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Review

Use of noninvasive imaging to identify causes of skeletal fragility in adults with diabetes: a review

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Abstract

Diabetes, a disease marked by consistent high blood glucose levels, is associated with various complications such as neuropathy, nephropathy, retinopathy, and cardiovascular disease. Notably, skeletal fragility has emerged as a significant complication in both type 1 (T1D) and type 2 (T2D) diabetic patients. This review examines noninvasive imaging studies that evaluate skeletal outcomes in adults with T1D and T2D, emphasizing distinct skeletal phenotypes linked with each condition and pinpointing gaps in understanding bone health in diabetes. Although traditional DXA-BMD does not fully capture the increased fracture risk in diabetes, recent techniques such as quantitative computed tomography, peripheral quantitative computed tomography, high-resolution quantitative computed tomography, and MRI provide insights into 3D bone density, microstructure, and strength. Notably, existing studies present heterogeneous results possibly due to variations in design, outcome measures, and potential misclassification between T1D and T2D. Thus, the true nature of diabetic skeletal fragility is yet to be fully understood. As T1D and T2D are diverse conditions with heterogeneous subtypes, future research should delve deeper into skeletal fragility by diabetic phenotypes and focus on longitudinal studies in larger, diverse cohorts to elucidate the complex influence of T1D and T2D on bone health and fracture outcomes.

Keywords: diabetes, type 1 diabetes, type 2 diabetes, BMD, QCT, HR-pQCT, DXA, TBS, MRI, skeletal fragility

Lay Summary

Diabetes, a disease marked by consistent high blood glucose levels, is associated with various complications such as neuropathy, nephropathy, retinopathy, and cardiovascular disease. Notably, increased fracture risk has emerged as a significant complication in both type 1 (T1D) and type 2 (T2D) diabetic patients. This review examines noninvasive imaging studies that evaluate fracture outcomes in adults with T1D and T2D, emphasizing distinct skeletal phenotypes linked with each condition and pinpointing gaps in understanding bone health in diabetes. Notably, existing studies present heterogeneous results possibly due to variations in design, outcome measures, and potential misclassification between T1D and T2D. Thus, the true nature of diabetic fracture risk is yet to be fully understood. As T1D and T2D are diverse conditions with heterogeneous subtypes, future research should delve deeper into fracture risk by diabetic phenotypes and focus on longitudinal studies in larger, diverse cohorts to elucidate the complex influence of T1D and T2D on bone health and fracture outcomes.

Introduction

Diabetes is a highly prevalent disease characterized by habitually elevated blood glucose levels. In the USA alone, more than 37 million adults have diabetes, accounting for over 11% of the population.[1] The major categories of the disease include type 1 diabetes (T1D, 5%–10% of cases) and type 2 diabetes (T2D, 90%–95% of cases)[2] which differ in pathophysiology and clinical manifestation. T1D, typically diagnosed in children or young adults, is an autoimmune condition that leads to the destruction of insulin-producing pancreatic beta cells resulting in little to no insulin production. In contrast, T2D is often diagnosed in adulthood, is strongly associated with obesity and lifestyle factors, and is characterized by insulin resistance.

Both T1D and T2D lead to chronic hyperglycemia if not adequately managed, which can result in complications like neuropathy, nephropathy, retinopathy, and cardiovascular disease. More recently, skeletal fragility has emerged as a common and potentially severe complication of diabetes. This is particularly notable as fracture risk increases with age and nearly 30% of individuals over age 65 have diabetes.[3] Both T1D and T2D are associated with an increased risk of fracture.[4-13] In meta-analyses, individuals with T1D had a 30%–88% increased risk of fracture at any skeletal site,[8-10] with a 3.8- to 8.7-fold increased risk of hip fracture.[4-11] and 2.9-fold increased risk of vertebral fracture[6] compared to similar-aged controls without diabetes. The increase in fracture risk among individuals with T2D is more moderate compared to those with T1D,[4,11] with meta-analyses reporting that individuals with T2D have 20% to 70% increased risk of hip and other nonvertebral fractures compared to nondiabetic controls.[4,5,7,9-13] Regardless of diabetic type, there is significant heterogeneity in fracture risk,[4-13] suggesting some individuals with diabetes have substantially greater risk of fracture than others, possibly due to the substantial heterogeneity in the pathophysiology

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and resulting clinical phenotypes within T1D and T2D.[14-17] Overall, factors associated with greater duration or severity of diabetic disease herald increased risk of fractures.[18,19]

The reason for higher fracture risk in those with diabetes is multifactorial, with increased risk of falls and reduced bone strength likely to be key contributors. However, the increased risk of falling, in part due to hypoglycemic events, only partially explains the increased risk of fracture in adults with diabetes.[20-27] Importantly, the factors that diminish bone strength and increase skeletal fragility in patients with diabetes have not yet been fully elucidated. Although one possible factor is reduced bone quantity, increased fracture risk in those with T1D is only partially explained by lower areal bone mineral density (aBMD) measurements via DXA.[4] Moreover, paradoxically, individuals with T2D have normal to elevated aBMD, yet increased fracture risk.[28] As aBMD by DXA underestimates fracture risk in both T1D and T2D,[4,29] numerous other skeletal imaging techniques have been utilized to better understand the factors which may negatively impact bone strength, thereby increasing fracture risk, in patients with diabetes. Several important contributors to whole bone strength can be assessed with noninvasive imaging, including bone mass (bone density and BMC), morphology (geometry and shape), and microarchitecture. Noninvasive imaging has also been utilized to quantify bone marrow adiposity, another potential contributor to skeletal fragility.[30,31]

The aim of this review is to discuss the key findings from studies that have used noninvasive imaging to assess skeletal outcomes in adults with T1D and T2D. Furthermore, we highlight the varying skeletal phenotypes associated with T1D and T2D and identify knowledge gaps regarding bone health in the setting of diabetes. Although antidiabetic medications have been shown to influence the risk of hip fracture,[32-34] their effect on fracture risk and bone density is out of the scope of this review.

Impact of diabetes on areal bone mineral density (aBMD), trabecular bone score (TBS), and hip structural analysis (HSA) by DXA

With DXA, a 2D projection of the proximal femur, lumbar spine and/or forearm is used to assess aBMD. Although DXA-derived aBMD is the clinical standard for osteoporosis diagnosis and evaluation of fracture risk, its 2D acquisitions cannot reflect structural aspects of the bone and prohibit independent assessment of cortical and trabecular bone. To compensate for this limitation, additional DXA-based analyses have been developed. Trabecular bone score (TBS), a texture metric of grey-level variations in lumbar spine DXA images, is intended to reflect bone quality via indirect measurement of bone structure. A higher TBS value indicates better bone "structure" and lower risk of fracture.[35,36] Another DXA-based method, hip structural analysis (HSA), uses 2D DXA scans to derive measurements of femoral geometry (eg, hip axis length, cross-sectional area, cortical thickness, buckling ratio, cross-sectional moment of inertia, section modulus) by making a few assumptions: constant mineral density, circular cross-sectional shape at the neck and shaft and elliptical shape at the trochanter, and a fixed percentage of cortical bone at different anatomical regions.[37] Additionally, 3D modeling methods have been developed to derive the cortex, femoral shape, and trabecular macrostructure from conventional hip DXA scans, called 3D-DXA.[38]

Areal bone mineral density

Most studies have reported lower aBMD in T1D compared to nondiabetic controls, particularly at the hip, although the magnitude of difference between T1D and nondiabetic controls varies substantially between studies.[39-41] This deficit in hip aBMD appears to occur early in the disease[42-44] and persists throughout early and middle adulthood.[45-48] For example, a meta-analysis showed that femoral neck aBMD is mildly lower (~0.45 standard deviation deficit), whereas lumbar spine aBMD is similar to or slightly lower in T1D compared to controls.[41] These moderate aBMD deficits in T1D only partially explain the increased risk of fracture.[4] Longitudinal studies in adults with T1D, particularly older adults, are lacking and therefore it is unknown whether individuals with T1D are more prone to accelerated bone loss than those without diabetes.

Diabetic history and complications may influence aBMD in patients with T1D. For example, increased HbA1c is associated with lower aBMD in individuals with T1D at the hip, but not the spine.[6,41,49] In older adults with T1D, nephropathy, but not neuropathy or retinopathy, has been associated with lower total hip aBMD.[49,50] As data are limited, further studies are needed to better define the association between diabetic complications and aBMD in T1D.

Paradoxically, although T2D is associated with increased fracture risk, numerous studies have showed that individuals with T2D have normal to high aBMD at both lumbar spine and hip (~0.25–0.50 standard deviation higher), perhaps due to increased body weight and/or hyperinsulinemia.[4,51] Although aBMD underestimates fracture risk in T2D and those with T2D have higher fracture rate at a given T-score than nondiabetics,[29] aBMD does stratify fracture risk among them.[29,52] Longitudinal studies have suggested that women with T2D experience greater age-related declines in aBMD, particularly at the hip, which might contribute to their higher risk of fracture.[53-55] Meta-analyses in T2D have shown a positive association between BMI and both spine and hip aBMD.[4,51] However, in some studies, higher aBMD among T2D remains even after adjustment for BMI,[51] suggesting that other mechanisms contribute to increased aBMD, such as insulin resistance and hyperinsulinemia.[56,57] Importantly, T2D is known to develop along a continuum starting with prediabetes and insulin resistance and culminating in diabetes, and eventually hypoinsulinemia. Studies suggest that even at the earlier stage of prediabetes, aBMD is already elevated compared to normoglycemic individuals, perhaps due to hyperinsulinemia.[58-60] However, over time, worsening insulin resistance has negative effects on bone; the longitudinal Study of Women's Health Across the Nation found that greater increase in insulin resistance is associated with more rapid BMD decline among nondiabetics.[61]

As with T1D, diabetes characteristics may influence aBMD in patients with T2D. One meta-analysis found that HbA1c was positively associated with aBMD at the lumbar spine and hip,[51] whereas another meta-analysis found no association between aBMD and HbA1c or diabetes duration.[4] In the Rotterdam study, individuals with T2D and poor glycemic control (HbA1c $\geq$ 7.5%) had higher lumbar spine and hip aBMD than individuals with well-controlled diabetes (HbA1c <7.5%).[62] In contrast, glycemic control did not influence aBMD in the Health, Aging, and Body Composition Study, though longer duration of diabetes was negatively associated

with hip aBMD.[63] Similarly, men with T2D duration greater than 5 yr had lower hip aBMD compared to those with shorter T2D duration.[64] More studies are needed to understand how the evolution of diabetes, from insulin resistance to T2D with complications, affects BMD.

Trabecular bone score

Despite similar lumbar aBMD between individuals with T1D and non-diabetic controls, some studies report lower TBS in T1D,[23,65-67] whereas others show no differences.[68,69] Patients with T1D and history of any clinical fracture (excluding ribs, toes and fingers) have lower TBS values than those with T1D and no prior fracture, despite having similar lumbar aBMD.[68] When considering diabetic complications, a large study found no association between TBS and HbA1c or presence of nephropathy in patients with T1D.[49] However, TBS data in T1D are limited and further studies are needed, particularly with larger sample sizes and in prospective cohorts to determine whether TBS predicts fracture risk in T1D.

Numerous studies have reported lower TBS in individuals with T2D compared to nondiabetic controls (−1.5% to −15.6%).[70-81] Notably, TBS is lower among women, but not men, with T2D compared to nondiabetic controls.[82-86] A few studies have further reported a negative association between TBS and HbA1c.[71,83,87,88] However, these studies are difficult to interpret, as TBS is negatively associated with waist circumference,[77,88] abdominal soft tissue thickness,[80,89] and visceral fat mass,[90] suggesting TBS might be reflecting body composition in those with T2D, rather than deficits in bone structure. Accordingly, additional studies are needed to delineate the extent to which increased abdominal fat contributes to lower TBS values among individuals with T2D. An update to TBS (v4.0)[91] has been introduced that minimizes the body composition associations; however few studies of diabetic skeletal fragility have used the newer software version that accounts for soft tissue thickness.

TBS has also been evaluated as a predictor of fracture in T2D. In a Canadian cohort of postmenopausal women with T2D, low TBS values predicted incident major osteoporotic fractures independently of aBMD.[70] In addition, reduced TBS is associated with prevalent vertebral fractures in those with T2D,[78,92-95] although only one study included men.[94] It is unclear to what extent abdominal thickness may modulate the observed relationships between TBS and fracture risk in diabetes, as studies were performed with TBS prior to soft tissue correction. Thus, future prospective studies are required to assess whether TBS v4.0 also predicts fracture in those with T2D, particularly among men.

Hip structural analysis

A few studies have used HSA to assess hip geometry in individuals with T1D. In middle-aged men with T1D, hip strength indices by HSA were similar to healthy age-, weight-, and height-matched controls.[96] However, in slightly older men and women, T1D was associated with deficits in hip geometry, including thinner cortices and higher buckling ratios.[97] Furthermore, in middle-aged adults with T1D, earlier onset of diabetes was associated with a smaller femoral neck, including smaller cross-sectional area, section modulus, and outer diameters.[98] Due to the limited number of studies examining hip structure among T1D, small sample sizes, and lack of information about hip structure in individuals with fracture, it remains unknown whether deficits in hip structure contribute to increased fracture risk in T1D.

Similarly, little is known regarding altered hip structure in individuals with T2D. Pre- and postmenopausal women with T2D have unfavorable hip structure compared to non-diabetics, with lower composite strength, section modulus, cross-sectional moment of inertia and buckling ratio, as well as regionally higher stresses at the femoral neck.[78,81,99-102] However, these studies vary in reported outcomes and adjustment for cofounders. One study found no differences in HSA outcomes between men with T2D and nondiabetic controls.[103] Another study applied 3D-DXA in a cohort of men and women with T2D but did not identify any impairment in 3D-DXA–derived cortical and trabecular parameters compared to nondiabetic controls.[81]

Quantitative computed tomography and peripheral quantitative computed tomography

Like DXA, quantitative computed tomography (QCT) enables imaging at numerous anatomical sites relevant to bone fragility assessment, including the proximal femur, lumbar spine, and distal radius. In contrast to DXA, QCT permits 3D evaluation of bone morphology and structure, differentiation between trabecular and cortical bone compartments, and quantification of volumetric BMD (vBMD) if a reference phantom or internal calibration is used. However, QCT is limited in its ability to evaluate bone microstructure, including trabecular bone microarchitecture and cortical porosity. Peripheral quantitative computed tomography (pQCT) is also used to assess bone density and geometry but is limited to a relatively small region within the appendicular skeleton, generally the radius and tibia.[104,105]

Only a handful of studies have used QCT to assess bone health in individuals with T1D (Table 1).[106-108] Specifically, in young adult men with relatively well-controlled T1D ($n = 17$, age 18–49 yr), CT scans of the hip and spine revealed cortical deficits in the proximal femur, but normal trabecular bone in both the hip and lumbar spine compared to nondiabetic age- and sex- matched controls ($n = 18$).[106,107] In contrast, another study showed that spine DXA-aBMD and vertebral trabecular vBMD were lower among young adult men, but not women, with T1D compared to age- and sex-matched controls.[108] Given the limited and conflicting CT-based imaging studies in patients with T1D, additional investigations are needed.

Studies using QCT scans have shown that older adults with T2D have greater vBMD at the femoral neck[109,110] and lumbar spine[63,109,111] compared to age- and sex-matched nondiabetic controls (Table 1). However, patients with T2D may not benefit from elevated BMD, as they have deficits in femoral neck geometry[112] and similar ratio of estimated fall force to bone strength (ie, load-to-strength ratio[113]) at the hip and spine compared to nondiabetic controls, indicating that improvements in bone strength are offset by higher loads upon falling.[109] In contrast, in younger cohorts of adults with T2D (mean age < 65 yr), no differences have been detected in hip or spine vBMD compared to controls,[111,114-116] suggesting that age and/or T2D duration may play an important role in diabetes-related differences in BMD. Notably, postmenopausal women with T2D and prior history of fragility fracture have lower femoral neck vBMD compared to non-fracturing patients with T2D, but similar vBMD compared to nondiabetic controls,[110] suggesting measures of vBMD by

Table 1. Volumetric bone mineral density at the spine and hip as measured with QCT. Reported as percent differences in means between adults with diabetes and nondiabetic controls.

First author	Year	Sample size (% diabetic)	% Female	Age (yr)	Spine		Femoral neck		
					Level	Tb.BMD	Tot.BMD	Tb.BMD	Ct.BMD
Type 1 Diabetes									
Ishikawa	2015	35 (49%)	0	38	L2-L4	−5.1%	−8.8%		**−4.2%**
Barmpa	2023	212 (56%)	55	30	L3	**−7.3%**			
Barmpa (Women)	2023	117 (56%)	100	31	L3	−1.9%			
Barmpa (Men)	2023	95 (56%)	0	29	L3	**−13.7%**			
Type 2 Diabetes									
Strotmeyer	2004	2979 (19%)	43	73	L3	**15.1%**			
Register (Women)	2006	483 (85%)	100	62	T12-L3	0.1%			
Register (Men)	2006	398 (92%)	0	63	T12-L3	−5.3%			
Melton	2008	700 (7%)	57	72	L1-L3	**16.3%**	**15.6%**	**19.5%**	**5.4%**
Baum	2012	26 (50%)	100	59	L1-L3	4.7%			
Patsch (Fx−)	2013	33 (48%)	100	61	L1-L3	−6.8%			
Patsch (Fx+)	2013	34 (50%)	100	66	L1-L3	22.0%			
Heilmeier (Fx−)	2015	39 (51%)	100	60			**8.5%**	14.4%	4.0%
Heilmeier (Fx+)	2015	38 (50%)	100	63			−0.4%	−13.5%	4.4%
Wang (Women)	2022	4420 (7%)	100	64	L1-L2	**−28.2%**			
Wang (Men)	2022	5889 (10%)	0	59	L1-L2	−4.6%			
Gao (50–65 yr)	2022	163 (54%)	100	59	L1-L3	16.5%			
Gao (>65 yr)	2022	150 (59%)	100	73	L1-L3	**46.7%**			

Proportion of females (%) and mean age are presented for the diabetic group. Data presented as percent difference between reported unadjusted group means for diabetic vs control, unless otherwise specified. Abbreviations: Ct, cortical; Tb, trabecular; Tot, total (integral) Fx−, no fracture; Fx +, fracture Bold indicates significant difference between those with diabetes and nondiabetic controls ($P < .05$).

QCT might identify patients with T2D at highest risk of fracture. However, it is also possible that individuals who suffered a fracture subsequently lost bone mass, and therefore evaluation of vBMD in prospective cohorts is needed to elucidate whether QCT will be useful to predict fracture risk in patients with T2D.

Due to its very low radiation dose, pQCT has been frequently used in pediatric diabetic populations, but few studies have been conducted in adults with diabetes. Deficits in pQCT measures have been observed in the tibia of young adult women,[117] the radius of middle-aged adults,[118] and the radius and tibia postmenopausal women with T1D,[119] with lower trabecular vBMD and cortical thickness compared to nondiabetic controls. Importantly, postmenopausal women who were diagnosed with T1D before the age of 20 had greater deficits in pQCT measures compared to those diagnosed later in life, with lower total vBMD (−28%), trabecular vBMD (−30%) and cortical thickness (−15%) at the tibia.[119] In older adults with T2D, most studies show greater total and trabecular vBMD (+3–15%) but lower cross-sectional area (−5%) at the distal radius and tibia, and no significant differences in cortical bone, compared to nondiabetics.[109,120-123]

High-resolution peripheral quantitative computed tomography

An increasing number of studies are using high-resolution peripheral quantitative computed tomography (HR-pQCT) for 3D evaluation of vBMD, geometry, and microstructure at the distal radius and tibia. At a relatively small isotropic voxel size (82 μm and 61 μm for the first- and second-generation scanners, respectively) and low radiation dose (<5 μSv per scan), HR-pQCT allows for assessment of cortical and trabecular bone compartments. A standardized analysis provides measures of total, cortical, and trabecular vBMD, trabecular bone microarchitecture (ie, trabecular number, thickness, and separation), cortical thickness, and cortical porosity.[124] In addition, HR-pQCT images can be used to build finite element models to estimate bone strength.[124]

Like QCT, only a few cross-sectional studies have evaluated trabecular bone microarchitecture and cortical bone microstructure via HR-pQCT in adults with T1D (Table 2). A recent meta-analysis proposed a T1D bone phenotype defined by trabecular deficits at the radius but no differences at the tibia.[125] However, few individual studies exhibit this proposed T1D phenotype (Table 2), possibly due to the small number of studies included in the meta-analysis (4), half of which were in adolescents.[125] Overall, some studies found that adults with T1D have lower total vBMD,[126,127] but no differences in failure load at the radius and similar vBMD and failure load at the tibia[126,128] compared to nondiabetic controls. When considering microstructure, most studies suggest that patients with T1D have similar trabecular and cortical bone microstructure at both the radius and tibia compared to nondiabetic controls (Table 2).[50,126-128] In contrast to these studies, a large recent cross-sectional study in men and women with T1D[129] showed greater total vBMD, cortical vBMD, cortical area, and cortical thickness with lower cortical porosity at the radius compared to nondiabetic controls, potentially due to the relatively small proportion of patients with diabetic complications.

Consideration of clinical factors and comorbidities is critical when examining diabetic bone disease. For patients with T1D, age at diagnosis[127] and presence of complications such as microvascular diseases[126] and neuropathy[50,128] have been shown to affect bone outcomes. For example, the presence of microvascular diseases was associated with significant trabecular bone deficits and lower bone strength at the radius and tibia in older adults with T1D.[126] These differences persisted after adjustment (age, BMI, sex, disease duration, glycemic control), suggesting that the presence of microvascular disease may be an independent risk factor for trabecular bone microarchitecture deficits.[126] In contrast, recent studies have not shown an association between neuropathy and deficits in

Table 2. Bone density, microarchitecture, and biomechanical strength at the tibia and radius as measured with HR-pQCT. Reported as percent differences in means between adults with type 1 diabetes (T1D) and nondiabetic controls.

First author	Year	Sample size (% T1D)	% Female	Age (yr)	Volumetric BMD			Trabecular microarchitecture			Cortical microstructure			Failure load
					Tot.BMD	Ct.BMD	Tb.BMD	Tb.N	Tb.Th	Tb.Sp	Ct.Ar	Ct.Th	Ct.Po	
Radius														
Shanbhogue	2015	110 (50%)	49	46	**−10.7%**	**−3.1%**	−8.2%	−4.0%	−4.2%	5.7%	−3.3%	**−8.0%**	15.9%	−2.1%
Vilaca (N−)[a]	2021	40 (50%)	40	50	4.9%	0.0%	1.8%	−1.0%	2.9%	1.0%	11.6%	12.5%	−21.2%	8.9%
Vilaca (N+)	2021	40 (50%)	40	48	1.3%	0.1%	1.8%	−4.0%	5.7%	6.2%	10.2%	8.3%	27.3%	11.1%
Xu	2021	64 (50%)	0	34	**−16.1%**	−0.1%	**−21.7%**	−6.8%	**−11.5%**	**11.3%**	-	−13.4%	−4.8%	-
Sewing[b]	2022	136 (43%)	41	60	↑	↑	↓	↑	↑	↑	-	↓	↓	↓
Rasmussen	2023	269 (41%)	58	53	**17.0%**	**4.2%**	4.6%	0.0%	−3.0%	0.0%	**12.0%**	**8.6%**	**−50.0%**	**8.7%**
Tibia														
Shanbhogue	2015	110 (50%)	49	46	−6.8%	−2.2%	−5.8%	−3.9%	−2.7%	−1.0%	−4.2%	−5.3%	11.3%	−2.5%
Vilaca (N−)[a]	2021	40 (50%)	40	50	5.0%	1.0%	9.3%	8.3%	0.0%	−9.3%	3.1%	−0.8%	−17.4%	5.9%
Vilaca (N+)	2021	40 (50%)	40	48	−2.3%	−5.3%	5.8%	8.9%	−2.5%	−17.2%	−3.2%	−6.5%	28.7%	4.2%
Xu	2021	64 (50%)	0	34	**−12.4%**	−2.5%	−10.0%	3.8%	**−7.1%**	−1.3%	-	−12.6%	21.3%	-
Sewing[b]	2022	136 (43%)	41	60	↓	↓↓	↓	↓	↓	↑	-	↓↓	↓	↓↓
Rasmussen	2023	269 (41%)	58	53	**7.0%**	**4.9%**	4.4%	0.0%	−2.4%	0.0%	6.9%	3.4%	−11.1%	**10.3%**

Proportion of females (%) and mean age are presented for the diabetic group. Data presented as percent difference between reported unadjusted group means for T1D vs control, unless otherwise specified. [a] Ct.BMD, Tb.Sp, Ct.Po calculated as percent difference of medians for T1D vs control. [b] Published data presented as estimates of the difference; percent difference could not be calculated. Arrows indicate direction of estimate. Double arrows indicate significant difference between T1D vs nondiabetic controls. Abbreviations: Ct, cortical; Ct.Ar, cortical area; Ct.Th, cortical thickness; Ct.Po, cortical porosity; Tb, trabecular; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; Tot, total (integral) N−,without neuropathy; N+, with neuropathy Bold text or double arrows indicate significant difference between those with diabetes and nondiabetic controls ($P < .05$).

trabecular bone, but rather deficits in cortical bone. In adults with T1D, increased cortical porosity[128] and diminished cortical vBMD[50] were associated with the presence of neuropathy. More studies are needed to better understand bone microarchitecture outcomes in T1D and to establish which clinical factors and comorbidities common in patients with diabetes may influence the observed skeletal heterogeneity.

Numerous studies have used HR-pQCT in individuals with T2D, though findings are heterogeneous. Patients with T2D generally have similar to enhanced total vBMD,[129,130] trabecular microarchitecture,[129-132] and cortical thickness[129,132,133] at both the radius and tibia compared to nondiabetic controls (Table 3). Differences in cortical porosity have been mixed, with some studies showing an increase in porosity,[131,134-138] while others have found no difference compared to controls.[20,129,133,139,140] A recent meta-analysis sought to synthesize these results in a proposed a T2D skeletal phenotype with improved trabecular bone structure and cortical thickness at the radius and tibia with greater cortical porosity only at the load-bearing tibia.[125] As with T1D, it is important to consider clinical factors and comorbidities among those with T2D. After adjustment for weight or BMI, differences in trabecular and cortical bone measures in patients with T2D no longer differed from nondiabetic controls,[130,133,139,141] suggesting body composition may play an important role in the T2D skeletal phenotype. Furthermore, increased soft tissue thickness overlying the radius or tibia leads to decreased measures of total and cortical vBMD,[142] suggesting that HR-pQCT outcomes must be interpreted carefully when comparing individuals with different body size and BMI. Patients with longer T2D duration, presence of microvascular complications, or higher fasting glucose levels may have higher cortical porosity[134,137-139] but more advantageous trabecular microarchitecture compared to nondiabetic controls.[133] This suggests that the primary T2D phenotype might be dominated by deficits in cortical bone, but it is not clear whether the cortical bone deficits (often quite small) are driving the skeletal fragility or serving as a biomarker of disease severity and/or duration. Additional investigations, including longitudinal studies, are needed to clarify the connection between clinical factors, altered bone microstructure, and fracture risk in diabetes.

Bone marrow adiposity from MRI

In contrast to the imaging modalities mentioned previously, MRI enables 3D evaluation of trabecular bone microstructure and bone marrow composition without ionizing radiation. However, MRI does not enable quantification of BMD. To date, a few studies with small sample sizes have used MRI techniques in patients with diabetes. Patients with T1D have similar bone marrow adipose tissue (BMAT) content in the lumbar spine, distal femur, and proximal tibia compared to nondiabetic controls.[143-145] Postmenopausal women with T2D also have similar BMAT content at the spine compared to controls.[116,146,147] Data in men with T2D are conflicting, with one study showing increased vertebral BMAT content[123] and another showing decreased vertebral BMAT content[148] compared to nondiabetic controls. Much work remains to be done to evaluate trabecular bone and BMAT using MRI in adults with diabetes.

Table 3. Bone density, microarchitecture, and biomechanical strength at the tibia and radius as measured with HR-pQCT. Reported as percent differences in means between adults with type 2 diabetes (T2D) and nondiabetic controls.

First author	Year	Sample size (% T2D)	% Female	Age (yr)	Volumetric BMD			Trabecular microarchitecture			Cortical microstructure			Failure load
					Tot.BMD	Ct.BMD	Tb.BMD	Tb.N	Tb.Th	Tb.Sp	Ct.Ar	Ct.Th	Ct.Po	
Radius														
Burghardt	2010	38 (50%)	100	63	−2.2%	−3.0%		3.4%	−0.9%	−4.0%	0.3%	−0.7%	**123.9%**	2.9%
Shu	2011	50 (50%)	100	63	9.2%	4.6%	4.1%	6.3%	−3.2%	7.3%	4.1%	7.6%		
Farr	2014	60 (50%)	100	66		−0.8%		**5.0%**	−2.8%	**−5.6%**		**5.9%**	31.5%	
Yu	2015	100 (22%)	100	60	5.2%	**−2.5%**	2.3%	−3.2%	0.0%	9.3%	2.0%	−2.2%	**26.1%**	0.8%
Paccou (Women)[a]	2016	155 (7%)	100	77		−1.5%	5.9%	8.0%	−5.5%	−9.4%	18.3%	8.2%	**26.5%**	
Paccou (Men)[a]	2016	177 (10%)	0	77		**−2.7%**	5.9%	**6.4%**	0.8%	**−6.1%**	−3.6%	−6.3%	**28.2%**	
Shanbhogue (MVD−)	2016	52 (50%)	65	51	−3.1%	−2.1%	3.1%	−1.0%	4.1%	−0.2%	−0.4%	1.9%	11.3%	7.0%
Shanbhogue (MVD+)	2016	50 (50%)	52	65	−3.5%	**−1.3%**	11.2%	11.2%	2.8%	−8.6%	0.1%	−9.0%	31.9%	4.6%
Nilsson	2017	1053 (9%)	100	78	**12.6%**	**2.1%**		**14.2%**	0.0%	**−16.9%**	**11.8%**		**16.2%**	**12.9%**
Patsch (Women)[b]	2017	33 (52%)	100	58	14.0%	*2.2%*	*10.3%*	***15.6%***	−4.9%	−13.4%	29.0%	***24.0%***		
Patsch (Men)[b]	2017	52 (50%)	0	57	10.9%	*4.6%*	*3.2%*	***14.4%***	−9.8%	−13.5%	13.6%	***19.9%***		
de Waard	2018	344 (19%)	37	63	1.4%	−1.8%	1.9%	1.6%	0.0%	−2.1%		2.7%	16.3%	3.6%
Samelson	2018	1069 (12%)	42	66	0.1%	−0.3%	0.0%	−0.5%	0.8%	1.7%		−0.5%	5.4%	−3.0%
Starr	2018	92 (46)	100	62		−0.4%	**15.2%**	7.3%	**6.8%**	−1.9%	5.8%	6.5%	−5.0%	
Samakkarnthai	2020	279 (61%)	44	69		−0.5%	−6.0%	3.6%	1.8%	0.0%	**4.7%**	3.1%	−15.0%	4.7%
Heilmeier (Fx−)	2021	22 (45%)	100	59	1.7%	−1.8%	−9.8%	1.6%	−12.0%	−0.2%	8.5%	10.3%	38.5%	−0.9%
Heilmeier (Fx+)	2021	22 (45%)	100	63	−0.4%	**−6.6%**	−2.0%	1.1%	−4.0%	−1.1%	5.8%	3.8%	**103.8%**	−2.9%
Vigevano	2021	112 (38%)	0	51	−3.3%	−0.1%	−5.4%		0.0%	**5.2%**		−3.5%	0.0%	−5.0%
Rasmussen	2023	217 (40%)	52	62	**25.3%**	**3.1%**	**20.5%**	**11.6%**	1.5%	**−15.2%**	**22.9%**	**13.6%**	−25.0%	**21.5%**
Tibia														
Burghardt	2010	38 (50%)	100	63	**9.2%**	−0.6%	13.1%	−0.9%	**13.8%**	−0.5%	7.8%	7.0%	36.2%	11.2%
Shu	2011	50 (50%)	100	63	−3.2%	2.9%	−2.9%	0.0%	−1.4%	5.4%	10.5%	−7.7%		
Farr	2014	60 (50%)	100	66		1.6%		−2.0%	5.1%	−1.0%		**6.6%**	−3.8%	
Yu	2015	100 (22%)	100	60	−0.7%	−1.8%	−1.4%	−4.3%	2.7%	7.8%	2.3%	2.4%	14.3%	1.2%
Paccou (Women)[a]	2016	155 (7%)	100	77		−0.5%	6.2%	−4.3%	0.0%	3.5%	1.1%	−1.0%	3.1%	
Paccou (Men)[a]	2016	177 (10%)	0	77		**−3.4%**	2.2%	**7.0%**	−6.8%	−6.3%	7.4%	2.7%	**25.3%**	
Shanbhogue (M−)	2016	52 (50%)	65	51	2.9%	0.9%	2.2%	−3.7%	6.3%	7.2%	4.1%	2.2%	−9.8%	−2.5%
Shanbhogue (M+)	2016	50 (50%)	52	65	3.2%	−3.2%	8.7%	−5.1%	14.1%	6.7%	7.2%	0.8%	35.6%	6.3%
Nilsson	2017	1053 (9%)	100	78	**11.2%**	1.9%		**10.7%**	0.0%	**−13.2%**	**12.0%**		5.8%	**7.7%**
Patsch (Women)[b]	2017	33 (52%)	100	58	18.0%	*3.5%*	*8.9%*	***24.6%***	−12.1%	−19.4%	30.1%	*25.9%*		
Patsch (Men)[b]	2017	52 (50%)	0	57	−1.4%	*−1.0%*	*2.7%*	***25.0%***	−18.0%	−20.8%	0.2%	*−2.1%*		
de Waard	2018	344 (19%)	37	63	5.5%	0.4%	5.4%	**7.2%**	−12.5%	−8.7%		9.7%	4.8%	11.1%
Samelson	2018	1069 (12%)	42	66	1.2%	**−2.2%**	3.7%	2.4%	1.8%	−3.0%		−1.8%	**7.2%**	−2.5%
Starr	2018	92 (46)	100	62		−3.6%	**9.9%**	3.4%	0.0%	−3.7%	1.8%	0.8%	10.7%	
Samakkarnthai	2020	279 (61%)	44	69		−0.5%	7.5%	0.8%	**3.9%**	1.1%	2.2%	1.6%	11.9%	**3.9%**
Heilmeier (Fx−)	2021	22 (45%)	100	59	0.1%	5.9%	−9.0%	−9.7%	−1.0%	11.5%	2.1%	4.4%	−29.2%	−0.6%
Heilmeier (Fx+)	2021	22 (45%)	100	63	−9.3%	−3.4%	−11.3%	−4.5%	−9.3%	11.1%	9.7%	1.8%	**17.7%**	3.3%
Vigevano	2021	112 (38%)	0	51	−5.8%	1.1%	−8.0%		0.0%	**4.8%**		−2.6%	0.0%	**−4.8%**
Rasmussen	2023	217 (40%)	52	62	**14.3%**	**3.4%**	**16.0%**	**8.7%**	−1.5%	**−11.6%**	**19.4%**	**12.1%**	0.0%	**31.4%**

Proportion of females and mean age are presented for the diabetic group. Data presented as percent difference between reported unadjusted group means for T2D vs control, unless otherwise specified. [a]Calculated as percent difference of medians for T2D vs control. [b]Data reported on adjusted group means. Authors analyzed only a select number of measures, which are italicized. Abbreviations: Ct, cortical; Ct.Ar, cortical area; Ct.Th, cortical thickness; Ct.Po, cortical porosity; Tb, trabecular; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; Tot, total (integral) Fx−, no fracture; Fx+, fracture; M−, no microvascular disease; M+, microvascular disease Bold text indicates significant difference between those with diabetes and non-diabetic controls ($P < .05$).

Conclusion

As patients with diabetes have increased risk of fracture that is not well explained by DXA-BMD, other noninvasive imaging techniques have been implemented to elucidate the diabetic skeletal phenotype, including measures of 3D bone density, microstructure, and strength. Overall, adults with T1D are characterized by mildly lower aBMD at the hip as well as lower total vBMD but similar microarchitecture at the radius and tibia. In contrast, adults with T2D generally have normal to elevated aBMD and vBMD with improved trabecular but deficient cortical bone structure at the radius and tibia.

Studies of bone density and structure in both T1D and T2D are notably heterogeneous in their findings. These conflicting results might in part be due to factors such as differences in study design, outcome assessments, adjustments for potential confounders, and/or possible misclassification of T1D and T2D when using electronic medical records to identify subjects. However, it is also critical to recognize that diabetes is a heterogenous group of hyperglycemic disorders with varying pathophysiology and clinical tendencies.[17] For example, a new categorization of phenotypic diabetes subtypes has been proposed based on a combination of clinical phenotypes and pathophysiology, encompassing severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity–related diabetes, and mild age–related diabetes.[17] The risk of diabetic complications, such as nephropathy and neuropathy, appears to vary based on these diabetes subtypes.[17,149,150] Genotypic information may be able to further aid in categorizing diabetic phenotypes.[151] Overall, improved classification into more homogeneous diabetes subtypes offers the potential for more accurate phenotypic characterizations that may portend different types of skeletal fragility.

Our current understanding of diabetic bone disease as evaluated through clinical imaging presents significant knowledge gaps. Predominantly, the existing literature is characterized by cross-sectional studies with relatively small sample sizes, necessitating robust prospective, longitudinal research encompassing larger cohorts of both T1D and T2D populations to elucidate the impact of diabetes on bone health. It is also imperative to incorporate greater racial and ethnic diversity in future studies. Moreover, larger studies are needed to facilitate stratification based on the history of diabetes and associated comorbidities, something that is paramount to comprehensively discern fracture risk within the vast and varied diabetic population. For T2D, a conspicuous gap lies in the limited research available on men, with the current literature disproportionately skewed toward postmenopausal women.

Furthermore, recognizing the progressive nature of T2D—which often originates from obesity, progresses through metabolic syndrome/insulin resistance, and culminates into diabetes—is essential. Although initial phases might be manageable through lifestyle alterations, unchecked progression can lead to poorly controlled diabetes and subsequent complications, like macro- and microvascular diseases. Epidemiological data consistently suggest that fracture risk in diabetes depends on multiple factors, such as the disease's duration, insulin use, microvascular complications, and glycemic management. As such, the relationship between bone fragility and diabetes may fluctuate depending on the disease's stage. Notably, the initial stages of insulin resistance might even have a paradoxical enhancement effect on bone health, making comparisons with baseline health challenging, as these individuals could be starting from an inadvertently advantageous position induced by insulin resistance.[152] Current evidence is equivocal about whether prediabetes is associated with increased risk of fracture.[153,154] Thus, longitudinal studies along the progression of diabetes are desperately needed to gain further insight.

Finally, given the rapidly changing landscape of treatments for obesity and diabetes, additional studies are needed to understand the effects of these interventions on skeletal health in adults with diabetes.[155] Several pharmacological treatments for diabetes, such as thiazolidinediones and canagliflozin, are already known to have negative skeletal effects and to increase risk of fracture.[156] Indeed, one limitation of existing work is the confounding factor of diabetic treatments, which are accounted for differently in different studies and may contribute to the heterogeneity of skeletal outcomes in this population. Furthermore, newer antidiabetic agents, especially those resulting in pronounced weight loss such as with GLP-1 agonists, will likely have resultant skeletal effects.[156] As the prevalence of diabetes continues to rise globally, understanding the full spectrum of side effects associated with treatment modalities is imperative.

In summary, diabetic skeletal fragility remains to be well characterized. There is an opportunity to recognize that both T1D and T2D are heterogeneous diseases and future studies should consider assessing skeletal fragility by phenotypic diabetic subtypes.[14-17] Further research including longitudinal studies and larger, more diverse populations are needed to fully understand the nuanced effects of T1D and T2D on bone structure and fracture outcomes in this growing population.

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Author contributions

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Conflicts of interest

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Data availability

Data available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

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