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ORIGINAL ARTICLE

Peripheral quantitative computed tomography-derived bone parameters in men with impaired fasting glucose and diabetes

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Abstract

Introduction Individuals with type 2 diabetes mellitus (T2DM) are at higher risk of fracture, but paradoxically do not have reduced bone mineral density. We investigated associations between peripheral quantitative computed tomography (pQCT) and glycaemia status.

Materials and methods Participants were men ($n = 354$, age 33–92 year) from the Geelong Osteoporosis Study. Diabetes was defined by fasting plasma glucose (FPG) ≥ 7.0 mmol/L, self-report of diabetes and/or antihyperglycaemic medication use and impaired fasting glucose (IFG) as FPG 5.6–6.9 mmol/L. Bone measures were derived using pQCT (XCT2000) at 4% and 66% radial and tibial sites. Linear regression was used, adjusting for age, body mass index and socio-economic status.

Results At the 4% site, men with T2DM had lower adjusted bone total area, trabecular area and cortical area at the radius (all − 6.2%) and tibia (all − 6.4%) compared to normoglycaemia. Cortical density was higher for T2DM at the radius (+5.8%) and tibia (+8.0%), as well as adjusted total bone density at the tibial site (+6.1%). At the 66% site, adjusted total bone area and polar stress strain index were lower for T2DM at the radius (− 4.3% and − 8.0%). Total density was also higher for T2DM (+1.2%).

Only cortical density at the 4% tibial site was different between IFG and normoglycaemia in adjusted analyses (+4.5%).

Conclusion Men with T2DM had lower total bone area, trabecular area, cortical area and polar stress strain index than the other two groups; however, total density and cortical density were higher. Only one difference was observed between IFG and normoglycaemia; increased tibial cortical density.

Keywords Impaired fasting glucose · Type 2 diabetes · Men · Peripheral quantitative computed tomography

Introduction

Individuals with type 2 diabetes (T2DM) are at a higher risk for fracture [1–4] but do not have a reduced bone mineral density (BMD) as assessed by dual energy X-ray absorptiometry (DXA) [1, 5–8]. Calculations using the FRAX tool including BMD have also been reported to underestimate fracture risk for individuals with T2DM [9–11], further complicating fracture risk assessments.

Alternative techniques for assessing bone have been utilised in an attempt to improve fracture risk assessments for individuals with T2DM. For example, trabecular bone score (TBS), a measure that reflects bone microarchitecture [12], has been shown to be lower in individuals with T2DM compared to those without the condition [7, 13–16]. Impact microindentation, a measure of bone material properties in vivo, as well as bone turnover markers, reflecting a reduced bone turnover, have also been reported to be reduced in individuals with T2DM [17–26]. Consideration of these observed differences in bone between individuals with and without T2DM can allow improvement of fracture risk predictions for those with the condition. Indeed, some

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studies have shown that FRAX calculations can be improved for individuals with T2DM by adjusting for TBS [10, 11, 13].

Another potential technique is peripheral quantitative computed tomography (pQCT), which provides information about microarchitecture properties at the radius and tibia [27]. The pQCT technique also has several advantages over measurements of BMD using DXA, in that it can differentiate between cortical and trabecular bone, as well as provide a volumetric (three dimensional) measure of BMD rather than areal (two dimensional). Several studies have identified differences in pQCT-derived bone parameters for individuals with T2DM. One such study showed that individuals with T2DM had a higher trabecular, but lower cortical volumetric BMD [28]. The study also reported a lower polar stress strain index, a measure of bone strength, at the radius for individuals with T2DM. Another study similarly reported that at the distal radius and tibia, patients with T2DM had a higher volumetric BMD; however, they also had a smaller bone area [29]. At the midshaft sites for the radius and tibia, they had a lower total bone area and although there was no difference in volumetric BMD, individuals with T2DM had a lower bone bending strength. Bone measures derived from pQCT have been associated with fracture risk [30, 31], and thus this technique may provide additional information beyond DXA to improve assessments of fracture risk for individuals with T2DM.

A limitation of these previous studies is that an intermediate glycaemia group has not been considered, known as impaired fasting glucose (IFG). Individuals with IFG present a key target for the prevention of diabetes and its associated complications. Details regarding the development of complications of T2DM in this stage, including bone health, are poorly understood. Thus, the aim of this study was to investigate if pQCT-derived parameters of bone are different for individuals with IFG or T2DM compared to those with normoglycaemia.

Materials and Methods

Participants

Participants were drawn from the Geelong Osteoporosis Study, an observational cohort study including residents of the Barwon Statistical Division in south-eastern Australia. The study has been described in detail elsewhere [32] and involved an age-stratified random sampling technique. Participants were not selected on the basis of any disease and are representative of the Australian population [33]. Women were recruited from the year1993–1997 and men from 2001–2006. Participants have returned for follow-up assessments every few years. The data for this study are drawn from the 15 year follow-up for men (2016–2020), as this was the first visit where pQCT-derived measures were collected. At the time of writing, 625 men had participated. Participants of the GOS are predominantly Caucasian (99%).

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Barwon Health Human Research Ethics Committee approved the study (approval number 00/56). Informed consent was obtained from all individual participants included in the study.

Glycaemia status

Fasting plasma glucose (FPG) measurements were taken in the morning following an overnight fast within a few weeks of pQCT measurements. Participants were provided with a referral to attend a local pathology service for the measurements. They were informed not to change their usual habits (e.g. diet and medication use) and to fast overnight. Staff at the pathology centre confirmed fasting status, performed the analyses and provided the data back to the study. Participants who were confirmed as not fasting were excluded from the analyses. Fasting glycaemia status was determined for 471 of the 625 participants. Men were classified as having diabetes if they had FPG $\geq$ 7.0 mmol/L, self-reported the condition and/or use of antihyperglycaemic medications. IFG was classified according to the American Diabetes Association criteria (FPG 5.6–6.9 mmol/L [34]). Medical records were reviewed by a physician to identify two men with type 1 diabetes, who were excluded from this study. Type of antihyperglycaemic medication was self-reported and categorised as metformin, insulin, sulfonylureas and "other" (sodium-glucose co-transporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists).

Peripheral quantitative computed tomography

Measurements of the non-dominant limb were made using a soft, non-elastic tape measure with the elbow or knee bent at ~ 90 degrees. The radial length was measured from the humeroradial joint cleft to the styloid process, while the tibial length was measured from the medial joint cleft to the distal end of the medial malleolus. When a participant had sustained a fracture of the non-dominant limb, the dominant limb was measured instead.

Standard transverse scans were performed at 4% and 66% of radial and tibial length using a peripheral computed

tomography instrument (XCT 2000, Stratec Medizintechnik, Pforzheim, Germany). A reference marker was placed along the flattest surface of the radial endplate, or the plateau of the tibial endplate. The thresholds provided by the software manufacturer (BonAlyse software, BonAlyse Oy, Jyvaskyla, Finland) were used to analyse the scans. At the 4% site for both radius and tibia, the periosteal surface of the bone epiphysis was determined by contour algorithmic thresholds at 180 mg/cm^3, with Peel mode 1 and trabecular compartment detection set to 45% of bone area. At the 66% site, the surface was determined by a 280 mg/cm^3 threshold (Peel mode 1, 100% of bone area). Cortical bone was selected by a 711 mg/cm^3 threshold. Quality assurance measurements were made each day using the pQCT device.

The variables used in this study for the 4% site included bone mineral content (g), total area (mm^2), total density (mg/cm^3), trabecular area (mm^2), trabecular density (mg/cm^3), cortical area (mm^2) and cortical density (mg/cm^3). For the 66% site: bone mineral content (g), total area (mm^2), total density (mg/cm^3), cortical area (mm^2), cortical density (mg/cm^3), cortical thickness (mm) and polar stress strain index (mm^3). Polar stress strain index provides information about the bone bending and torsional strength.

Scan quality was assessed by at least two authors based on published protocols [35, 36]. Of 469 men, 420 completed a radial scan and of these, 41 scans were excluded due to movement ($n=3$) or measurement error ($n=38$). Tibial scans were completed by 408 men, of which 38 were excluded due to measurement error leading to incorrect positioning of the scans. Men who provided complete pQCT data for the radius 4% site ($n=376$) were eligible for inclusion in the study. Participants using glucocorticoids ($n=10$), thiazolidinediones ($n=1$) or medications with a positive effect on bone ($n=11$) were excluded, resulting in 354 men being included in the study (Fig. 1).

Other measures

Weight and height were measured using digital scales and a Harpenden stadiometer to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as weight (kg)/height(m)^2. BMD at the femoral neck, total hip and lumbar spine were measured using DXA (GE-Prodigy, GE Lunar, Madison, WI, USA). TBS iNsight software (Version 2.2) was used to obtain TBS values from lumbar spine scans.

Lifestyle factors and medication use were documented by self-report. Alcohol consumption was ascertained using the Victorian Cancer Council Food Frequency Questionnaire [37]. Consumption was categorised as "high" (≥ 30 g/day) and "low" (<30 g/day). Mobility was categorised as "high" which corresponded to "very active" and "active" or "low," which corresponded to "sedentary", "limited", "inactive", "chair or bedridden" and "bedfast." Smoking status was classified as current or not. Data were collected and managed by the Research Electronic Data Capture (REDCap) tool, hosted by Barwon Health [38].

Prior low trauma fractures (excluding the face, skull and digits) were ascertained by self-report and confirmed using radiological reports where possible. The index of relative socio-economic advantage and disadvantage (IRSAD) is an indicator of socio-economic status and was determined for each participant. The IRSAD accounts for both disadvantage and advantage, represented by low and high scores, respectively. The IRSAD scores were divided into quintiles, where quintile 1 represents the most disadvantaged and quintile 5 the most advantaged.

Statistical analyses

Normality of continuous variables was assessed using the Shapiro–Wilk test. Height, femoral neck BMD and TBS were parametric, while fasting plasma glucose, age, weight and BMI were non-parametric. Parametric and non-parametric continuous variables were presented as mean ± SD or median (IQR), respectively. ANOVA and Kruskal–Wallis tests were used to assess differences in parametric and non-parametric continuous variables, as appropriate. Categorical variables were presented as *n* (%) and differences were assessed using a Chi-square test.

Linear regression models were used to investigate associations between glycaemia status and pQCT-derived bone parameters. The following variables that differed between the glycaemia groups were included in the models: age, BMI and IRSAD.

An additional analysis was completed which randomly matched participants with IFG or T2DM with participants from the normoglycaemia group of the same age. Participants were age matched in a 3 to 1 ratio (3 normoglycaemia, 1 IFG/T2DM). These analyses were completed for IFG and T2DM separately.

Models were checked for interaction terms between glycaemia use and these variables. Residuals were tested for model fit and potential polynomial modelling. No evidence was observed indicating a need for polynomial modelling. A p value of <0.05 was considered significant. Analyses were completed using Minitab (Minitab, version 19, State College, PA, USA) and STATA (Version 15.1. StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

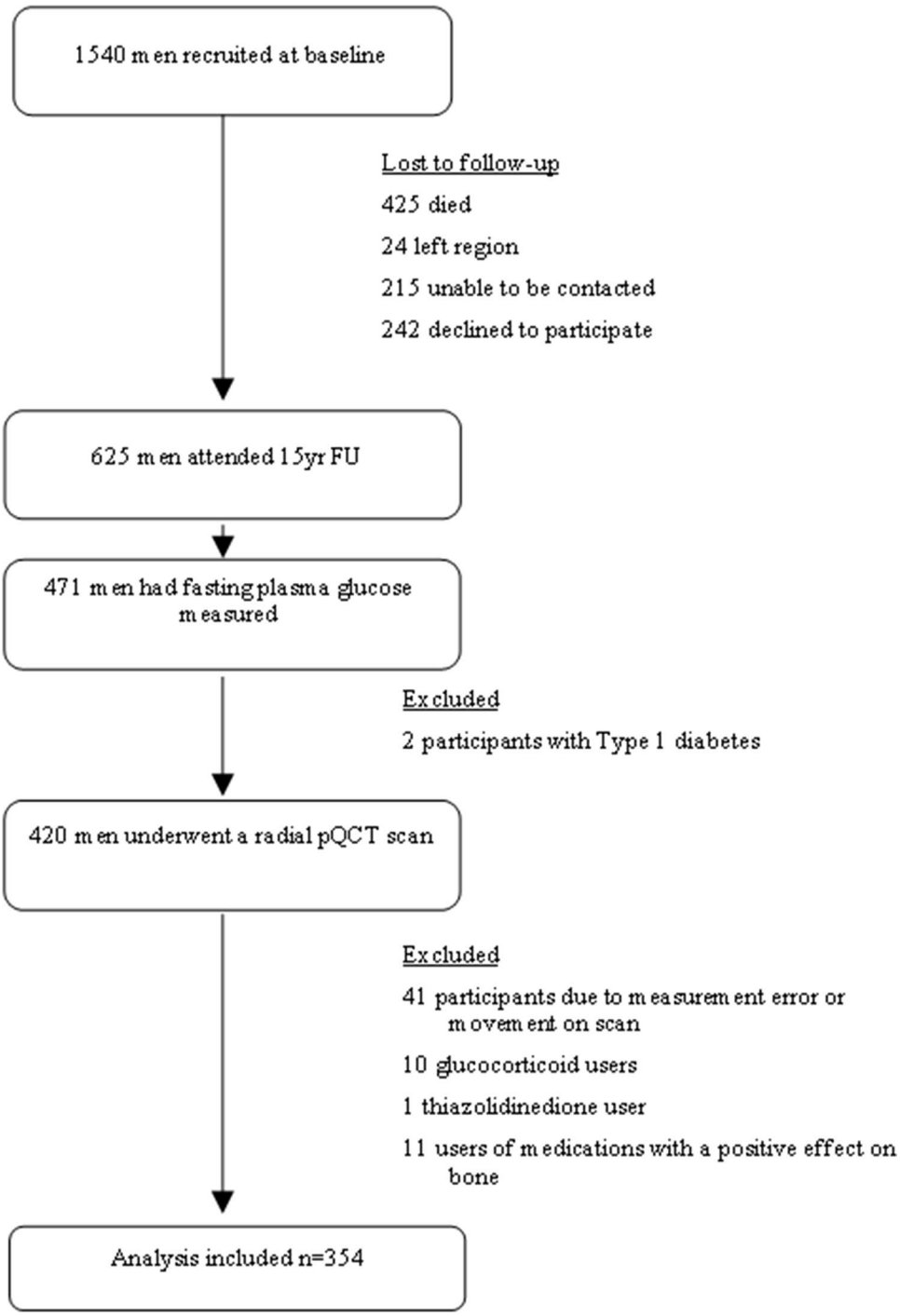

Fig. 1 Flowchart of participant inclusion and exclusion in this study

Results

Of the 354 men included in this study, 260 (73.4%) had normoglycaemia, 55 (15.5%) had IFG and 39 (11.0%) had T2DM. The descriptive statistics of the participants are presented in Table 1. Compared to men with normoglycaemia, men with IFG and T2DM were older and had higher BMI. IRSAD also differed between the groups, where men with T2DM were overrepresented in two most disadvantaged quintiles compared to the other two groups. No differences in mean femoral neck, total hip or lumbar spine BMD were detected between the groups; however, mean TBS was lower for men with IFG or T2DM compared to the normoglycaemia group. Most men with T2DM were taking at least one antihyperglycaemic medication, with the most common being metformin, followed by "other" (SGLT2 inhibitors, DPP-4 inhibitors and GLP-1 receptor antagonists) and sulfonylureas. There were 20 (51.3%) men taking

Table 1 Descriptive statistics of the participants ($n=354$) stratified by glycaemia status

	Normoglycaemia ($n=260$)	Impaired fasting glucose ($n=55$)	Diabetes ($n=39$)	p value
Fasting plasma glucose (mmol/L)	4.9 (4.7–5.2)	5.8 (5.6–6.1)	7.2 (6.3–8.9)	**< 0.001**
Age (year)	62.2 (52.5–71.4)	69.1 (61.5–75.9)	72.9 (64.1–78.8)	**< 0.001**
Weight (kg)	82.3 (74.3–92.0)	88.1 (76.6–95.7)	82.8 (79.0–93.4)	0.058
Height (cm)	175.1 ± 7.0	174.4 ± 7.3	172.6 ± 7.6	0.121
BMI (kg/m^2)	26.8 (24.8–29.6)	28.7 (26.6–30.6)	28.5 (25.6–31.2)	**0.002**
Alcohol consumption ≥ 30 g/day	50 (19.2)	17 (30.9)	6 (15.4)	0.105
Low mobility	54 (20.8)	18 (32.7)	9 (23.1)	0.159
Current smoker	20 (7.7)	3 (5.5)	1 (2.6)	[c]
Prior fracture	41 (15.8)	5 (9.1)	5 (12.8)	0.421
IRSAD				**0.031**
Quintile 1 (most disadvantaged)	41 (15.9)	4 (7.3)	11 (29.0)	
Quintile 2	51 (19.8)	12 (21.8)	12 (31.6)	
Quintile 3	51 (19.8)	16 (29.1)	8 (21.1)	
Quintile 4	77 (29.8)	15 (27.3)	3 (7.9)	
Quintile 5 (most advantaged)	38 (14.7)	8 (14.6)	4 (10.5)	
Femoral neck BMD (g/cm^2)	0.960 ± 0.134	0.985 ± 0.125	0.949 ± 0.112	0.359
Total hip BMD (g/cm^2)	1.037 ± 0.137	1.081 ± 0.153	1.060 ± 0.131	0.082
Lumbar spine BMD (g/cm^2)	1.304 ± 0.187	1.357 ± 0.201	1.369 ± 0.235	0.053
Trabecular bone score	1.268 ± 0.142	1.212 ± 0.131	1.225 ± 0.140	**0.010**
Diabetes medication use[a]				
Any	–	–	30 (76.9)	
Metformin	–	–	24 (61.5)	
Insulin	–	–	4 (10.3)	
Sulfonylureas	–	–	11 (28.2)	
Other diabetes medications[b]	–	–	17 (43.6)	

Data are presented as mean ± SD, median (IQR) or n (%)

Missing data: IRSAD $n=3$, femoral neck BMD $n=4$, total hip BMD $n=4$, lumbar spine BMD $n=15$

Bold values indicate where statistically significant associations were observed

BMI body mass index; *IRSAD* index of relative socio-economic advantage and disadvantage; *BMD* bone mineral density

[a]Note that some participants may be taking more than one type of medication for diabetes

[b]Includes medications such as SGLT2 inhibitors, DPP-4 inhibitors and GLP-1 receptor antagonists

[c]There were too few men who were current smokers to conduct statistical analyses

more than one type of antihyperglycaemic medication. The median (IQR) age of onset for T2DM was 59.0 (53.0–68.0, range 40.0–76.1) years and duration of diabetes was 11.2 (5.8–20.1, range 0.4–25.8) years.

Radius

Table 2 shows the results for pQCT-derived bone parameters at the radius. In adjusted analyses, at the 4% radial site, men with T2DM had lower total bone area (− 6.2%), trabecular area (− 6.2%), cortical area (− 6.2%) and a higher cortical density (+ 5.8%) than the normoglycaemia group. At the 66% site, in adjusted analyses, total bone area (− 4.3%) and polar stress strain index (− 8.0%) were lower for men with T2DM compared to the normoglycaemia group. Total bone density was also higher (+ 1.2%) for men with T2DM at the 66% site.

Further investigation within the T2DM group showed that higher FPG was associated with a lower total bone area at the 66% site (β coefficient: − 5.533, $p=0.033$). There was also evidence of an association for a higher FPG with a lower polar stress strain index at the 66% site (β coefficient: − 14.343, $p=0.068$). No associations were detected for age of onset or duration of diabetes.

Tibia

Table 3 shows the results for pQCT-derived bone parameters at the tibia. In unadjusted analyses, at the 4% tibial site, men with T2DM had a lower total bone area (− 5.6%),

Table 2 Values (mean, 95% CI) for the pQCT-derived bone parameters at the radius according to glycaemia status

Unadjusted	Normoglycaemia	Impaired fasting glucose	*p* value[a]	Diabetes	*p* value[b]
Radius 4% site					
Bone mineral content (g)	1.654 (1.623–1.685)	1.722 (1.656–1.789)	0.068	1.597 (1.517–1.676)	0.186
Total area (mm^2)	511.5 (502.7–520.2)	520.4 (501.3–539.4)	0.405	487.4 (464.8–510.0)	0.052
Total density (mg/cm^3)	326.6 (320.5–332.7)	334.8 (321.5–348.0)	0.269	331.0 (315.3–346.7)	0.604
Trabecular area (mm^2)	230.0 (226.1–234.0)	234.0 (225.5–242.6)	0.406	219.2 (209.0–229.4)	0.051
Trabecular density (mg/cm^3)	215.8 (211.0–220.7)	224.5 (214.0–235.0)	0.142	215.2 (202.7–227.7)	0.921
Cortical area (mm^2)	281.4 (276.6–286.3)	286.3 (275.9–296.8)	0.405	268.2 (255.8–280.7)	0.052
Cortical density (mg/cm^3)	417.1 (409.1–425.1)	424.9 (407.4–442.3)	0.425	425.7 (405.0–446.4)	0.446
Radius 66% site					
Bone mineral content (g)	1.404 (1.380–1.428)	1.445 (1.394–1.497)	0.149	1.349 (1.287–1.411)	0.106
Total area (mm^2)	176.9 (173.6–180.2)	182.3 (175.3–189.4)	0.173	174.6 (166.0–183.1)	0.613
Total density (mg/cm^3)	800.0 (788.2–811.8)	798.5 (773.1–823.9)	0.918	780.8 (750.1–811.5)	0.253
Cortical area (mm^2)	107.8 (105.9–109.8)	111.3 (107.1–115.5)	0.143	103.5 (98.4–108.6)	0.117
Cortical density (mg/cm^3)	1142.6 (1137.7–1147.4)	1138.0 (1127.5–1148.5)	0.436	1133.0 (1120.3–1145.6)	0.165
Cortical thickness (mm)	2.847 (2.794–2.899)	2.893 (2.780–3.006)	0.470	2.728 (2.592–2.865)	0.112
Polar stress strain index (mm^3)	425.2 (414.0–436.5)	428.1 (403.9–452.4)	0.833	398.4 (369.1–427.7)	0.093
Adjusted*	Normoglycaemia	Impaired fasting glucose	*p* value[a]	Diabetes	*p* value[b]
Radius 4% site					
Bone mineral content (g)	1.653 (1.623–1.683)	1.712 (1.646–1.778)	0.113	1.635 (1.555–1.715)	0.685
Total area (mm^2)	514.1 (505.4–522.8)	513.5 (494.4–532.5)	0.956	482.1 (458.9–505.4)	**0.013**
Total density (mg/cm^3)	324.8 (318.8–330.7)	336.9 (324.0–349.9)	0.097	341.8 (326.1–357.6)	0.050
Trabecular area (mm^2)	231.2 (227.3–235.1)	230.9 (222.4–239.5)	0.955	216.8 (206.4–227.3)	**0.013**
Trabecular density (mg/cm^3)	217.7 (208.4–227.1)	229.0 (216.4–241.6)	0.656	227.2 (212.2–242.2)	0.055
Cortical area (mm^2)	282.9 (278.1–287.7)	282.5 (272.1–293.0)	0.957	265.3 (252.5–278.1)	**0.013**
Cortical density (mg/cm^3)	414.8 (407.1–422.6)	428.3 (411.4–445.3)	0.160	439.0 (418.3–459.7)	**0.034**
Radius 66% site					
Bone mineral content (g)	1.406 (1.383–1.430)	1.434 (1.383–1.486)	0.336	1.362 (1.298–1.426)	0.204
Total area (mm^2)	180.2 (173.9–186.5)	180.6 (172.2–189.0)	0.916	172.4 (162.2–182.6)	**0.005**
Total density (mg/cm^3)	790.3 (767.7–812.9)	803.5 (773.5–833.6)	0.942	800.1 (763.5–836.7)	**0.048**
Cortical area (mm^2)	108.0 (106.1–110.0)	110.5 (106.3–114.8)	0.292	104.5 (99.3–109.8)	0.222
Cortical density (mg/cm^3)	1140.4 (1135.7–1145.2)	1141.8 (1131.6–1152.0)	0.815	1143.5 (1130.8–1156.2)	0.659
Cortical thickness (mm)	2.837 (2.786–2.889)	2.909 (2.797–3.021)	0.258	2.797 (2.657–2.936)	0.595
Polar stress strain index (mm^3)	437.8 (415.8–459.8)	426.1 (396.8–455.3)	0.492	402.8 (367.2–438.4)	**0.044**

Bold values indicate where statistically significant associations were observed

*Models adjusted for age, body mass index and index of relative socio-economic advantage and disadvantage (IRSAD)

[a]*P* value comparing normoglycaemia and IFG

[b]*P* value comparing normoglycaemia and diabetes

trabecular area (− 5.6%) and cortical area (− 5.6%) compared to the normoglycaemia group. Following adjustment for other variables, associations were sustained for total bone area (− 6.4%), trabecular area (− 6.4%) and cortical area (− 6.4%). Differences were also observed for total bone density (+ 6.1%) and cortical density (+ 8.0%) between men with T2DM and normoglycaemia in adjusted analyses. Men with IFG had a higher bone mineral content (+ 6.2%) than the normoglycaemia group in unadjusted analyses, but this was not sustained following adjustment for other variables. In adjusted analyses, men with IFG had a higher cortical density (+ 4.5%) than the normoglycaemia group. No associations were observed at the 66% site.

Within the T2DM group, higher FPG was associated with a lower total bone density at the 4% site (β coefficient: − 10.676, $p = 0.044$). No associations were observed for age of onset or duration of diabetes.

No interaction terms were identified in any of the models.

Table 3 Values (mean, 95%CI) for the pQCT-derived bone parameters at the tibia according to glycaemia status

Unadjusted	Normoglycaemia	Impaired fasting glucose	*p* value[a]	Diabetes	*p* value[b]
Tibia 4% site					
Bone mineral content (g)	4.234 (4.155–4.313)	4.497 (4.321–4.673)	**0.008**	4.155 (3.944–4.367)	0.491
Total area (mm^2)	1328.0 (1307.6–1348.5)	1369.1 (1323.3–1414.8)	0.108	1253.7 (1198.9–1308.6)	**0.013**
Total density (mg/cm^3)	320.7 (315.1–326.3)	330.7 (318.2–343.2)	0.152	332.6 (317.6–347.6)	0.145
Trabecular area (mm^2)	597.5 (588.3–606.7)	616.0 (595.4–636.5)	0.108	564.0 (539.4–588.7)	**0.013**
Trabecular density (mg/cm^3)	252.5 (247.7–257.3)	258.6 (247.9–269.4)	0.307	255.7 (242.8–268.5)	0.654
Cortical area (mm^2)	730.5 (719.3–741.8)	753.1 (728.0–778.3)	0.108	689.7 (659.5–719.8)	**0.013**
Cortical density (mg/cm^3)	376.5 (369.6–383.4)	389.7 (374.3–405.0)	0.125	395.5 (377.1–414.0)	0.058
Tibia 66% site					
Bone mineral content (g)	4.721 (4.637–4.805)	4.792 (4.606–4.979)	0.496	4.616 (4.394–4.837)	0.380
Total area (mm^2)	761.3 (746.6–776.1)	783.5 (750.7–816.4)	0.227	745.9 (707.0–784.9)	0.467
Total density (mg/cm^3)	626.5 (615.7–637.3)	620.3 (596.2–644.4)	0.644	622.8 (594.2–651.4)	0.813
Cortical area (mm^2)	356.8 (349.8–363.8)	361.6 (346.0–377.2)	0.581	349.1 (330.6–367.6)	0.445
Cortical density (mg/cm^3)	1109.4 (1104.6–1114.3)	1103.2 (1092.5–1114.0)	0.302	1101.2 (1088.5–1114.0)	0.238
Cortical thickness (mm)	4.267 (4.177–4.358)	4.267 (4.065–4.469)	0.998	4.203 (3.963–4.442)	0.621
Polar stress strain index (mm^3)	3312.0 (3233.9–3390.1)	3454.0 (3280.0–3627.9)	0.144	3147.5 (2941.3–3353.8)	0.143
Adjusted*	Normoglycaemia	Impaired fasting glucose	*p* value[a]	Diabetes	*p* value[b]
Tibia 4% site					
Bone mineral content (g)	4.241 (4.164–4.318)	4.431 (4.257–4.604)	0.054	4.224 (4.011–4.437)	0.886
Total area (mm^2)	1333.7 (1313.6–1353.8)	1343.1 (1297.7–1388.4)	0.715	1248.2 (1192.7–1303.7)	**0.005**
Total density (mg/cm^3)	319.9 (314.3–325.5)	331.7 (319.2–344.3)	0.096	339.3 (323.9–354.7)	**0.022**
Trabecular area (mm^2)	600.0 (591.0–609.1)	604.3 (583.9–624.6)	0.714	561.6 (536.6–586.5)	**0.005**
Trabecular density (mg/cm^3)	252.4 (247.4–257.3)	258.0 (246.9–269.1)	0.372	258.6 (245.0–272.3)	0.401
Cortical area (mm^2)	733.7 (722.6–744.7)	738.8 (713.9–763.7)	0.715	686.6 (656.1–717.2)	**0.005**
Cortical density (mg/cm^3)	375.2 (368.4–381.9)	392.1 (376.9–407.3)	**0.049**	405.3 (386.7–423.9)	**0.003**
Tibia 66% site					
Bone mineral content (g)	4.722 (4.640–4.804)	4.765 (4.580–4.950)	0.682	4.691 (4.467–4.914)	0.800
Total area (mm^2)	765.1 (750.2–779.9)	772.9 (739.5–806.2)	0.678	744.2 (703.9–784.5)	0.346
Total density (mg/cm^3)	623.4 (612.8–634.0)	625.8 (602.0–649.7)	0.859	634.3 (605.5–663.1)	0.493
Cortical area (mm^2)	356.5 (349.7–363.2)	359.9 (344.7–375.1)	0.691	356.7 (338.3–375.1)	0.982
Cortical density (mg/cm^3)	1107.0 (1102.3–1111.7)	1107.3 (1096.7–1117.8)	0.969	1109.7 (1096.9–1122.4)	0.709
Cortical thickness (mm)	4.249 (4.162–4.336)	4.285 (4.089–4.481)	0.745	4.313 (4.076–4.549)	0.626
Polar stress strain index (mm^3)	3316.3 (3236.6–3396.0)	3429.9 (3250.9–3608.9)	0.261	3188.7 (2972.3–3405.0)	0.283

Bold values indicate where statistically significant associations were observed

*Models adjusted for age, body mass index and index of relative socio-economic advantage and disadvantage (IRSAD)

[a]*P* value comparing normoglycaemia and IFG

[b]*P* value comparing normoglycaemia and diabetes

Age-matched analyses

After age matching, there were no differences in age between the normoglycaemia and IFG groups (median (IQR) normoglycaemia: 69.2 years (63.1–76.2), IFG: 69.1 years (61.5–75.9), $p = 0.736$). Age was also not different between the age-matched normoglycaemia and T2DM groups (median (IQR) normoglycaemia: 73.3 years (64.7–79.8), T2DM: 72.9 years (64.1–78.8), $p = 0.684$).

The results from the age-matched analyses were very similar to those obtained in the above non-matched analyses. Most differences observed were for the unadjusted analyses. In the age-matched analyses, at the radial 4% site, unadjusted bone mineral content and trabecular density were higher in those with IFG compared to normoglycaemia (Supplementary Table 1). At the tibial 4% site, men with IFG also had higher unadjusted total and cortical density compared to normoglycaemia (Supplementary Table 2). At the 66%

tibial site, men with IFG had higher adjusted bone mineral content than the normoglycaemia group; however, prior to age matching, this association was close to significance ($p = 0.054$, Table 3). Additionally, the association observed in the non-matched analyses for cortical density at the 66% tibial site was not significant after age matching, but this association was of borderline significance ($p = 0.049$, Table 3). None of the directions of association were different between the age-matched and non-matched analyses and all other associations observed were the same as those in Table 3.

For men with T2DM, several unadjusted associations were significant in the age-matched analyses that were not significant in the non-matched analyses. These included total, trabecular and cortical area (radial 4% site) as well as total and cortical density (radial and tibial 4% site) and polar stress strain index (radial 66% site) (Supplementary Tables 3 and 4). The directions of the associations were not different to the non-matched analyses. For the adjusted analyses, total density at the 4% radial site was significant in the age-matched analyses, but it was close to significance in the non-matched analyses ($p = 0.050$, Table 2). Additionally, the significant associations observed in the linear regression analyses above for total area and total density at the radial 66% site were no longer significant in the age-matched analyses (Supplementary Table 3). However, the difference observed in the actual value for these variables in the non-matched analyses was small (total area: 180.2 vs 172.4 mm^2 and total density: 790.3 vs 800.1 mg/cm^3) and the difference was unlikely to be clinically meaningful. No other associations observed in the age-matched analyses were different to the non-matched analyses.

Discussion

In adjusted analyses, this study reported that total bone area, as well as trabecular and cortical area were lower at the 4% site for both the radius and tibia in men with T2DM compared to normoglycaemia. Additionally, at the 4% site, cortical density was higher for men with T2DM at the radius and tibia, and total bone density was higher at the tibia. We also report that total bone area and polar stress strain index at the 66% radius site were lower for men with T2DM. Total density was also higher for men with T2DM at this site. Only one pQCT parameter was different between IFG and normoglycaemia in adjusted analyses; higher cortical density at the 4% tibial site. We also report that femoral neck BMD was not different between the glycaemia groups; however, TBS was lower for men with IFG and T2DM. This is similar to previous reports from our group [8, 16] and others [1, 7, 18, 21, 39–41].

In this study, we did not detect substantial differences in pQCT-derived bone parameters between the IFG and normoglycaemia groups. This is consistent with previous reports from the GOS for other bone variables (BMD, TBS and bone material strength index) [8, 16, 20] and fracture risk [3]. These observations support the idea that changes in bone morphology leading to increased fracture risk are associated with a diagnosis of T2DM and not early changes in insulin resistance.

There are a few studies that have examined pQCT-derived bone variables in individuals with and without T2DM. A study by Ho-Pham et al. [28] conducted pQCT measurements for 1,729 participants (1,115 women, 614 men) aged ≥ 30 years from Ho Chi Minh City as part of the Vietnam Osteoporosis Study. The study showed that compared to controls, individuals with T2DM had a lower cortical bone density at the radius and tibia as well as a lower bone strength (polar strength stress index) at the radius; both measures were evaluated at the 38% site. Individuals with T2DM also had greater trabecular bone density at the 4% site for the radius and tibia. It is difficult to compare our results with this study due to differences in sample populations, as well as site of pQCT scan acquisition. The ascertainment of diabetes also differs between our study and this one; our study utilised FPG, self-report and medication use to define glycaemia status, whereas the Ho-Pham et al. study used HbA1c level of ≥ 6.5%. Despite this, both studies have reported a reduced bone strength for individuals with T2DM. Another study by Petit et al. [29] included men aged ≥ 65 years from the Osteoporotic Fractures in Men (MrOS) study. The authors reported that at the 4% site for the radius and tibia, men with T2DM had a higher bone density compared to men without T2DM, but a smaller total bone area, aligning our study. At the cortical-rich sites for the tibia (66% site) and radius (33% site), the total bone area was lower for men with T2DM; however, the bone bending strength was also reduced at this site. Again, this is similar to our study; a reduced bone area and bone strength, with increased bone density. Our study does differ from the Petit et al. study however, in that the age range is wider (33–96 years vs ≥ 65 years) and the methods for ascertaining diabetes differ. The Petit et al. study used self-report of diagnosis or current use of antihyperglycaemic medications, as FPG and HbA1c data were not available. Despite these differences, the results are consistent between the studies.

These observations of reduced bone area with increased bone density as assessed by pQCT have been discussed by Petit et al. [29], suggesting that this may explain the elevated or normal BMD for individuals with T2DM. A similar or increased amount of bone in a smaller area could be interpreted as a higher BMD value using DXA. However, the higher density was not sufficient to compensate for the reduced area, as shown by reduced bone strength

for individuals with T2DM. We have previously reported that with increasing age, parameters of bone area measured using pQCT increase to compensate for a decrease in parameters of bone density [42]. However, this was not observed in this study for men with T2DM. The lower bone area for men with T2DM compared to normoglycaemia was not explained by a smaller outer bone perimeter at either the radius (66% site, normoglycaemia: 47.0 ± 3.4, T2DM: 46.7 ± 3.3 mm, $p = 0.624$) or the tibia (66% site, normoglycaemia: 97.6 ± 7.2 mm, T2DM: 96.6 ± 6.1 mm, $p = 0.492$). It is currently unclear why individuals with T2DM have smaller bone area; however, a reduction in bone turnover, particularly bone formation has been suggested as a potential reason for this observation. It has been reported that individuals with T2DM have a lower bone turnover compared to controls [26, 43, 44] reflecting a decrease in bone formation, leading to a delay in mineralisation [45, 46] and a lower bone area. Additionally, insulin stimulates bone formation through binding to receptors on osteoblasts [47, 48] and with the development of insulin deficiency in T2DM, this effect would be reduced, potentially leading to a reduced bone size.

There are extant data from studies utilising high-resolution peripheral quantitative computed tomography (HR-pQCT), although results from the two techniques, pQCT and HR-pQCT, are not directly comparable. HR-pQCT data have shown broadly similar results to standard pQCT, where cortical parameters such as volumetric BMD, cortical thickness and cortical porosity are poorer for individuals with T2DM; however, trabecular parameters are positively affected [18, 49–53]. These studies also reported lower cross-sectional area in those with T2DM. This suggests that HR-pQCT detects alterations in bone, but many of these parameters are not visible using pQCT due to a lower resolution. However, it is clear that there are bone deficits for individuals with T2DM that can be detected with standard pQCT and may aid in explaining the increased risk of fracture in clinical setting where HR-pQCT may not be appropriate. Studies using HR-pQCT also align with reports that indicate bone changes occur with T2DM and not IFG [49].

This study has some strengths and limitations. The participants in this study were a randomly selected sample of men and were not selected on the basis of disease. However, some men were excluded from the analyses due to inability to assume the correct position for the pQCT scan which may have introduced bias. It is also possible that loss to follow-up could have resulted in a healthy survivor effect, which may have affected those with T2DM to a greater extent than those with normoglycaemia or IFG. This study did not include women, and future studies should confirm these observations in a female cohort. Participants were predominantly Caucasian, and thus the results may not be generalised to other populations. Diabetes ascertainment utilised multiple different methods including FPG level, self-report and medication use. We also excluded individuals with type 1 diabetes. However, FPG was measured at a single time point and no data for longer-term glucose regulation such as haemoglobin A1c were available. We also did not have data for original and secondary diabetes. We had data for a range of potential confounders; however, residual confounding may be possible. Although pQCT-derived bone parameters have been reported to be associated with fracture [30, 31], this was a cross-sectional study and we were unable to evaluate whether the observed differences are predictive of incident fracture. Further research is needed to investigate associations between pQCT and glycaemia status in women to determine if the results are similar between the sexes. Additionally, longitudinal studies examining fracture as an outcome are needed to determine whether pQCT variables could be useful for predicting which individuals with or without T2DM will sustain a fracture.

Conclusion

Men with T2DM had lower mean adjusted total bone area, trabecular area, cortical area at both the radius and tibia than the normoglycaemia group. Polar stress strain index was also lower at the radius. Total bone density and cortical density were higher for men with T2DM compared to the normoglycaemia group at both the radius and tibia. Only one difference was detected between men with normoglycaemia and IFG; cortical density at the tibia. These data can provide further insight towards understanding the heightened risk of fracture for those with T2DM despite normal or elevated DXA-derived BMD.

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Author contributions KLH-K: study planning, data collection and analysis, interpretation, manuscript writing. KBA: data collection and management, critical reviewing of the manuscript. MCT: data collection and management, critical reviewing of the manuscript. SXS: data collection and management, critical reviewing of the manuscript. JWH: data interpretation and critical reviewing of the manuscript. NKH: critical reviewing of the manuscript. MAK: data interpretation and critical reviewing of the manuscript. JAP: study planning, funding acquisition, data interpretation and critical reviewing of the manuscript.

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Data Availability Statement Data are available upon reasonable request.

Declarations

Conflict of interest All authors have no conflicts of interest.

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