94].

Transiliac bone biopsy, a tissue-level procedure allowing for in situ measurements of static and dynamic bone remodeling, demonstrates a low turnover state in T2DM, though published data are limited [95]. In the study noted above, a subset of participants agreed to transiliac biopsy (T2DM, $n=5$; controls, $n=4$) with histomorphometry showing reduced bone formation rate, mineralizing surface, osteoid surface and osteoblast surface in T2DM women, consistent with tissue-level evidence of reduced remodeling.

In a larger study comparing bone histomorphometry in postmenopausal women without diabetes to those with T2DM on insulin ($n=35$ and $n=25$, respectively), investigators reported diminished osteoid volume (−40%, $p=0.035$), mineralizing surface (−52%, $p=0.022$) and prolonged mineralization lag time (+268%, $p=0.013$) in women with T2DM compared to women without diabetes [96]. Interestingly, there was decreased new mineral formation, or decreased mineral apposition rates, in both T2DM and women with impaired glucose tolerance ($n=26$) compared to normal controls. These dynamic indices of impaired bone remodeling in early and late-stage T2DM at the tissue-level were consistent with reduced serum markers of bone formation (Procollagen I Intact N-Terminal Propeptide [P1NP], −25%) and resorption (C-terminal telopeptide of type I collagen test [CTX], −30%) in T2DM compared to normal ($p<0.05$).

The exact mechanism by which T2DM adversely impacts bone remodeling is likely multifactorial and may depend on disease duration [45]. There are data showing that, to some extent, AGEs bind to AGE receptors on osteoclasts (RAGEs) and increase bone resorption [97]. Indirectly, AGEs may stimulate the production of inflammatory cytokines such as IL-1, IL-6, and TNF-alpha, which can further accelerate bone resorption [98, 99]. This may be especially true in earlier disease states and has been demonstrated clinically with positive associations between CML, pentosidine and clinical fracture in T2DM [100, 101]. Over time, and with presumably greater AGE accumulation in the bone, AGEs may act to suppress bone resorption and formation, as described above [45, 63–66]. These later-stage effects of AGEs on bone remodeling would be in greater alignment with transiliac bone biopsy as well as bone turnover marker data (C-telopeptides, P1NP, bone-specific alkaline phosphatase) showing relatively adynamic bone in longstanding T2D [94, 96]. It would similarly explain why there are some clinical studies that fail to show an association between circulating pentosidine and fractures [102, 103]. Bone that is not remodeling does not liberate AGEs into the bloodstream for measurement. There may also be a role for the changes in insulin levels linked to the progression of the disease.

Insulin is typically an anabolic hormone to bone, but with increased diabetes duration and the development of pancreatic insufficiency, decreased insulin levels may result in reduced bone collagen formation [104]. Finally, hyperglycemia fluctuations in blood glucose levels as is commonly seen in T2DM may inhibit bone remodeling [105, 106]. In a study conducted by Starup-Linde and colleagues, research participants with and without T2DM ($n=100$ per group) were equipped with continuous glucose monitor sensors for a total of three days. The investigators determined that in participants with T2DM, both the mean amplitude of glycemic excursions as well as the peak dawn glucose levels were inversely associated with low bone resorption and formation as measured by CTX and P1NP, respectively [107].

Diabetes Duration and Fracture Risk

As has been described above, there are multiple factors that impact bone quantity and quality in T2DM with direct implications for impaired bone strength. Many of these factors do not arise overnight, but rather, they arise and accumulate over time as additional "hits" to an already-compromised skeleton (Fig. 1). There is no clear threshold beyond which T2DM transitions from a protective state to one of increased bone fragility, but the data do show that duration of diabetes correlates with increased fracture risk. That is, longer periods of insulin resistance, often accompanied by insulin use, put patients at particularly high risk for fracture. For example, in the Women's Health Initiative Observational Study ($n=93{,}676$), postmenopausal women with clinically reported T2DM were at increased risk for fracture (RR 1.26) despite greater hip and spine BMD [3]. In the meta-analysis conducted by Vilaca et al. [16], investigators queried data from more than 17 million participants with types 1 and 2 diabetes for relationships between age, gender, body mass index and diabetes duration and hip or non-vertebral fracture. The risk of fracture at both sites was elevated (RR1.33, 1.19–1.49 hip, RR 1.19, 1,11–1.28 non-vertebral) in participants with T2DM, particularly for insulin users or those with disease duration > 10-years. Moreover, there are also data from large cohort analyses showing that men and women with self-reported or non-insulin-requiring disease have reduced bone strength compared to individuals without diabetes. As noted, in the Study of Osteoporotic Fractures, postmenopausal women with non-insulin-requiring diabetes were at increased risk of hip (RR 1.82, 95% CI, 1.24–2.69) and proximal humerus (RR, 1.94; 95% CI, 1.24–3.02) fractures [11]. That increased bone fragility was seen in potentially milder disease may be particularly relevant when considering which parameters of bone quantity and quality are more likely to influence skeletal health in diabetes.

Type 1 Diabetes and Fracture Risk

The primary focus of this review was T2DM and its association with skeletal complications. It should be stated that T1DM, or autoimmune destruction of the pancreatic islet cells resulting in insulin deficiency, is also associated with increased fracture risk. In fact, fracture risk in T1DM may be higher in men and women compared to T2DM [108]. There are areas of overlap with respect to the pathophysiology of bone fragility in both types of diabetes. Both conditions are associated with hyperglycemia, and later stages of T2DM may result in pancreatic insufficiency with insulin deficiency. However, patients may differ phenotypically. Bone mineral density is typically lower in T1DM as opposed to normal to greater in T2DM. This is often accompanied by lower BMI and younger age of onset in type 1 disease. In both conditions, bone turnover may be low, and there may be a role for AGE deposition in the skeleton embrittling bones and leading to bone fragility [109, 110]. Microarchitecturally, deficits appear to be in the trabecular compartment for type 1 disease versus cortical compartment with type 2 disease [111]. Neither condition is immune from the micro and macrovascular complications associated with hyperglycemia, particularly in poorly controlled disease. The resultant impact on kidney function, vision, the nervous system, and microvascular and other end organs could drive increased fall risk in addition to having direct implications for healthy tissue remodeling and strength. Continued investigations of both disease states will likely lend important insight into an overlapping rationale for increased bone fragility in diabetics. These factors will be important for future work in improving screening detection, prevention, and interventions to reduce the morbidity and mortality associated with fracture.

Knowledge Gaps and Future Directions

T2DM is a complex disease state. As such, it is unlikely that there is a singular etiology of bone fragility in men and women with glycemic dysregulation. Epidemiologic studies suggest that skeletal compromise in T2D results from more than the increased falls, medication use and renal dysfunction; these large cohort studies, however, were not necessarily designed to measure nuanced and bone-specific outcomes. Rather, they have allowed for hypothesis generation and deeper investigations into factors beyond bone quantity, as measured by DXA, and into parameters of bone quality that also determine bone strength. Note that even studies of bone quality have not demonstrated wholly consistent outcomes due to limitations in study design. Unlike animal models, human research participants must be carefully screened for inclusion and exclusion criteria that best answer

the question at hand. In a disease such as T2DM, there are confounders to take into account – many quite relevant to bone health. Overly curated study populations queried for the pathophysiology of increased fracture risk in T2DM may mask differences in mechanical properties and composition and limit applicability to real-world observations. On the other hand, inclusion of all stages and severities of T2DM in clinical studies may not capture how progressive glycemic derangement compromises the skeleton, via microvascular damage, AGE deposition, aberrant remodeling and/or other factors that grow in significance over time.

Ideally, more clinical studies would include bone samples derived from research participants in addition to imaging and biochemical analyses to more fully investigate differences in T2DM material properties and AGE content, though these tests cannot be done in vivo. Transiliac bone biopsy is not without morbidity and complexity. Human bone samples can be more easily collected opportunistically, though these are derived from a pre-selected and specialized cohort deemed appropriate for surgery. Many samples are needed to demonstrate differences in AGE content amongst normal and T2DM study groups, and studies may still be underpowered to show concurrent differences in bone material properties, as discussed by Vaidya et al. [77]. While AGEs appear to be a promising and unifying mechanism underpinning much of the increased fracture risk observed in T2D, prospective studies are needed using bone tissue from a larger, more diverse T2D population to confirm detrimental changes in bone toughness and strength. Such a finding, along with the knowledge that all end-organ damage in T2D has negative repercussions for skeletal health, could drive future interventions with reductions in morbidity and mortality in this high-risk population.

Summary and Conclusions

- Measures of bone quantity (DXA, CT, HRpQCT) do not adequately predict fracture risk in women and men with T2DM, necessitating consideration of parameters of bone quality in this disease state.
- Several mechanisms have been proposed to understand the effect of T2DM on bone quality, specifically tissue fragility (Figure 1). However, the contribution of each mechanism to clinical fracture risk remains unknown.
- Despite normal to greater BMD, women with T2DM have less robust hip geometry calculated via HSA compared to women without diabetes. These differences in hip cross- sectional area, and resistance to compression and bending appear less pronounced in men with T2DM.
- A growing body of evidence indicates that, although cancellous microarchitecture is relatively maintained in T2DM, cortical bone microarchitecture may be preferentially impacted by glucose dysregulation.
- In addition, tissue material properties are also affected in T2DM. The differences in bone tissue composition with T2DM, which include greater concentrations of AGEs and increased tissue mineral content, are generally but not universally associated with stiffer, stronger, and more brittle tissue. Prospective studies are required to investigate whether a causal link exists between differences in composition and altered mechanical properties.
- Bone remodeling parameters are reduced in T2DM, as evidenced by circulating serum markers as well as at the tissue-level in bone biopsy samples. Reduced remodeling may contribute to bone embrittlement.
- Changes over time in bone quantity and quality in T2DM are likely to be interrelated and to have cumulatively adverse effects on skeletal health with more advanced glucose dysregulation.

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  This comprehensive study of bone quality showed that cortical bone of individuals with T2DM and fragility fracture had greater AGEs and porosity andlower strength and toughness vs. non-DM controls. Cortical fAGEs were inversely related to the yield- and ultimate strain of T2DM bone, suggesting arole of AGEs in tissue-level embrittlement in this population.

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Declarations

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