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Clinical Research Article

Risk Factors for Bone Microarchitecture Impairments in Older Men With Type 2 Diabetes—The MrOS Study

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Abstract

Context: Impaired bone microarchitecture, assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT), may contribute to bone fragility in type 2 diabetes (T2DM) but data on men are lacking.

Objective: To investigate the association between T2DM and HR-pQCT parameters in older men.

Methods: HR-pQCT scans were acquired on 1794 participants in the Osteoporotic Fractures in Men study. T2DM was ascertained by self-report or medication use. Linear regression models, adjusted for age, race, body mass index, limb length, clinic site, and oral corticosteroid use, were used to compare HR-pQCT parameters by diabetes status.

Results: Among 1777 men, 290 had T2DM (mean age, 84.4 years). T2DM men had smaller total cross-sectional area at the distal tibia ($P = .028$) and diaphyseal tibia ($P = .025$), and smaller cortical area at the distal ($P = .009$) and diaphyseal tibia ($P = .023$). Trabecular indices and cortical porosity were similar between T2DM and non-T2DM. Among men with T2DM, in a model including HbA1c, diabetes duration, and insulin use, diabetes duration ≥ 10 years, compared with <10 years, was significantly associated with higher cortical porosity but with higher trabecular thickness at the distal radius. Insulin use was significantly associated with lower cortical area and thickness at the distal radius and diaphyseal tibia and lower failure load at all 3 scan sites. Lower cortical area, cortical thickness, total bone mineral density, cortical bone mineral density, and failure load of the distal sites were associated with increased risk of incident nonvertebral fracture in T2DM.

Conclusion: Older men with T2DM have smaller bone size compared to those without T2DM, which may contribute to diabetic skeletal fragility. Longer diabetes duration was associated with higher cortical porosity and insulin use with cortical bone deficits and lower failure load.

Key Words: type 2 diabetes mellitus, bone microarchitecture, bone strength, high-resolution peripheral quantitative computed tomography, fracture risk

Abbreviations: AGE, advanced glycation end product; BMD, bone mineral density; BMI, body mass index; Ct.Ar, cortical area; Ct.Th, cortical thickness; DR, distal radius; DT, distal tibia; HR-pQCT, high-resolution peripheral quantitative computed tomography; MrOS, Osteoporotic Fractures in Men; PT, diaphyseal tibia; T2DM, type 2 diabetes mellitus; Tt.Ar, total cross-sectional area.

Fragility fractures are a major public health burden on our society and are associated with significant morbidity, excess mortality, and high health care costs. It is estimated that 1 in 2 women and 1 in 5 men older than age 50 years will have a fragility fracture in their remaining lifetime (1). Fracture risk is increased in patients with type 2 diabetes mellitus (T2DM) compared to individuals without diabetes. A recent meta-analysis reported an increased relative risk of total fracture of 1.22 with T2DM (2). Besides elevated fracture risk, patients with T2DM have increased mortality following a

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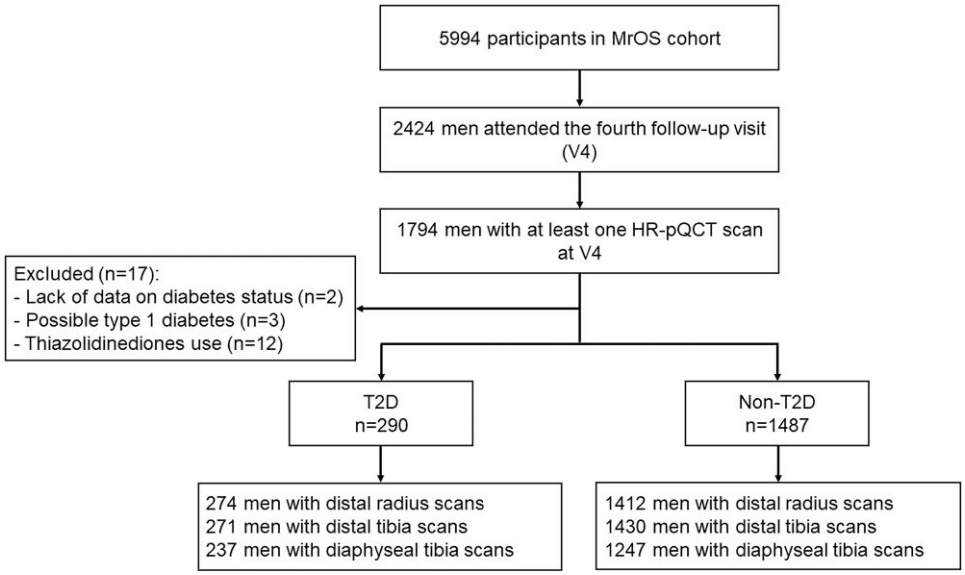

Figure 1. Flow chart of the MrOS study participants included in the study.

fracture compared to patients without diabetes (3). Thus, the development of effective clinical interventions to prevent fracture in adults with diabetes are urgently needed. However, the underlying mechanisms of bone fragility in diabetes are complex and not completely understood.

Surprisingly, areal bone mineral density measured by dual-energy X-ray absorptiometry is commonly normal or even higher in T2DM compared with individuals without diabetes mellitus (4, 5). Deficits in bone microarchitecture, identifiable with high-resolution peripheral quantitative computed tomography (HR-pQCT), may contribute to increased bone fragility for a given areal bone mineral density. Results from previous studies have not been consistent with some (6-8), but not all (9), reporting increased cortical porosity with T2DM. Most studies have been small and included only women. One larger study, based on the Framingham cohort, reported increased cortical porosity and smaller cross-sectional area for women and men combined, but only included 75 men with diabetes (10).

In addition, among patients with T2DM, diabetes-related factors might contribute to deficits in bone microarchitecture, including glycemic control, longer duration of the disease, insulin use, and advanced glycation end products (AGEs) deposition. However, little is known about these associations, particularly in men.

In this study, we undertook an assessment of the associations between diabetes status and volumetric bone mineral density (BMD), bone microarchitecture, and strength in older men, using data from the Osteoporotic Fractures in Men (MrOS) cohort. Additionally, we examined the association between diabetes-related factors and HR-pQCT-derived bone parameters among men with T2DM. As an exploratory aim, we also investigated whether bone microarchitecture predicts incident nonvertebral fracture in older men with diabetes.

Methods

Study Design and Participants

Data from the MrOS study, a multicenter observational study designed to determine risk factors for fractures in older men, was used (11). From March 2000 to April 2002, the MrOS study enrolled 5994 men aged 65 years or older from 6 communities in the United States: Birmingham, AL; Minneapolis, MN; Palo Alto, CA; the Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, CA (12). The study has been approved by the institutional review board of each center, and all participants provided written informed consent. From May 2014 to May 2016, 2424 participants attended a fourth follow-up visit. Of the 1794 participants who had at least 1 evaluable HR-pQCT scan, 2 men were excluded for lack of data on diabetes status, 3 for possible type 1 diabetes, and 12 for thiazolidinedione use (Fig. 1).

Diabetes Status, Anthropometric and Biochemical Assessments

At the fourth follow-up visit, participants were asked about demographics, diabetes status, and current medication use. Men were asked if they had ever been diagnosed with diabetes, and, if yes, at what age they were diagnosed. Current medication use included any prescription medication used in the previous 30 days.

Body weight and height were measured using a standard weighing scale and a stadiometer, respectively. Body mass index (BMI) was calculated as weight (kilograms [kg]) divided by the square of the height (meter [m]) (kg/m^2).

Serum was collected from blood samples drawn after an overnight 12-hour fast and stored at −70 °C. Hemoglobin A1C (%) was measured in 249 stored frozen whole blood samples from diabetes participants by capillary electrophoresis (Capillarys 2 Flex Piercing Sebia, Lisses, France). Urinary pentosidine was obtained from 24-hour urine of 166 diabetes participants by quantitative sandwich enzyme immunoassay (Cusabio Technology LLC, Italy). Anti-GAD antibodies were analyzed in 44 of 46 men who reported insulin treatment (fluid phase radioimmunoassay kit, Medipan, CentaK anti-GAD65M).

Diabetes status was based on self-report of a diabetes diagnosis or current use of diabetes medications. Two men were excluded because of a lack of information on diabetes status.

Three men were excluded for possible type 1 diabetes, including 2 with a younger age at diagnosis and one with elevated anti-GAD levels. Twelve men were excluded for thiazolidinedione use.

HR-pQCT Imaging

Bone morphology, microarchitecture, and volumetric BMD of the distal radius (DR), distal tibia (DT), and diaphyseal tibia (PT) were assessed using a second-generation HR-pQCT scanner (Scanco XtremeCT II, Scanco Medical AG, Bruttisellen, Switzerland) (13). Scans were acquired at the distal radius (9 mm from the articular surface), distal tibia (22 mm from the articular surface), and diaphyseal tibia (centered at 30% of tibia length) with an isotropic voxel size of 61 µm spanning a length of 10.2 mm (168 slices) (14). The radius from the nondominant forearm and the tibia from the ipsilateral leg were scanned unless a participant reported a prior extremity fracture or had metal in the scan region. A quality control phantom was scanned daily to monitor the long-term stability of the system. All scans were graded using a 5-point motion artifact scale (1 = superior, 5 = poor) to score image quality and only images with grades 1 to 3 were considered to be of sufficient quality for evaluation (15). To assess bone density and structure, HR-pQCT images of the radius and tibia were processed by a fully automated segmentation technique as previously described (16) and the following bone parameters were calculated: total BMD, total cross-sectional area (Tt.Ar), trabecular BMD, trabecular area, trabecular number, trabecular thickness, cortical BMD, cortical area (Ct.Ar), cortical thickness (Ct.Th), and cortical porosity. Linear microfinite element analysis was performed to estimate failure load under axial compression. Briefly, axial compression conditions were applied with an apparent strain of 1%, a tissue modulus of 10 GPa, and Poisson's ratio of 0.3, as previously described (17). The failure load was estimated by calculation of the reaction force at which 7.5% of the elements exceed a local effective strain of 0.7% (17).

Fractures Ascertainment

MrOS participants were contacted every 4 months to ask about clinical fracture events and ascertain vital status. Self-reported fractures were centrally adjudicated by physician review of radiology reports, and radiographs if needed. In this analysis, any confirmed nonspine fractures were included. Pathological fractures were excluded. Fractures were not excluded based on degree of trauma (18).

Statistical Analysis

Characteristics of participants with and without diabetes were compared using chi-square tests for categorical variables, ANOVA for continuous variables, and Kruskal-Wallis nonparametric tests for skewed variables.

We used multiple linear regression models to determine the association between diabetes status and HR-pQCT parameters, adjusted for potential confounders. Cortical porosity was skewed. We therefore used the log transformation of this variable in analyses. The adjusted mean for cortical porosity was back transformed to report the results. To assess the associations between HR-pQCT parameters and diabetes-related characteristics among men with diabetes, we initially used linear regression models adjusted for age, race, clinic site, and BMI. For those characteristics with statistically significant associations in these models (HbA1c, diabetes duration, and insulin use, but not urine pentosidine), we then considered a multivariable model that included all 3 characteristics as well as age, race, clinical sites, BMI, limb length, and oral corticosteroid use. To standardize effect sizes, all outcome HR-pQCT measures were transformed to have mean = 0 and SD = 1. Last, Cox proportional hazards models were used to estimate the association of each HR-pQCT parameter with incident nonvertebral fracture among men with diabetes. All analyses were adjusted for age, race (White vs others), clinical sites, BMI, limb length, and oral corticosteroid use. All significance levels reported ($P < .05$) were 2-sided. Analyses are considered hypothesis-generating and were not adjusted for multiple testing. Results are interpreted cautiously, given the assessment of multiple HR-pQCT parameters and exposures.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Participant Characteristics

The general characteristics of MrOS participants according to diabetes status are shown in Table 1. Among a total of 1777 men, 290 individuals had T2DM. The mean age of the participants was 84.4 (±4.2) years. The majority of men in both groups were White. Participants with T2DM were heavier and had a significantly higher average BMI. Among those with T2DM, 214 (74.3%) used blood glucose-lowering agents, 43 (14.9%) used insulin, 136 (47.2%) used metformin, 81(28.1%) used sulfonylureas, 26 (9.0%) used dipeptidyl peptidase inhibitors, and none used GLP-1 receptor agonists. Of the men with T2DM, 64.4% had diabetes duration of 10 years or longer and 10.8% had HbA1c of 7.5% or higher.

Comparison of HR-pQCT Derived Bone Parameters by T2DM Status

The mean values, adjusted for age, race, clinic site, BMI, limb length, and oral corticosteroid use of the HR-pQCT parameters of the distal radius, distal tibia, and diaphyseal tibia according to diabetes status are shown in Table 2. Individuals with T2DM had smaller total cross-sectional area at the distal and diaphyseal tibia (DT Tt.Ar: difference −1.86% [$P = .028$]; PT Tt.Ar: difference −1.67% [$P = .025$]). Total cross-sectional area at the distal radius was also smaller in men with T2DM but the difference was not statistically significant (−1.41%, $P = .156$). T2DM was also associated with lower cortical area at the distal and diaphyseal tibia (DT Ct.Ar: difference −3.70% [$P = .009$]; PT Ct.Ar: difference −1.89% [$P = .023$]) than non-T2DM. Cortical area fraction, cortical thickness, and cortical porosity did not differ by T2DM status. Total BMD did not differ by T2DM status, but individuals with T2DM had 0.59% higher cortical BMD at the diaphyseal tibia than non-T2DM ($P = .012$). Trabecular indices (trabecular BMD, trabecular area, trabecular number, and trabecular thickness) at all 3 scan sites did not differ by T2DM status. Estimated failure load was lower in T2DM than non-T2DM at the distal radius and distal tibia but was statistically different only at the diaphyseal tibia (difference −1.72%, $P = .049$).

Table 1. Characteristics of MrOS participants at visit 4

	Non-T2DM (n = 1487)	n	T2DM[a] (n = 290)
Age (y), mean ± SD	84.47 ± 4.25		84.29 ± 4.01
Race (White), n (%)	1350 (90.79)		255 (87.93)
BMI (kg/m^2), mean ± SD	26.63 ± 3.55		28.02 ± 4.21
Weight (kg), mean ± SD	79.09 ± 12.07		82.98 ± 13.87
Height (cm), mean ± SD	172.24 ± 6.89		171.95 ± 6.74
Oral corticosteroid use	43 (2.90)		8 (2.78)
Total hip BMD (g/cm^2), mean ± SD	0.93 ± 0.15		0.96 ± 0.15
Femoral neck BMD (g/cm^2), mean ± SD	0.75 ± 0.13		0.78 ± 0.15
Diabetes duration (y), mean ± SD	—	289	16.22 ± 14.07
Diabetes duration ≥ 10 y, n (%)	—		186 (64.4%)
HbA1c %, mean ± SD	—	249	6.31 ± 0.93
HbA1c ≥ 7.5%, n (%)	—		27 (10.8%)
Pentosidine (pmol/mL), mean ± SD	—		29.48 ± 48.22
Cr-adj pentosidine (pmol, mg Cr), mean ± SD	—		3.86 ± 5.67
Diabetes medication, n (%)		288	
Any hypoglycemic drug	—		214 (74.31)
Insulin	—		43 (14.93)
Metformin	—		136 (47.22)
Sulfonylureas	—		81 (28.13)
Dipeptidyl peptidase inhibitors	—		26 (9.03)
Other	—		11 (3.82)
HR-pQCT measures			
Distal radius			
Failure load (N)	4862.56 ± 1344.06		4914.05 ± 1308.41
Total vBMD (mg/cm^3)	274.36 ± 62.06		279.48 ± 57.75
Cross-sectional area (mm^2)	397.31 ± 66.89		391.27 ± 61.99
Trabecular vBMD (mg/cm^3)	169.89 ± 40.19		173.87 ± 36.41
Trabecular area (mm^2)	335.86 ± 68.93		329.75 ± 63.70
Trabecular number (mm^{-1})	1.40 ± 0.22		1.43 ± 0.20
Trabecular thickness (mm)	0.25 ± 0.02		0.25 ± 0.02
Cortical vBMD (mg/cm^3)	795.73 ± 68.59		796.17 ± 71.55
Cortical area (mm^2)	66.09 ± 14.11		66.14 ± 14.97
Cortical thickness (mm)	0.96 ± 0.23		0.96 ± 0.23
Cortical area fraction	0.17 ± 0.05		0.17 ± 0.05
Cortical porosity (%)	0.02 ± 0.01		0.02 ± 0.01
Distal tibia			
Failure load (N)	13 529.88 ± 2972.98		13 427.68 ± 2797.56
Total vBMD (mg/cm^3)	279.18 ± 55.83		281.76 ± 52.64
Cross-sectional area (mm^2)	895.44 ± 137.64		876.24 ± 133.05
Trabecular vBMD (mg/cm^3)	184.43 ± 38.69		186.36 ± 35.08
Trabecular area (mm^2)	762.80 ± 146.49		744.88 ± 142.18
Trabecular number (mm^{-1})	1.35 ± 0.22		1.35 ± 0.19
Trabecular thickness (mm)	0.27 ± 0.02		0.27 ± 0.02
Cortical vBMD (mg/cm^3)	779.34 ± 80.48		777.83 ± 83.84
Cortical area (mm^2)	138.77 ±31.11		137.44 ± 31.30
Cortical thickness (mm)	1.47 ± 0.34		1.47 ± 0.33
Cortical area fraction	0.16 ± 0.05		0.16 ± 0.05
Cortical porosity (%)	0.04 ± 0.02		0.04 ± 0.02
Diaphyseal tibia			
Failure load (N)	20 095.28 ± 2741.46		19 901.51 ± 2455.51

(*continued*)

Table 1. Continued

	Non-T2DM (n = 1487)	n	T2DM[a] (n = 290)
Total vBMD (mg/cm^3)	730.51 ± 79.12		733.34 ± 75.01
Cross-sectional area (mm^2)	440.06 ± 52.73		434.86 ± 44.86
Cortical vBMD (mg/cm^3)	995.67 ± 35.34		998.93 ± 33.19
Cortical area (mm^2)	312.55 ± 40.95		309.26 ± 36.36
Cortical thickness (mm)	6.15 ± 0.89		6.12 ± 0.84
Cortical area fraction	0.71 ± 0.07		0.71 ± 0.07
Cortical porosity (%)	0.02 ± 0.01		0.02 ± 0.01

Abbreviations: BMD, bone mineral density; BMI, body mass index; Cr-adj, creatinine-adjusted pentosidine; HR-pQCT, high-resolution peripheral quantitative computed tomography; MrOS, Osteoporotic Fractures in Men; T2DM, type 2 diabetes mellitus; vBMD, volumetric bone mineral density.
[a]Thiazolidinedione users (N = 12) were excluded.

Association of Diabetes-related Factors With HR-pQCT Derived Bone Parameters

Among men with diabetes, higher HbA1c (7.5% vs <7.5%), longer duration of diabetes (≥10 years vs <10 years) and insulin use (vs no insulin use), but not urine pentosidine levels, were each associated with at least 1 HR-pQCT parameter in separate models adjusted for age, race, clinic site, and BMI (data not shown).

The associations between HbA1c, diabetes duration, insulin use, and HR-pQCT derived bone parameters in a model including all 3 diabetes-related risk factors are shown in Table 3. Results are standardized to allow easier comparison across HR-pQCT parameters. After adjustment for diabetes duration, insulin use, age, race, clinic site, BMI, limb length, and oral corticosteroid use, men with an HbA1c level ≥ 7.5% had a significantly higher cortical area, cortical thickness, and failure load at the diaphyseal tibia and no significant differences in other HR-pQCT parameters compared to men with an HbA1c level < 7.5% (Ct.Ar: $P = .035$; Ct.Th: $P = .045$; failure load: $P = .022$). In a model adjusted for HbA1c, insulin use, age, race, clinic site, BMI, limb length, and oral corticosteroid use, diabetes duration ≥ 10 years was associated with higher trabecular thickness at the distal radius ($P = .002$) and distal tibia ($P = .041$) and increased cortical BMD at the diaphyseal tibia ($P = .053$; trend). Additionally, men with a diabetes duration ≥ 10 years had higher cortical porosity at the distal radius compared to men with a diabetes duration < 10 years ($P = .036$). After adjustment for HbA1c, diabetes duration, age, race, clinic site, BMI, limb length and oral corticosteroid use, insulin use in men with T2DM was associated with lower cortical area, cortical area fraction, and cortical thickness at the distal radius (Ct.Ar: $P = .005$; cortical area fraction: $P = .026$; Ct.Th: $P = .017$) and diaphyseal tibia (Ct.Ar: $P = .010$; cortical area fraction: $P = .033$; Ct.Th: $P = .002$) as compared to the noninsulin users. Insulin users had lower total BMD at all 3 scan sites (DR: $P = .032$; DT: $P = .034$; PT: $P = .050$) and lower trabecular BMD ($P = .025$) at the distal tibia than noninsulin users. In addition, insulin users had lower failure load at all 3 scan sites as compared to the noninsulin users (DR: $P = .009$; DT: $P = .007$; PT: $P = .006$).

Association of HR-pQCT Derived Bone Parameters With Incident Nonvertebral Fractures in T2DM

There were 26 nonvertebral fractures in 23 T2DM men, including ribs/sternum (8), hip (5), humerus (3), wrist (3), femur (2), hands (1), ankle (1), toes (2), and facial bones (1). Among men with T2DM, after adjusting for age, race, clinic site, BMI, limb length, and oral corticosteroid use, lower cortical area fraction was associated with increased risk of incident nonvertebral fracture, with associations varying from HR = 2.36 (95% CI, 1.24-4.46) per SD decrease at the distal radius to HR = 2.01 (95% CI, 1.25-3.24) per SD decrease at the distal tibia and HR = 1.51 (95% CI, 0.94-2.41; trend) at the diaphyseal tibia (Table 4). Results were similar for cortical thickness, with associations ranging from HR = 1.89 (95% CI, 1.08-3.31) per SD cortical thickness decrease at the distal radius to HR = 1.60 (95% CI, 0.97-2.66; trend) per SD decrease at the distal tibia and HR = 1.55 (95% CI, 1.00-2.38) at the diaphyseal tibia. Lower total BMD at the distal radius (HR = 1.69 per SD decrease [95% CI, 1.02-2.80]) and lower cortical BMD at the distal radius and tibia (DR: HR = 2.02 per SD decrease [95% CI, 1.26-3.23], DT: HR = 1.84 per SD decrease [95% CI, 1.20-2.84]) were each associated with increased risk of incident nonvertebral fracture. Additionally, lower failure load was associated with an increased risk of incident nonvertebral fracture at the distal radius (HR = 1.74 per SD decrease [95% CI, 1.02-2.94]). In contrast, no significant associations were observed between the incident nonvertebral fracture and other HR-pQCT parameters.

Discussion

In this large study, we found that men with T2DM had smaller bone size compared to those who did not have T2DM. Moreover, the smaller bone size among men with T2DM translated to a lower bone strength at the diaphyseal tibia. In contrast, cortical porosity and trabecular indices did not differ by T2DM status. These findings suggest that smaller bone size may characterize bone disease in older men with T2DM. Furthermore, we found that a longer duration of diabetes is associated with increased cortical porosity, and insulin use is associated with lower failure load and with cortical bone deficits.

The lesser total cross-sectional area observed in men with T2DM in our study is consistent with 2 other recent studies with men and women combined (10, 19), including the large Framingham cohort. Our finding is also consistent with previous cross-sectional studies using pQCT (20, 21), including a study in the MrOS cohort by Petit et al (21) that found smaller total bone area in men with T2DM, as compared to men without T2DM. During aging, healthy individuals undergo an

Table 2. HR-pQCT parameters, adjusted mean stratified by diabetes status

HR-pQCT measures	T2DM	Non-T2DM	% Difference	*P*-value
Distal radius				
Failure load (N)	4846 (4690, 5003)	4870 (4801, 4939)	−0.48	.790
Total vBMD (mg/cm^3)	276 (268, 283)	275 (272, 278)	0.30	.833
Cross-sectional area (mm^2)	392 (385, 399)	398 (395, 401)	−1.41	.156
Trabecular vBMD (mg/cm^3)	172 (167, 177)	170 (168, 172)	1.09	.481
Trabecular area (mm^2)	332 (324, 339)	336 (333, 340)	−1.30	.285
Trabecular number (mm^{-1})	1.41 (1.39, 1.44)	1.40 (1.39, 1.42)	0.71	.480
Trabecular thickness (mm)	0.25 (0.25, 0.25)	0.25 (0.25, 0.25)	0.22	.655
Cortical vBMD (mg/cm^3)	794 (786, 802)	795 (792, 799)	−0.22	.688
Cortical area (mm^2)	65.07 (63.43, 66.71)	66.32 (65.60, 67.04)	−1.87	.178
Cortical thickness (mm)	0.95 (0.92, 0.97)	0.96 (0.95, 0.97)	−1.60	.300
Cortical area fraction	0.17 (0.16, 0.18)	0.17 (0.17, 0.17)	−0.86	.623
Back transformed cortical porosity	0.013 (0.012, 0.014)	0.014 (0.014, 0.015)	−6.22	.067
Distal tibia				
Failure load (N)	13 278 (12937, 13619)	13 549 (13401, 13697)	−1.97	.160
Total vBMD (mg/cm^3)	278 (272, 284)	279 (276, 282)	−0.41	.743
Cross-sectional area (mm^2)	**881 (867, 894)**	**897 (891, 903)**	**−1.86**	**.028**
Trabecular vBMD (mg/cm^3)	186 (182, 191)	184 (182, 186)	1.12	.414
Trabecular area (mm^2)	753 (738, 767)	764 (758, 771)	−1.51	.155
Trabecular number (mm^{-1})	1.34 (1.32, 1.37)	1.35 (1.34, 1.36)	−0.46	.654
Trabecular thickness (mm)	0.27 (0.27, 0.28)	0.27 (0.27, 0.27)	0.74	.176
Cortical vBMD (mg/cm^3)	771 (762, 780)	780 (776, 784)	−1.13	.077
Cortical area (mm^2)	**134 (130, 138)**	**139 (138, 141)**	**−3.70**	**.009**
Cortical thickness (mm)	1.44 (1.40, 1.47)	1.47 (1.46, 1.49)	−2.48	.081
Cortical area fraction	0.16 (0.15, 0.16)	0.16 (0.16, 0.16)	−1.95	.274
Back transformed cortical porosity	0.040 (0.038, 0.042)	0.040 (0.039, 0.041)	−0.14	.958
Diaphyseal tibia				
Failure load (N)	**19 762 (19447, 20076)**	**20 107 (19970, 20245)**	**−1.72**	**.049**
Total vBMD (mg/cm^3)	732 (722, 742)	730 (726, 734)	0.32	.664
Cross-sectional area (mm^2)	**433 (427, 439)**	**441 (438, 443)**	**−1.67**	**.025**
Cortical vBMD (mg/cm^3)	**1001 (997, 1005)**	**995 (993, 997)**	**0.59**	**.012**
Cortical area (mm^2)	**307 (302, 312)**	**313 (311, 315)**	**−1.89**	**.023**
Cortical thickness (mm)	6.07 (5.96, 6.18)	6.15 (6.10, 6.20)	−1.30	.186
Cortical area fraction	0.71 (0.70, 0.72)	0.71 (0.71, 0.72)	−0.30	.674
Back transformed cortical porosity	0.019 (0.018, 0.020)	0.018 (0.018, 0.019)	3.50	.373

Data are presented as adjusted mean (95% CI). T2DM (distal radius, n = 274; distal tibia, n = 271, diaphyseal tibia, n = 237); non-T2DM (distal radius, n = 1412; distal tibia, n = 1430; diaphyseal tibia n = 1247). Thiazolidinedione users (N = 12) were excluded. Models adjusted for age, race, clinic site, BMI, limb length, and oral corticosteroid use. *P*-values in bold are statistically significant ($P < .05$).
Abbreviations: BMI, body mass index; HR-pQCT, high-resolution peripheral quantitative computed tomography; T2DM, type 2 diabetes mellitus; vBMD, volumetric bone mineral density.

active bone geometric adaptation to compensate for the decreased bone mass by apposition at the periosteal surface of new bone material, thereby increasing bone area and enhancing bone bending strength (22, 23). Thus, T2DM might hinder the compensatory increase in bone area that typically occurs with age, potentially influencing bone health in older men. Reasons for detrimental effect of T2DM on total bone area are not readily clear. Smaller total bone area could indicate failure in adaptive responses to elevated mechanical loading resulting in failure to compensate for diabetes-related bone loss and decreased bone strength, which may contribute to increased fracture risk in T2DM (24). Further, consistent with most previous HR-pQCT studies, trabecular microarchitecture indices (trabecular number and thickness) were similar in T2DM than those without diabetes (7, 10, 25).

In contrast to prior studies (6, 7, 10, 25), we found that cortical porosity did not differ by T2DM status. Although cortical porosity was not statistically different in our cohort, we found that T2DM patients with diabetes duration ≥ 10 years had increased cortical porosity at the distal radius, suggesting that cortical porosity is not a characteristic of all T2DM patients but of a subgroup characterized by longstanding diabetes (≥ 10 years). Therefore, long diabetes duration may contribute to the development of cortical porosity in T2DM patients and thereby increase fracture risk. These findings are consistent with a previous cross-sectional study that

Table 3. Standardized association between HbA1c, diabetes duration, insulin use, and HR-pQCT parameters in men with T2DM

	HbA1c ≥ 7.5% vs < 7.5%		Diabetes duration ≥ 10 y vs <10 y		Insulin vs no insulin	
HR-pQCT measures	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**
Distal radius						
Failure load	0.059 (−0.345, 0.463)	.775	0.169 (−0.107, 0.444)	.229	**−0.493 (−0.861, −0.125)**	**.009**
Total vBMD	0.176 (−0.230, 0.583)	.394	0.220 (−0.057, 0.497)	.118	**−0.405 (−0.775, −0.035)**	**.032**
Cross-sectional area	0.022 (−0.324, 0.368)	.900	−0.164 (−0.400, 0.072)	.172	−0.064 (−0.379, 0.252)	.691
Trabecular vBMD	0.203 (−0.219, 0.624)	.344	0.255 (−0.032, 0.542)	.082	−0.273 (−0.657, 0.111)	.162
Trabecular area	0.011 (−0.343, 0.366)	.950	−0.193 (−0.435, 0.049)	.118	0.059 (−0.265, 0.382)	.721
Trabecular number	0.252 (−0.144, 0.648)	.211	0.083 (−0.187, 0.353)	.546	−0.123 (−0.484, 0.238)	.503
Trabecular thickness	0.080 (−0.339, 0.499)	.707	**0.459 (0.174, 0.745)**	**.002**	−0.274 (−0.656, 0.107)	.158
Cortical vBMD	0.041 (−0.345, 0.427)	.835	−0.116 (−0.379, 0.147)	.385	−0.309 (−0.660, 0.043)	.085
Cortical area	0.041 (−0.356, 0.438)	.839	0.139 (−0.132, 0.409)	.314	**−0.515 (−0.877, −0.154)**	**.005**
Cortical thickness	0.074 (−0.329, 0.477)	.717	0.189 (−0.086, 0.464)	.177	**−0.447 (−0.814, −0.080)**	**.017**
Cortical area fraction	0.087 (−0.302, 0.476)	.659	0.188 (−0.077, 0.453)	.164	**−0.403 (−0.756, −0.049)**	**.026**
Log transformed cortical porosity	0.027 (−0.386, 0.441)	.897	**0.302 (0.020, 0.584)**	**.036**	−0.169 (−0.546, 0.208)	.378
Distal tibia						
Failure load	0.105 (−0.305, 0.514)	.615	0.112 (−0.156, 0.381)	.410	**−0.503 (−0.869, −0.136)**	**.007**
Total vBMD	0.111 (−0.305, 0.527)	.600	0.112 (−0.160, 0.385)	.418	**−0.403 (−0.775, −0.031)**	**.034**
Cross-sectional area	0.033 (−0.313, 0.380)	.849	−0.068 (−0.295, 0.159)	.556	0.023 (−0.288, 0.333)	.886
Trabecular vBMD	−0.046 (−0.466, 0.374)	.830	0.225 (−0.050, 0.500)	.108	**−0.430 (−0.806, −0.055)**	**.025**
Trabecular area	−0.014 (−0.372, 0.344)	.939	−0.078 (−0.312, 0.156)	.512	0.075 (−0.245, 0.395)	.645
Trabecular number	0.112 (−0.295, 0.520)	.587	0.053 (−0.214, 0.319)	.698	−0.180 (−0.545, 0.184)	.330
Trabecular thickness	−0.080 (−0.514, 0.354)	.716	**0.296 (0.012, 0.580)**	**.041**	0.223 (−0.612, 0.165)	.258
Cortical vBMD	0.126 (−0.277, 0.529)	.540	−0.188 (−0.452, 0.075)	.161	−0.159 (−0.519, 0.202)	.387
Cortical area	0.208 (−0.215, 0.631)	.334	0.065 (−0.212, 0.342)	.645	−0.246 (−0.624, 0.133)	.202
Cortical thickness	0.155 (−0.265, 0.575)	.468	0.065 (−0.210, 0.340)	.642	−0.169 (−0.545, 0.208)	.378
Cortical area fraction	0.138 (−0.270, 0.545)	.506	0.048 (−0.219, 0.315)	.725	−0.208 (−0.573, 0.156)	.261
Log transformed cortical porosity	−0.348 (−0.795, 0.098)	.126	0.078 (−0.214, 0.370)	.600	0.126 (−0.274, 0.525)	.536
Diaphyseal tibia						
Failure load	**0.477 (0.069, 0.886)**	**.022**	−0.054 (−0.329, 0.221)	.701	**−0.520 (−0.886, −0.155)**	**.006**
Total vBMD	0.286 (−0.166, 0.737)	.214	0.164 (−0.140, 0.467)	.289	−0.404 (−0.808, −0.001)	.050
Cross-sectional area	0.171 (−0.240, 0.582)	.412	−0.194 (−0.470, 0.082)	.167	−0.139 (−0.507, 0.228)	.455
Cortical vBMD	−0.161 (−0.628, 0.306)	.498	0.310 (−0.004, 0.624)	.053	−0.103 (−0.521, 0.314)	.627
Cortical area	**0.444 (0.031, 0.858)**	**.035**	−0.103 (−0.381, 0.175)	.464	**−0.490 (−0.860, −0.121)**	**.010**
Cortical thickness	**0.448 (0.011, 0.885)**	**.045**	−0.029 (−0.322, 0.265)	.847	**−0.612 (−1.003, −0.222)**	**.002**
Cortical area fraction	0.349 (−0.093, 0.792)	.121	0.070 (−0.227, 0.368)	.642	**−0.432 (−0.827, −0.036)**	**.033**
Log transformed cortical porosity	0.124 (−0.340, 0.588)	.600	−0.180 (−0.492, 0.132)	.256	0.263 (−0.152, 0.678)	.213

Beta is per SD increase in the HR-pQCT measure. HbA1c ≥ 7.5% (n = 27), HbA1c < 7.5% (n = 222); Diabetes duration ≥ 10 (n = 186), Diabetes duration < 10 years (n = 103); Insulin (n = 43), no insulin (n = 245). Thiazolidinedione users (N = 12) were excluded. Models adjusted for HbA1c, diabetes duration, insulin use as well as age, race, clinic site, BMI, limb length and oral corticosteroid use. Bold indicates statistically significant association (*P*-value < .05).
Abbreviations: HR-pQCT, high-resolution peripheral quantitative computed tomography; T2DM, type 2 diabetes mellitus; vBMD, volumetric bone mineral density.

reported increased cortical porosity in T2DM patients with microvascular disease but not in those without microvascular disease (26).

In addition, we characterized the risk factors that may contribute to deficits in bone microarchitecture in T2DM men, as most of the studies did not report on characteristics related to diabetes. In contrast to the Maastricht study (19) that reported no differences in cortical indices with increasing T2DM duration, we found that diabetes duration ≥ 10 years was associated with higher cortical porosity. Differences in results between our studies may be attributable in part to differences in the characteristics of participants. Our study included only men, whereas the Maastricht study included both women and men. In addition, participants with T2DM in our study had a mean diabetes duration of 16.2 years, whereas participants in the Maastricht study had a mean diabetes duration of 3 years. In contrast to the cortical bone deficits, we found that longer diabetes duration was associated with increased trabecular thickness. These findings suggest that long-term disease may contribute to increased cortical porosity and therefore to increased fracture risk in diabetic men.

In contrast to our hypothesis, we found that poor glycemic control (average HbA1c over the previous 6-8 weeks) was associated with higher failure load, cortical area, and cortical

Table 4. Associations between HR-pQCT measures and incident nonvertebral fracture in T2DM men

	Distal radius N = 272, # Fx = 21		Distal tibia N = 269, # Fx = 22		Diaphyseal tibia N = 237, # Fx = 19	
HR-pQCT measures	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Failure load (N)	**1.74 (1.02-2.94)**	**.041**	1.31 (0.84-2.06)	.239	1.47 (0.92-2.34)	.104
Total vBMD (mg/cm^3)	**1.69 (1.02-2.80)**	**.044**	1.32 (0.83-2.10)	.235	1.29 (0.84-1.98)	.240
Cross-sectional area (mm^2)	0.91 (0.54-1.53)	.729	1.11 (0.65-1.88)	.705	1.16 (0.70-1.93)	.567
Cortical vBMD (mg/cm^3)	**2.02 (1.26-3.23)**	**.004**	**1.84 (1.20-2.84)**	**.006**	0.99 (0.62-1.56)	.951
Cortical area (mm^2)	**2.36 (1.24-4.46)**	**.009**	**2.01 (1.25-3.24)**	**.004**	1.51 (0.94-2.41)	.088
Cortical thickness (mm)	**1.89 (1.08-3.31)**	**.025**	1.60 (0.97-2.66)	.068	**1.55 (1.00-2.38)**	**.049**
Cortical area fraction	**2.25 (1.19-4.26)**	**.012**	**1.85 (1.07-3.22)**	**.028**	1.40 (0.92-2.12)	.119
Log transformed cortical porosity	1.33 (0.87-2.04)	.186	1.02 (0.66-1.59)	.921	0.97 (0.62-1.51)	.876
Trabecular vBMD (mg/cm^3)	1.13 (0.72-1.78)	.589	0.84 (0.56-1.26)	.388	—	—
Trabecular area (mm^2)	0.78 (0.47-1.28)	.323	0.91 (0.55-1.52)	.729	—	—
Trabecular number (mm^{-1})	1.02 (0.64-1.60)	.950	0.97 (0.63-1.50)	.885	—	—
Trabecular thickness (mm)	1.15 (0.73-1.82)	.551	0.71 (0.47-1.08)	.113	—	—

HR is per 1 SD decrease in the HR-pQCT parameter. Thiazolidinedione users (N = 12) were excluded. Models are adjusted for age, race, clinic site, BMI, limb length, and oral corticosteroid use. Results in bold are statistically significant ($P < .05$).
Abbreviations: BMI, body mass index; Fx, fracture; HR-pQCT, high-resolution peripheral quantitative computed tomography; T2DM, type 2 diabetes mellitus; vBMD, volumetric bone mineral density.

thickness at the diaphyseal tibia in men with T2DM, although insulin use was associated with reduced failure load, cortical area, and cortical thickness in the same model. However, of all the patients with T2DM in our study population, only 27 (9.3%) had poorly controlled HbA1c levels (≥7.5%) and the majority (n = 22 276.6%) had well-controlled HbA1c levels (<7.5%). This might explain the absence of an association between poor glycemic control and deficits in bone parameters in our study. These results are consistent with previous studies that investigated the association between glycemic control and bone parameters in fairly well-controlled diabetic patients (26, 27). In addition, we found that pentosidine was not associated with any deficits in HR-pQCT derived bone parameters. The formation of AGEs correlates with glycemic control. Long-term hyperglycemia is associated with increased accumulation of AGEs in bone collagen, which negatively affects bone material properties. There are more limited data suggesting that AGEs may also affect bone density (28) and bone microarchitecture (27, 29-32).

Previous findings from the MrOS study have shown that diabetic men who were treated with insulin had a higher fracture risk than those who were not treated with insulin (33). In the present study, we showed that diabetic insulin users had lower failure load, cortical area, cortical thickness, and total and trabecular BMD compared to noninsulin users, even after adjustment for poor glycemic control and diabetes duration. A direct negative effect of insulin on bone seems unlikely. However, insulin use is a marker of more severe disease. The association of insulin use with worse cortical indices, BMD, and bone strength may be due to effects of other factors, such as microvascular complications, on bone.

Furthermore, we observed that cortical area, cortical thickness, and cortical BMD, but not cortical porosity, were associated with the incident nonvertebral fracture in men with diabetes. However, trabecular parameters were not associated with incident fracture. In contrast, studies in broader populations (34, 35), including in the full MrOS cohort (36), have identified both trabecular and cortical parameters as predictive of incident fracture.

This is the largest study to date on HR-pQCT-derived bone parameters and diabetes in older men. However, the study also has limitations. HR-pQCT has limited ability to detect small cortical pores. The available measure of cortical porosity may not detect differences in micropores, though cortical BMD would reflect these micropores. However, the contribution of cortical porosity, particularly small vs large pores, to bone strength and fracture risk remains incompletely understood. Medications were self-reported and only included recent use. Our assessment of glycemic control relied on only one measurement of HbA1c close to the time of the HR-pQCT measurements. It is not clear whether HbA1c measurements over a longer period would be more strongly associated with bone density and microarchitecture. Importantly, because this is an exploratory study, we did not correct for multiple comparisons. Although our findings suggest an association between diabetes and bone size, these results should be interpreted with caution and confirmed by other studies. Moreover, study participants were male volunteers who were healthy enough to attend a clinic visit and were mainly White; our results may not apply to other populations.

In conclusion, our data show that, in men, T2DM was associated with a smaller bone size. Interestingly, among men with T2DM, a longer duration of the disease and the use of insulin were associated with deterioration in cortical bone. Reduced bone size may contribute in part to the higher fracture risk observed among patients with T2DM. Future studies are required to unravel the mechanisms underlying the changes in bone size in T2DM patients.

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Author Contributions

M.F.: Validation, visualization, writing-original draft, writing-review and editing. A.V.S.: Conceptualization, formal analysis, methodology, project administration, supervision, validation, visualization, writing-review and editing. A.J.B.: Validation and writing-review and editing. D.B.: Validation and writing-review and editing. E.O.: Supervision, validation, and writing-review and editing. E.S.S.: Validation and writing-review and editing. E.V.: Validation and writing-review and editing. G.B.: Methodology. G.L.: Methodology. G.W.: Validation and writing-review and editing. L.Y.L.: Formal analysis, software, and writing-review and editing. M.B.: Validation and writing-review and editing. N.N.: Conceptualization, supervision, validation, visualization, writing-review and editing.

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Data Availability

Data from MrOS are available at https://mrosonline.ucsf.edu. The data that support the findings of this study are not publicly available due to privacy or ethical restrictions. The data are available from the corresponding author upon reasonable request.

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