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ORIGINAL RESEARCH

Bone Microarchitecture in Men and Women with Diabetes: The Importance of Cortical Porosity

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Abstract High-resolution peripheral quantitative computed tomography (HR-pQCT) captures novel aspects of bone geometry, volumetric bone mineral density and offers the ability to measure bone microarchitecture, but data relating measures obtained from this technique to diabetic status are inconsistent in women and lacking in men. Here, we report an analysis from the Hertfordshire Cohort Study, where we were able to study associations between bone microarchitecture from HR-pQCT of distal radius and distal tibia in 332 participants (177 men and 155 women) aged 72.1–81.4 years with or without diabetes mellitus (DM); $n = 29$ (18 men and 11 women) and $n = 303$, respectively. Statistical analyses were performed separately for women and men. The mean (SD) age of participants was 76.4 (2.6) and 76.1 (2.5) years in women and men, respectively. Participants with DM differed significantly in terms of weight in both women (70.4 ± 12.3 vs. 80.3 ± 18.3 kg; $p = 0.015$) and men (81.7 ± 11.4 vs. 92.8 ± 16.3 kg; $p < 0.001$) but no differences were found in height, smoking status, alcohol intake, social class and physical activity among women or men. Analyses in women revealed that cortical pore volume (Ct.Po.V) was higher in participants with DM and close to statistical significance for cortical porosity (Ct.Po) ($\beta = 0.76$ [0.12, 1.41] z-score, $p = 0.020$ and $\beta = 0.62$ [−0.02, 1.27] z-score, $p = 0.059$, respectively) at the distal radius. Adjustment for weight did not materially affect the relationship described for Ct.Po.V ($\beta = 0.74$ [0.09, 1.39], $p = 0.027$) and Ct.Po ($\beta = 0.65$ [−0.01, 1.30], $p = 0.053$) at the distal radius. After adjustment for weight, analyses in men revealed that Ct.Po and Ct.Po.V were higher in participants with DM ($\beta = 0.57$ [0.09, 1.06] z-score, $p = 0.021$ and $\beta = 0.48$ [0.01, 0.95] z-score, $p = 0.044$, respectively) at the distal tibia. Analyses of distal radial and tibial trabecular bone parameters according to diabetic status revealed no significant differences among men or women after adjustment for weight. We found higher cortical porosity and cortical pore volume at the distal tibia in men with DM and higher cortical pore volume at the distal radius in women with a non-significant tendency for higher cortical porosity. The results of our study suggest that deficits in cortical bone exist both in older men and women with DM.

Keywords Diabetes mellitus · Osteoporosis · High-resolution peripheral quantitative computed tomography · Cortical porosity

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Introduction

Bone is now recognized as another tissue subject to diabetic complications. Indeed, diabetes is an independent risk factor for fragility fractures at skeletal sites such as the hip, spine, and distal forearm [1, 2]. Two meta-analyses, which

included data on more than 1 million participants, reported an odds ratio of 1.4–1.7 for hip fractures in patients with diabetes [3, 4]. However, discrepancies exist between bone mineral density (BMD), FRAX® and fracture risk in patients with type 2 diabetes mellitus (T2DM). Indeed, fracture risk is higher for a given femoral neck BMD T-score and age or for a given FRAX® probability in patients with T2DM compared to non-diabetic controls [5].

These findings suggest abnormalities in bone "quality", such as bone material properties and microarchitecture. A few previous studies have used high-resolution peripheral quantitative computed tomography (HR-pQCT) to assess bone microarchitecture in patients with T2DM compared to non-diabetic subjects. Burghardt et al. found that T2DM women had higher cortical porosity and cortical pore volume at the distal radius than age and height-matched controls [6]. Porosity in the distal radius of these subjects was specifically associated with a deficit in biomechanical properties. Shu et al. found that T2DM women had bone microarchitecture that was not significantly different than controls [7], whereas Patsch et al. found higher cortical porosity at the distal radius in T2DM women with fragility fractures compared to T2DM women without fracture [8]. Recently, Farr et al. found compromised bone material strength and reduced serum markers of bone turnover in patients with T2DM but failed to distinguish bone microarchitectural abnormalities in comparison with controls [9].

Data relating measures obtained from HR-pQCT in patients with diabetes are inconsistent in women and lacking in men. Therefore, the aim of this study was to develop a better understanding in this area by investigating the relationships of bone geometry, volumetric BMD, and bone microarchitecture in patients with diabetes in a well-phenotyped cohort of older men and women from Hertfordshire.

Methods

Study Population

The Hertfordshire Cohort Study (HCS) is a population-based UK cohort of older adults. Study design and recruitment have been described in detail previously [10]. HCS participants were generally comparable with those in the nationally representative Health Survey for England [10]. In brief, we traced men and women born between 1931 and 1939 in Hertfordshire and who still lived there in 1998–2003 when a nurse-administered questionnaire and clinic visit were carried out. In 2011–2012, 592 men and women from the geographical area of East Hertfordshire were invited to take part in the study and a home visit which included a structured interview was conducted in 443 patients. Of these, 350 agreed to have a HR-pQCT scan 1 year later. The East and North Hertfordshire Ethical Committees granted approval for the study, and all participants gave written informed consent in accordance with the Declaration of Helsinki [11].

Demographic and Clinical Assessment

A structured interview was performed during a home visit in 2011–2012. Specifically, the following demographics were recorded: age, alcohol consumption, smoking status and physical activity. History of diabetes mellitus or high blood pressure (HBP) was obtained through self-report. Concomitant drugs, such as insulin, biguanides and sulphonylureas, were also recorded. Details regarding dietary calcium intake and socioeconomic status were available from the nurse-administered questionnaire conducted in 1998–2003. Height (cm) and weight (kg) were measured when participants attended for HR-pQCT assessment. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2).

Two groups of participants were constituted using data recorded during the structured interview in 2011–2012: using stringent criteria, diabetic participants were defined as those taking insulin, sulphonylureas, biguanides or thiazolidinediones ($n = 29$) and non-diabetic participants were defined as those not reporting taking any of these medications and not reporting having diabetes ($n = 303$). A limited number of participants ($n = 18$) were excluded because they had a self-report history of diabetes but were not taking insulin, sulphonylureas, biguanides or thiazolidinediones. Although these individuals could have diet-controlled diabetes, the diagnosis could not be verified from the data available.

High-Resolution Peripheral Quantitative Computed Tomography

Distal radial and tibial HR-pQCT (XtremeCT, Scanco Medical AG, Switzerland) scans were carried out of the non-dominant side except when it had previously fractured. Antero-posterior 2D scout views were performed to determine the region to be imaged. All scans were acquired by one of two trained technicians using standard positioning techniques. These were in keeping with the manufacturer's guidelines and as described by Boutroy et al. [12]. Each scan was assessed for motion artefact, and if present a second scan was performed. The quality of the measurements was assessed by using a 5-point scale recommended by the manufacturer (1, excellent; 2, good; 3, acceptable; 4, poor; 5, unacceptable) [13]. Only examinations with quality grades 1 through 3 were included in the study, while grades 4 and 5 were excluded. For this reason, we have excluded radius scans for 24 men and 19 women and tibia scans for 3 men and 5 women.

Image analysis was carried out using the standard manufacturer's method which has been described in detail previously [14, 15]. Standard morphologic analysis produced trabecular BMD (Tb.vBMD, mg/cm^3), trabecular number (Tb.N, per mm), trabecular thickness (Tb.Th, μm) and trabecular separation (Tb.Sp, μm). Each measure has been validated against micro-CT imaging [16]. Further analysis was performed using an automated segmentation algorithm. Assessments were made of total cross-sectional area (Tt. Area, mm^2), cortical area (Ct. Area, mm^2) and cortical density (Ct.vBMD, mg/cm^3). Cortical pore volume (Ct.Po.V, mm^3) was calculated as the volume of all voxels identified as intracortical pore space. The cortical porosity (Ct.Po, %) was calculated as the ratio of the Ct.Po.V to the total volume of the cortical compartment [17]. Cortical thickness (Ct.Th, μm) was determined from the threshold cortex image using a distance transform after removal of intracortical pores [18]. Short-term precision values (% CV) for cortical and trabecular BMD have been shown to range from 0.3 to 1.2 [19]. The effective dose to the subject during each scan was <3 μSv.

Statistical Methods

Statistical analyses were performed using STATA version 13.1. Variables were assessed for normality and transformed if necessary. Descriptive statistics for continuous variables are expressed as mean (standard deviation) or median, IQR and categorical variables as frequency (percentage). Differences in continuous variables among men and women with and without T2DM and between genders were assessed using Student's t-tests or Mann–Whitney tests and in categorical variables using Pearson's χ^2 test or Fisher's exact test, as appropriate. Statistical significance was defined as a p value of ≤ 0.05. HRpQCT variables were transformed using the Fisher–Yates rank-based inverse normal transformation to create z-scores.

Linear regression was used to examine the associations between diabetes and HR-pQCT bone parameters in the distal radius and tibia of men and women. These analyses were undertaken with and without adjustment for weight. Finally, as many tests were expected, we performed multiple testing corrections using the Bonferroni correction.

Results

Characteristics of Study Participants

Characteristics of study participants were compared among men and women by diabetic status (Table 1). The mean

Table 1 Characteristics for men and women, by diabetic status

Variables	Men (n = 177)			Women (n = 155)		
	Diabetic[a] (n = 18)	Non-diabetic[a] (n = 159)	p value	Diabetic[a] (n = 11)	Non-diabetic[a] (n = 144)	p value
Age (year)	76.8 ± 2.3	76.0 ± 2.5	0.196	77.1 ± 2.9	76.2 ± 2.6	0.279
Weight (kg)	92.8 ± 16.3	81.7 ± 11.4	**<0.001**	80.3 ± 18.3	70.4 ± 12.3	**0.015**
Height (cm)	173.2 ± 5.6	173.6 ± 6.6	0.824	161.2 ± 5.7	159.7 ± 5.7	0.384
BMI (kg/m^2)	30.9 ± 5.1	27.1 ± 3.4	**<0.001**	30.9 ± 6.9	27.6 ± 4.6	**0.029**
Ever smoked, n (%)	13 (72.2)	91 (57.2)	0.313	5 (45.5)	53 (36.8)	0.748
Alcohol intake[b], n (%)						
None/minimal	6 (33.3)	31 (19.5)	0.163	7 (63.6)	77 (53.5)	0.734
Low	5 (27.8)	77 (48.4)		4 (36.4)	50 (34.7)	
Moderate/high	7 (38.9)	51 (32.1)		0 (< 1)	17 (11.8)	
Social status, n (%)						
I-IIINM	4 (23.5)	67 (43.8)	0.126	3 (27.3)	66 (45.8)	0.348
IIIM-V	13 (76.5)	86 (56.2)		8 (72.7)	78 (54.2)	
Physical activity[c] (min/day)	148.2 [93.6–187.1]	193.6 [128.6–285.7]	0.076	215.2 [180.0–287.1]	206.1 [138.8–282.1]	0.684
Daily calcium intake (mg)	1178 [962–1362]	1222 [1011–1433]	0.461	1056 [892–1232]	1103 [939–1261]	0.464

Values are the mean ± SD or median [IQR] (significant results are indicated in bold)

BMI body mass index

[a] Diabetic = those reporting taking insulin, sulphonylureas biguanides or thiazolidinediones; non-diabetic = those not reporting taking any of these medications and no self-report of diabetes

[b] None/minimal = <1 unit per week; low = ≥1 unit and < 8 units for women or <11 units for men, per week; moderate/high = ≥8 units for women and ≥11 units for men, per week

[c] Average minutes per day spent walking outside, cycling, gardening, playing sports and doing housework in last 2 weeks

Table 2 Summary of HR-pQCT variables in men, by diabetic status

	Non-diabetic[a]			Diabetic[a]			*p* value
	N	Median	IQR	*N*	Median	IQR	
Radius							
Total area (mm^2)	138	417.9	385.6–467.9	14	410.9	375.9–474.4	0.610
Cortical area (mm^2)	139	70.2	61.0–77.4	14	67.7	62.1–71.9	0.556
Trabecular area (mm^2)	139	344.1	307.7–400.0	14	335.5	301.1–399.9	0.714
Trabecular density (mg/cm^3)	139	180.0	156.7–201.9	14	190.7	167.3–224.9	0.107
Trabecular number (cm^{-1})	139	23.6	22.3–24.9	14	25.1	23.2–26.5	**0.024**
Trabecular thickness (μm)	139	64.0	57.0–70.0	14	64.5	60.0–75.0	0.410
Trabecular separation (μm)	139	359.0	336.0–388.0	14	337.0	309.0–364.0	**0.033**
Cortical bone mineral density (mg/cm^3)	139	909.9	882.1–947.0	14	885.6	860.3–914.6	**0.032**
Apparent cortical thickness (μm)	139	802.7	701.7–923.0	14	752.1	708.5–847.6	0.531
Cortical porosity (%)	139	3.9	3.0–4.8	14	5.0	4.1–5.3	**0.013**
Cortical pore volume (mm^3)	139	22.3	16.7–27.4	14	28.2	21.0–32.2	**0.067**
Tibia							
Total area (mm^2)	155	913.3	815.3–1012.0	18	911.6	838.1–975.2	0.651
Cortical area (mm^2)	156	138.0	126.2–155.2	18	148.2	132.4–171.0	0.224
Trabecular area (mm^2)	156	769.6	660.7–868.4	18	763.8	670.0–836.9	0.492
Trabecular density (mg/cm^3)	156	189.8	164.2–212.3	18	194.0	176.4–216.4	0.555
Trabecular number (cm^{-1})	156	24.2	22.0–26.4	18	25.9	24.1–27.5	**0.041**
Trabecular thickness (μm)	156	66.0	57.0–71.0	18	61.5	57.0–63.0	0.175
Trabecular separation (μm)	156	346.5	320.0–389.0	18	324.5	303.0–356.0	0.062
Cortical bone mineral density (mg/cm^3)	156	874.1	837.3–908.7	18	844.6	803.5–874.7	**0.030**
Apparent cortical thickness (μm)	156	1165.7	1048.2–1373.7	18	1196.6	1094.4–1331.9	0.718
Cortical porosity (%)	156	8.7	7.2–10.4	18	10.9	9.3–13.5	**0.005**
Cortical pore volume (mm^3)	156	101.2	81.9–125.0	18	141.1	92.2–176.9	**0.005**

Diabetic = those reporting taking insulin, sulphonylureas, thiazolidinediones or biguanides; Non-diabetic = those not reporting taking any of these medications and no self-report of diabetes

Significant results are indicated in bold

(SD) age of participants was 76.4 (2.6) and 76.1 (2.5) years in women and men, respectively. Among men, participants with diabetes ($n = 18$) differed significantly in terms of weight (T2DM: 92.8 ± 16.3 kg; controls: 81.7 ± 11.4 kg, $p < 0.001$) and BMI (T2DM: 30.9 ± 5.1 kg/m^2; controls: 27.1 ± 3.4 kg/m^2, $p < 0.001$) from those without diabetes ($n = 159$). Among women, participants with diabetes ($n = 11$) also differed significantly in terms of weight (T2DM: 80.3 ± 18.3 kg; controls: 70.4 ± 12.3 kg, $p = 0.015$) and BMI (T2DM: 30.9 ± 6.9 kg/m^2; controls: 27.6 ± 4.6 kg/m^2, $p = 0.029$) from those without diabetes ($n = 144$). No differences were found regarding height, smoking status, alcohol intake, social class, physical activity or dietary calcium intake among women or men. Concomitant drugs were recorded for diabetic patients: insulin ($n = 8$; men, $n = 6$ and women, $n = 2$), biguanides ($n = 21$; men, $n = 14$ and women, $n = 7$), thiazolidinediones (n = 6) and sulphonylureas ($n = 12$; men, $n = 6$ and women, $n = 6$).

Bone Geometry, Volumetric BMD and Microarchitecture

Regarding HR-pQCT bone variables from the distal radius in men and women, with the exception of Ct.vBMD [median (IQR): men: 909.9 (881.4, 946.5); women 913.2 (871.2, 944.1) mg/cm^3], bone geometry, cortical and trabecular microstructure differed significantly between men and women ($p < 0.001$ for all parameters). Regarding HR-pQCT bone variables from the distal tibia in men and women, with the exception of Tb.Th (median (IQR): men: 63.5 (57.0, 71.0); women 63.0 (54.0, 71.0) μm) bone geometry, cortical and trabecular microstructure differed significantly between men and women ($p < 0.01$ for all parameters).

Comparison of bone parameters by diabetic status is shown in Table 2 for men and Table 3 for women. Comparison in men revealed that (i) Tb.N and Ct.Po were higher in diabetic participants [median (IQR): 25.1 (23.2,

Table 3 Summary of HR-pQCT variables in women, by diabetic status

	Non-diabetic[a]			Diabetic[a]			*p* value
	N	Median	IQR	*N*	Median	IQR	
Radius							
Total area (mm^2)	127	279.3	257.2–304.0	9	281.5	259.4–311.5	0.796
Cortical area (mm^2)	127	45.9	40.0–51.0	9	54.3	49.6–55.4	0.051
Trabecular area (mm^2)	127	235.1	206.3–259.2	9	237.9	201.2–259.5	0.763
Trabecular density (mg/cm^3)	127	144.6	108.9–167.2	9	153.1	116.7–174.1	0.713
Trabecular number (cm^{-1})	127	21.3	18.0–23.5	9	23.0	21.1–25.1	0.225
Trabecular thickness (μm)	127	55.0	50.0–63.0	9	52.0	51.0–59.0	0.365
Trabecular separation (μm)	127	413.0	367.0–508.0	9	374.0	341.0–414.0	0.308
Cortical bone mineral density (mg/cm^3)	127	914.2	871.5–944.9	9	900.5	891.1–937.5	0.700
Apparent cortical thickness (μm)	127	682.5	553.5–769.6	9	738.7	689.4–848.4	0.168
Cortical porosity (%)	127	3.4	2.4–4.1	9	4.3	3.2–5.1	**0.042**
Cortical pore volume (mm^3)	127	11.5	8.2–16.7	9	16.6	14.6–20.2	**0.016**
Tibia							
Total area (mm^2)	141	690.1	639.1–775.7	9	689.8	666.9–738.9	0.940
Cortical area (mm^2)	141	93.0	83.3–103.5	9	94.0	84.4–96.7	0.940
Trabecular area (mm^2)	141	600.1	538.0–698.1	9	605.3	580.1–652.6	0.962
Trabecular density (mg/cm^3)	141	166.4	145.5–194.9	9	176.7	159.3–186.4	0.681
Trabecular number (cm^{-1})	141	23.0	20.7–24.9	9	22.0	20.6–23.5	0.785
Trabecular thickness (μm)	141	63.0	54.0–70.0	9	63.0	57.0–67.0	0.959
Trabecular separation (μm)	141	374.0	339.0–420.0	9	387.0	360.0–422.0	0.968
Cortical bone mineral density (mg/cm^3)	141	816.4	768.1–859.0	9	812.7	753.7–859.9	0.940
Apparent cortical thickness (μm)	141	913.0	778.6–1069.4	9	904.2	832.1–963.3	0.701
Cortical porosity (%)	141	9.8	7.8–11.8	9	10.1	8.7–10.9	0.572
Cortical pore volume (mm^3)	141	72.5	56.8–90.1	9	81.9	53.6–96.3	0.713

[a] Diabetic = those reporting taking insulin, sulphonylureas, thiazolidinediones or biguanides; Non-diabetic = those not reporting taking any of these medications and no self-report of diabetes

Significant results are indicated in bold

26.5) vs. 23.6 (22.3, 24.9) per mm; $p = 0.024$ and 5.0 (4.1, 5.3) vs. 3.9 (3.0, 4.8) %; $p = 0.013$, respectively], whereas Ct.vBMD and Tb.Sp were lower [885.6 (860.3, 914.6) vs. 909.9 (882.1, 974.0) mg/cm^3; $p = 0.032$ and 337.0 (309.0, 364.0) μm; $p = 0.033$, respectively] at the distal radius (ii) Tb.N, Ct.Po and Ct.Po.V were higher in diabetic participants [median (IQR): 25.9 (24.1, 27.5) vs. 24.2 (22.0, 26.4) per mm; $p = 0.041$, 10.9 (9.3, 13.5) vs. 8.7 (7.2, 10.4) %; $p = 0.005$ and 141.1 (92.2, 176.9) vs. 101.2 (81.9, 125.0) mm^3; $p = 0.005$, respectively], whereas Ct.vBMD was lower [844.6 (803.5, 874.7) vs. 874.1 (837.3, 908.7) mg/cm^3; $p = 0.030$] at the distal tibia. Comparison in women revealed that Ct.Po and Ct.Po.V were higher [median (IQR): 4.3 (3.2, 5.1) vs. 3.4 (2.4, 4.1) %; $p = 0.042$ and 16.6 (14.6, 20.2) vs. 11.5 (8.2, 16.7) mm^3; $p = 0.016$, respectively] in diabetic participants at the distal radius.

The results of regression analyses are shown in Table 4 for women and Table 5 for men. Analyses in women revealed that Ct.Po.V was higher in participants with T2DM, whereas it was close to the margin of statistical significance for Ct.Po ($\beta = 0.76$ [0.12, 1.41] *z*-score, $p = 0.020$ and $\beta = 0.62$ [−0.02, 1.27] *z*-score, $p = 0.059$, respectively) at the distal radius. Adjustment for weight did not materially affect the relationship described for Ct.Po.V ($\beta = 0.74$ [0.09, 1.39], $p = 0.027$) and Ct.Po ($\beta = 0.65$ [−0.01, 1.30], $p = 0.053$).

At the distal tibia, analyses in men revealed that Ct.Po, Ct.Po.V and Tb.N were higher in participants with DM ($\beta = 0.74$ [0.27, 1.21] *z*-score, $p = 0.002$, $\beta = 0.75$ [0.28, 1.22] *z*-score, $p = 0.002$, and $\beta = 0.55$ [0.08, 1.03] *z*-score, $p = 0.024$ respectively), whereas Ct.vBMD and Tb.Sp were lower ($\beta = -0.50$ [−0.98, −0.02] *z*-score, $p = 0.040$ and $\beta = -0.50$ [−0.98, 0.03] *z*-score, $p = 0.038$ respectively). Adjustment for weight did not materially affect the relationship described for Ct.Po ($\beta = 0.57$ [0.09, 1.06], $p = 0.021$) and Ct.Po.V ($\beta = 0.48$ [0.01, 0.95], $p = 0.044$) but the relationships with Ct.vBMD, Tb.N and Tb.Sp were fully attenuated. At the distal radius, analyses in men revealed that Ct.Po, and Tb.N were higher in participants with DM ($\beta = 0.68$ [0.15, 1.22]

Table 4 Diabetes as an explanatory variable for HR-pQCT variables in men

	Unadjusted				Adjusted for weight			
	N	Regression coefficient	95 % CI	*p* value	*N*	Regression coefficient	95 % CI	*p* value
Radius								
Total area (FY *z*-score)	152	−0.15	(−0.69, 0.39)	0.582	152	−0.32	(−0.87, 0.22)	0.241
Cortical area (FY *z*-score)	153	−0.09	(−0.63, 0.46)	0.750	153	−0.39	(−0.92, 0.13)	0.142
Trabecular area (FY *z*-score)	153	−0.12	(−0.66, 0.42)	0.654	153	−0.24	(−0.79, 0.31)	0.387
Trabecular density (FY *z*-score)	153	0.53	(−0.01, 1.07)	0.055	153	0.39	(−0.16, 0.94)	0.163
Trabecular number (FY *z*-score)	153	0.66	(0.13, 1.19)	**0.015**	153	0.44	(−0.10, 0.97)	0.107
Trabecular thickness (FY *z*-score)	153	0.28	(−0.27, 0.83)	0.314	153	0.27	(−0.30, 0.83)	0.357
Trabecular separation (FY *z*-score)	153	−0.68	(−1.21, −0.15)	**0.013**	153	−0.46	(−0.99, 0.07)	0.088
Cortical bone mineral density (FY *z*-score)	153	−0.53	(−1.07, 0.00)	0.051	153	−0.46	(−1.01, 0.09)	0.102
Apparent cortical thickness (FY z-score)	153	−0.06	(−0.60, 0.48)	0.827	153	−0.25	(−0.79, 0.30)	0.374
Cortical porosity (FY *z*-score*z*-score)	153	0.68	(0.15, 1.22)	**0.013**	153	0.51	(−0.03, 1.05)	0.066
Cortical pore volume (FY *z*-score)	153	0.51	(−0.03, 1.05)	0.062	153	0.22	(−0.30, 0.75)	0.403
Tibia								
Total area (FY *z*-score)	173	−0.12	(−0.60, 0.37)	0.639	173	−0.38	(−0.86, 0.11)	0.130
Cortical area (FY *z*-score)	174	0.31	(−0.17, 0.79)	0.200	174	0.00	(−0.47, 0.46)	0.984
Trabecular area (FY *z*-score)	174	−0.16	(−0.65, 0.32)	0.506	174	−0.37	(−0.86, 0.13)	0.148
Trabecular density (FY *z*-score)	174	0.15	(−0.33, 0.63)	0.537	174	−0.03	(−0.52, 0.45)	0.888
Trabecular number (FY *z*-score)	174	0.55	(0.08, 1.03)	**0.024**	174	0.04	(−0.37, 0.46)	0.834
Trabecular thickness (FY *z*-score)	174	−0.28	(−0.76, 0.21)	0.259	174	−0.09	(−0.59, 0.40)	0.712
Trabecular separation (FY *z*-score)	174	−0.50	(−0.98, −0.03)	**0.038**	174	−0.02	(−0.44, 0.39)	0.908
Cortical bone mineral density (FY *z*-score)	174	−0.50	(−0.98, −0.02)	**0.040**	174	−0.45	(−0.95, 0.05)	0.078
Apparent cortical thickness (FY *z*-score)	174	0.11	(−0.38, 0.59)	0.664	174	0.02	(−0.48, 0.52)	0.929
Cortical porosity (FY *z*-score)	174	0.74	(0.27, 1.21)	**0.002**	174	0.57	(0.09, 1.06)	**0.021**
Cortical pore volume (FY *z*-score)	174	0.75	(0.28, 1.22)	**0.002**	174	0.48	(0.01, 0.95)	**0.044**

Significant results are indicated in bold

HRpQCT variables were transformed using the Fisher–Yates rank-based inverse normal transformation to create *z*-scores

z-score, $p = 0.013$, and $\beta = 0.66$ [0.13, 1.19] *z*-score, $p = 0.015$ respectively) whereas Tb.Sp was lower ($\beta = -0.68$ [−1.21, −0.15] *z*-score, $p = 0.013$). After adjustment for weight, the relationships described for Ct.Po, Tb.N and Tb.Sp were fully attenuated. When corrections were made for multiple testing, none of the results remained statistically significant.

Discussion

The aim of this study was to develop a better understanding of diabetes-related bone disease by investigating the relationships of bone geometry, volumetric BMD and bone microarchitecture in patients with and without T2DM in a well-phenotyped cohort of older men and women from Hertfordshire. We found higher cortical porosity and cortical pore volume at the distal tibia in men with T2DM and higher cortical pore volume at the distal radius in women with a non-significant trend for higher cortical porosity.

It is important to note that this is the first time that HR-pQCT has been used to assess the relationship between bone parameters and diabetes (those taking insulin and oral diabetic medications) in a cohort of older men. Moreover, our findings about higher Ct.Po and Ct.Po.V at the distal tibia in men with diabetes are of significant interest. Furthermore, we found higher Ct.Po.V at the distal radius in a cohort of older women, and higher Ct.Po was close to the margin of statistical significance.

Our results confirm previous studies, but not all [7, 9], demonstrating higher cortical porosity at the distal radius in women with T2DM [6, 8]. Shu et al. found that T2DM women had bone microarchitecture that was not significantly different from controls [7], although cortical porosity was not reported and the subset of subjects who underwent HR-pQCT scanning was small (14 subjects per group). In the Framingham HR-pQCT Study (men and women together), they found that participants with T2DM had significantly lower Ct.vBMD and higher cortical porosity at the distal tibia [20]. However, Patsch et al.

Table 5 Diabetes as an explanatory variable for HR-pQCT variables in women

	Unadjusted				Adjusted for weight			
	N	Regression coefficient	95 % CI	*p* value	*N*	Regression coefficient	95 % CI	*p* value
Radius								
Total area (FY *z*-score)	136	−0.14	(−0.81, 0.53)	0.682	136	−0.34	(−0.97, 0.30)	0.295
Cortical area (FY *z*-score)	136	0.59	(−0.07, 1.26)	0.079	136	0.42	(−0.22, 1.06)	0.199
Trabecular area (FY *z*-score)	136	−0.18	(−0.84, 0.49)	0.599	136	−0.34	(−0.98, 0.30)	0.292
Trabecular density (FY *z*-score)	136	0.00	(−0.67, 0.67)	0.994	136	−0.06	(−0.73, 0.62)	0.863
Trabecular number (FY *z*-score)	136	0.33	(−0.34, 1.00)	0.328	136	0.19	(−0.47, 0.84)	0.571
Trabecular thickness (FY *z*-score)	136	−0.35	(−1.00, 0.30)	0.285	136	−0.31	(−0.97, 0.34)	0.347
Trabecular separation (FY *z*-score)	136	−0.26	(−0.93, 0.41)	0.441	136	−0.13	(−0.79, 0.53)	0.700
Cortical bone mineral density (FY *z*-score)	136	−0.13	(−0.79, 0.53)	0.696	136	−0.10	(−0.77, 0.57)	0.761
Apparent cortical thickness (FY *z*-score)	136	0.49	(−0.17, 1.15)	0.145	136	0.46	(−0.21, 1.13)	0.178
Cortical porosity (FY *z*-score)	136	0.62	(−0.02, 1.27)	0.059	136	0.65	(−0.01, 1.30)	0.053
Cortical pore volume (FY *z*-score)	136	0.76	(0.12, 1.41)	**0.020**	136	0.74	(0.09, 1.39)	**0.027**
Tibia								
Total area (FY *z*-score)	150	−0.13	(−0.80, 0.53)	0.696	150	−0,46	(−1.11. 0.20)	0.169
Cortical area (FY *z*-score)	150	0.02	(−0.65, 0.69)	0.958	150	−0.31	(−0.96, 0.35)	0.356
Trabecular area (FY *z*-score)	150	−0.10	(−0.77, 0.56)	0.762	150	−0.38	(−1.04, 0.28)	0.259
Trabecular density (FY *z*-score)	150	0.11	(−0.56, 0.77)	0.747	150	−0.04	(−0.72, 0.64)	0.911
Trabecular number (FY *z*-score)	150	0.13	(−0.53, 0.79)	0.694	150	−0.23	(−0.86, 0.40)	0.474
Trabecular thickness (FY *z*-score)	150	−0.03	(−0.68, 0.62)	0.922	150	0.07	(−0.60, 0.73)	0.847
Trabecular separation (FY *z*-score)	150	−0.18	(−0.84, 0.48)	0.596	150	0.16	(−0.48, 0.81)	0.623
Cortical bone mineral density (FY *z*-score)	150	−0.04	(−0.71, 0.64)	0.915	150	−0.12	(−0.82, 0.57)	0.726
Apparent cortical thickness (FY z-score)	150	−0.13	(−0.80, 0.53)	0.688	150	−0.19	(−0.87, 0.50)	0.590
Cortical porosity (FY *z*-score)	150	0.23	(−0.44, 0.90)	0.503	150	0.21	(−0.49, 0.90)	0.560
Cortical pore volume (FY *z*-score)	150	0.13	(−0.54, 0.80)	0.702	150	−0.05	(−0.73, 0.63)	0.880

Significant results are indicated in bold

HRpQCT variables were transformed using the Fisher–Yates rank-based inverse normal transformation to create *z*-scores

found higher cortical porosity only in T2DM postmenopausal women with fragility fractures in comparison with T2DM postmenopausal women without fragility fractures ($n = 20$ per group) [8]. In a cortical pore laminar analysis, they found isolated high porosity in the midcortical region [21]. More recently, T2DM and higher fasting glucose were associated with higher Ct.Po and lower Ct.vBMD at the distal radius, but not at the distal tibia, in African-American women [22].

We found cortical bone porosity abnormalities both in men and women with T2DM. It remains to determine why those abnormalities were found at the distal tibia in men and at the distal radius in women. However, analyses in men also revealed higher Ct.Po at the distal radius but this relationship was attenuated after adjustment for weight. It is surprising to find a difference in Ct.Po not accompanied by a difference in Ct.vBMD which is more convincing. Analyses in men revealed lower Ct.vBMD at the distal tibia but this relationship was attenuated after adjustment for weight.

It is not fully understood why individuals with diabetes may have abnormalities in their cortical bone. The factors that determine cortical porosity are not well understood, but possible contributors include higher levels of advanced glycation end products (AGE) in the bone matrix. Recently, Fink et al. found that levels of the AGE pentosidine were related to cortical porosity at the radius in T2DM postmenopausal women [23]. Furthermore, matrix changes including the accumulation of AGEs are considered to influence bone strength, and there is a growing body of evidence that AGEs and their receptor (RAGE) system elicit oxidative stress generation and inflammatory responses [24]. Taken altogether, these data reinforce the notion that intracortical bone loss from cortical porosity is a significant skeletal complication of manifest diabetic bone disease and might compromise bone mechanical properties leading to an increased fracture risk. However, quantification of cortical porosity remains challenging both because pores of typical average open lumen diameter of

osteon (<80 μm) cannot be visualized by HR-pQCT and segmentation also remains challenging.

The strengths of our study include a well-phenotyped cohort of older men and women. There are several limitations to this study to acknowledge. Based on the cross-sectional nature of this study design, causality cannot be established because we are unable to determine temporal relationships between the variables. Furthermore, we were unable to distinguish type 1 from type 2 diabetic patients. However, given their medication histories, the majority were likely to be the latter. On this point, medication history was not independently validated through review of medical notes, although it would be unlikely for participants to erroneously state both that they were diabetic and that they were taking a specific medication used in this condition. Our study did not include contemporaneous laboratory assessments, so we could not investigate how bone metabolism in participants might have been specifically affected by glycaemia, glycaemic control, glycated Haemoglobin and their relationships with bone density and microarchitecture. Furthermore, duration of disease was unknown, although it may be of importance for bone microstructure impairment. Another limitation of our study is the relatively small number of individuals with diabetes. This limits the power of the study, particularly due to the fact that the group is divided into men and women for analyses. This may be one reason why associations were not maintained after Bonferroni correction. The finding that the associations identified were not robust to adjustment for multiple testing does attenuate the strength of the evidence provided but given the consistency with previous work, it is still felt that they unlikely to be due to chance alone. Moreover, assessment of bone strength using micro-finite element analysis was not realized. Finally, HR-pQCT data are restricted to the peripheral skeleton and do not provide a direct measure of bone impairment at axial regions such as hip and vertebrae which are both common sites of fragility fracture in T2DM patients.

In summary, this study highlights that men with T2DM had higher cortical porosity and cortical pore volume at the distal tibia in comparison with men without T2DM. Moreover, we found higher cortical pore volume at the distal radius in women with a non-significant trend for higher cortical porosity. Deficits in cortical bone porosity may confer a biomechanical disadvantage and explain the higher fracture rate observed in T2DM patients despite normal or higher areal bone mineral density. Further studies are urgently needed for a better understanding of the pathophysiologic process in diabetes-related bone disease.

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Compliance with Ethical Standards

Conflict of Interest Professor Cooper has received consultancy fees/honoraria from Servier; Eli Lilly; Merck; Amgen; Alliance; Novartis; Medtronic; GSK; Roche. Julien Paccou, Mark Edwards, Kate Ward, Karen Jameson, Charlotte Moss, Nicholas Harvey, and Elaine Dennison declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article contains studies with human subjects and all participants gave written informed consent in accordance with the Declaration of Helsinki. This studies did not include animals.

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