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Defects in cortical microarchitecture among African-American women with type 2 diabetes

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Abstract

Introduction/Purpose—Fracture risk is increased in patients with type 2 diabetes mellitus (DM2) despite normal areal bone mineral density (aBMD). DM2 is more common in African-Americans than in Caucasians. It is not known whether African-American women with DM2 have deficits in bone microstructure.

Methods—We measured aBMD at the spine and hip by DXA, and volumetric BMD (vBMD) and microarchitecture at the distal radius and tibia by HR-pQCT in 22 DM2 and 78 non-diabetic African-American women participating in the Study of Women Across the Nation (SWAN). We also measured fasting glucose and HOMA-IR.

Results—Age, weight, and aBMD at all sites were similar in both groups. At the radius, cortical porosity was 26% greater, while cortical vBMD and tissue mineral density were lower in women with DM2 than in controls. There were no differences in radius total vBMD or trabecular vBMD between groups. Despite inferior cortical bone properties at the radius, FEA-estimated failure load was similar between groups. Tibia vBMD and microarchitecture were also similar between groups. There were no significant associations between cortical parameters and duration of DM2 or HOMA-IR. However, among women with DM2, higher fasting glucose levels were associated with lower cortical vBMD ($r=-0.54$, $p=0.018$).

Conclusions—DM2 and higher fasting glucose are associated with unfavorable cortical bone microarchitecture at the distal radius in African-American women. These structural deficits may contribute to the increased fracture risk among women with DM2. Further our results suggest that hyperglycemia may be involved in mechanisms of skeletal fragility associated with DM2.

Keywords

diabetes mellitus type 2; African-American; HR-pQCT; bone microarchitecture; microfinite element analysis

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Introduction

African-American women have a higher risk of developing type 2 diabetes mellitus (DM2) than other ethnic groups [1]. Fracture risk is increased in patients with DM2 even though they have normal or higher bone mineral density (BMD) than adults without diabetes [2, 3]. While it is possible that microvascular complications associated with DM2 may increase risk of falls [4, 5], fracture risk is elevated in diabetics even after accounting for their increased fall incidence [6, 7]. Moreover, it has recently become apparent that the effects of hyperglycemia may also have direct negative effects upon bone strength that may not be reflected in DXA measurements of aBMD [8].

High-resolution peripheral quantitative computed tomography (HR-pQCT) allows in vivo assessment of trabecular and cortical bone microarchitecture that may contribute to bone strength independently of vBMD. Using this technique, two recent publications have reported abnormalities in cortical bone microarchitecture in adults with DM2 [9, 10]. These studies are limited by small sample sizes and having racially-mixed populations in the DM2 and control groups. We previously demonstrated that, in comparison to Caucasians, African-American women have higher trabecular vBMD at the radius, higher cortical vBMD and lower cortical porosity at the tibia, and larger cortical area and thickness at both the radius and tibia [11].

Given these differences in bone microarchitecture by race and the high prevalence of DM2 in African Americans, we sought to determine whether the adverse effects of DM2 on cortical bone seen in Caucasians are also seen in African-American women. We hypothesized that, despite overall improvements in cortical microstructure in African-American women as a whole, African-American women with DM2 would have cortical bone abnormalities as compared to non-diabetic women. Furthermore, we examined whether microarchitectural deficits associated with DM2 impact bone strength, as estimated by microfinite element analysis (μFEA). Lastly, to explore possible mechanisms that may contribute to altered bone microarchitecture, we determined the association between hyperglycemia, insulin resistance and bone microarchitecture.

Materials and Methods

Study cohort

We studied a subset of African-American women (n=100) who were participating in The Study of Women's Health Across the Nation (SWAN). Details of this subset of SWAN participants have been described in detail previously [11]. Briefly, SWAN is a multisite, multiethnic longitudinal study designed to characterize the biological and psychosocial changes that occur during the menopausal transition in a community-based cohort of 3302 women. All sites enrolled Caucasians, and each site also enrolled women belonging to one prespecified minority ethnic group. The Boston site specifically recruited African-American women. DXA and HR-pQCT measurements were performed at the Boston site in African-American women at study visit 11 or 12 (September 2008 – April 2011). The SWAN parent

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study and HR-pQCT substudy protocols were approved by the Institutional Review Board at MGH, and all women provided written informed consent.

Clinical data

Height and weight were measured using a fixed stadiometer and a digital scale with the participants wearing light clothing and no shoes. BMI was calculated as weight (in kilograms) divided by the square of height (in meters). Standardized interviews and self-administered questionnaires were used to obtain information on current clinical factors, including age (years), cigarette smoking (yes/no), alcohol intake (yes/no), medical diagnoses (including diabetes type 2), medication use, menopause stage, and physical activity (modified Baeke interview) [12]. History of fractures occurring after age 20 years was obtained by self–report. At the Boston SWAN site, all fractures in the preceding 15 years were confirmed by X–ray or physician reports. For the present analysis, fractures of the hand, foot, and face were excluded. Medications were self-reported, including any use of diabetes medications, steroids (defined by self report of glucocorticoid use >3 months at the baseline visit or report of use at ≥3 subsequent follow up visits), and/or osteoporosis medications (including all oral and intravenous bisphosphonates, selective estrogen receptor modulators, teriparatide, and calcitonin).

Diagnosis of DM2

Subjects were asked whether they had diabetes or used any medications for diabetes at every annual SWAN visit, from the baseline visit (1996–1997) through the current visits 11 (2008–2009) and 12 (2010–2011). Subjects were considered to have DM2 if they self-reported a history of diabetes or use of diabetic medications, or if they had a fasting blood glucose ≥126 mg/dL at any SWAN visit. Incident cases of DM2 were noted prospectively at the annual visits and allowed ascertainment of DM2 duration. Those subjects reporting history of diabetes at the baseline visit (n=7) were presumed to have a duration of diabetes of ≥12 years.

Glycemic indices

Serum insulin and glucose was measured from blood drawn after an overnight 12-h fast. Serum insulin was measured using a RIA procedure (Coat-a-Count; Diagnostic Products Corp., Los Angeles, CA). The quality control program for serum insulin in SWAN has been previously described [13]. Serum glucose was measured using a hexokinase-coupled reaction (Roche Molecular Biochemicals Diagnostics, Indianapolis, IN). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting serum glucose (in mg/dL) times fasting serum insulin (in uIU/mL) divided by the constant 405 [14].

Areal bone mineral density

Areal BMD (aBMD) of the posterior-anterior (PA) and lateral lumbar spine, total hip, femoral neck, and total body were measured by dual-energy X-ray absorptiometry, DXA (QDR4500A, Hologic Inc, Bedford, MA). The head was excluded from total body DXA measurements to avoid artifacts from metal jewelry and dental fillings. A standard quality control program was employed that included daily measurement of a Hologic DXA

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anthropomorphic spine phantom and visual review of every scan image by a local site investigator experienced in bone densitometry.

Volumetric bone density and bone microarchitecture measurements

On the same day as the DXA measurement, volumetric bone density and microarchitecture of the distal radius and tibia were assessed using high-resolution peripheral quantitative computed tomography (HR-pQCT, XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland) as previously described [11]. Quality control was maintained with daily scanning of the manufacturer's phantom, as well as visual inspection of each HR-pQCT scan by an investigator experienced in this technology. The standard analysis program (Scanco software version V6.0) was used to calculate trabecular geometry, density, and microarchitecture. To characterize cortical microarchitecture in greater detail, HR-pQCT images were processed by a semi-automated cortical bone segmentation technique as previously described [15]. After image segmentation, measures were obtained for cortical geometry, density, and porosity. This more precise segmentation was also used to calculate trabecular area and total area. Linear microfinite element analysis (μFEA) was used to estimate stiffness and failure load following uniaxial compression as previously described [16].

Statistical Analysis

African-American women with DM2 were compared with a control group of African-American women without DM2. Clinical characteristics of women with and without DM2 were compared using independent samples two-sided t-tests and/or chi-square tests. Unadjusted differences in means of HR-pQCT parameters between women with and without DM2 were examined using independent samples two-sided t-tests. In addition, the group comparisons were repeated using a multivariate linear regression model (PROC REG) while adjusting for covariates that were significantly different between groups and/or might have a strong independent effect on skeletal outcomes (e.g. use of osteoporosis medications, thiazolinediones, or glucocorticoids). Three women (1 with DM2, 2 without) were not fasting at the time of the blood draw and were therefore excluded from fasting glucose and HOMA-IR analyses. Pearson's correlations were used to test associations of HR-pQCT parameters with fasting glucose and HOMA-IR in the women with and without DM2. Women were also analyzed by categories of prediabetic/diabetic (fasting glucose ≥ 100 mg/dL) or normoglycemic (fasting glucose < 100 mg/dL). Statistical analysis was performed using SAS 9.3 software (SAS Institute Inc., Cary, NC). Data are reported as mean ± standard deviation (SD), unless otherwise noted.

Results

Cohort Characteristics

One hundred African-American women underwent HR-pQCT scanning of distal radius and tibia, of whom 22 had DM2 (Table 1). Women with and without DM2 were of similar age, weight/BMI, and had similar time since menopause. On average, women were 59.6 ± 2.6 years old and 94% of the cohort was postmenopausal at the time of the study visit. Women with DM2 were more likely to be active smokers (p=0.02). There were no differences in use

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of osteoporosis medications or glucocorticoids. As expected, women with DM2 had higher mean fasting glucose (p=0.02). DXA-based aBMD measurements at the spine, hip, and total body were similar in women with and without DM2. All of the 22 women with DM2 were taking diabetic medications, including 2 who were taking thiazolinediones. Median duration of DM2 was 11 years (range 1 to ≥12 years). Duration since diagnosis of DM2 was ≥10 years in 59% of women.

Volumetric BMD, microarchitecture, and estimated strength

Although there were no differences in total or trabecular bone density, women with DM2 had worse cortical bone microarchitecture at the radius compared to controls (Figure 1, Table 2). Specifically, radius cortical vBMD was 3% lower (p=0.040), while cortical porosity was 26% higher (p = 0.025) in women with DM2 than in controls. Furthermore, radius cortical TMD was also 2% lower in diabetics (p=0.045), which reflects a lower bone tissue density independent of macroscopic cortical pores. Trabecular microarchitecture at the radius did not differ between groups. Bone density and microarchitecture at the tibia were similar in women with DM2 and controls. Estimates of failure load and stiffness at the radius and tibia were also similar between women with DM2 and controls (Table 2).

Differences in cortical bone microstructure and density between women with DM2 and controls persisted after adjustment for smoking with minimal change in the point estimates (Supplemental Table 1), although some parameters were no longer statistically significant. Additional adjustments for osteoporosis medication use, glucocorticoid use, and thiazolinedione use did not substantially alter the results. Within the diabetic group, there were no differences in cortical microarchitecture by prevalent fracture status or by disease duration.

Correlations with fasting glucose and insulin resistance

Among the women with DM2, fasting glucose was negatively associated with cortical vBMD (r=−0.54, p=0.018) and cortical TMD (r=−0.58, p=0.009) at the radius (Figure 2A). Significant associations were not observed between fasting glucose and cortical vBMD or TMD among the controls (Figure 2B). Overall, women with fasting glucose ≥100 mg/dL had significantly greater cortical porosity (p=0.043) and cortical pore volume (p=0.009) than those with fasting glucose <100 mg/dL. There were no significant associations between fasting glucose and microarchitectural parameters at the tibia. Lastly, there were no significant associations between HOMA-IR and microarchitectural parameters at the radius or tibia.

Discussion

In this cross-sectional study of African-American women, most of whom were postmenopausal, we found that women with DM2 had lower cortical density and worse cortical microarchitecture at the distal radius. These cortical defects occurred despite being of similar age and weight, and having similar DXA-measured aBMD at the spine, hip and total body as controls. Furthermore, the differences in cortical porosity persisted after adjustment for smoking, use of osteoporosis medications, and glucocorticoids. These results

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demonstrate that HR-pQCT is providing information about skeletal fragility above and beyond what is possible with standard bone densitometry. Furthermore, the association of high fasting glucose with worse cortical parameters suggests that hyperglycemia may mediate these negative skeletal effects.

Our findings are consistent with two studies that identified high cortical porosity at the distal radius in mostly Caucasian women with DM2 [9], and in women with DM2 and prevalent fracture [10]. In contrast, other studies did not identify any differences in peripheral bone structure in subjects with DM2 as assessed by HR-pQCT [17, 18]. We did not find any significant differences in volumetric density or microarchitecture at the tibia, suggesting that the negative skeletal effects of DM2 were mitigated at this weight-bearing site. Furthermore, we did not find any evidence of disordered trabecular microarchitecture, which is consistent with most previous HR-pQCT studies [9, 10, 17, 18]. A study using magnetic resonance imaging (MRI) suggested that DM2 was associated with larger trabecular bone holes at the distal radius, but MRI is limited by lower resolution than is afforded by HR-pQCT [19]. In addition, although two studies using Trabecular Bone Score (TBS) suggested that DM2 is associated with defects in trabecular structure at the spine [20, 21], it should be noted that because it is derived from the projected measurement by DXA, TBS might also reflect defects in vertebral cortical architecture.

Importantly, many of the previously published studies may have been confounded by differences in racial composition in the comparison groups with and without DM2 [9, 10, 19]. We and others have previously reported that both cortical and trabecular microarchitectural differences exist between Caucasians, African-Americans [11], and Chinese-Americans [22, 23]. Our demonstration of microarchitectural differences between women with DM2 and controls within a homogeneous population of African-American women suggests that DM2, and not racial heterogeneity, explains the observed differences.

The mechanisms by which DM2 causes deficits in cortical bone density and microstructure are unknown. Some diabetes medications, such as thiazolinediones, may lower BMD [24], but adjustment for thiazolinedione use did not affect the significance of our findings. We did find that higher fasting glucose was associated with worsened cortical parameters, but the link between hyperglycemia and osteoclast or osteoblast activity is incompletely understood [25]. In addition, while a significant correlation was noted on a cohort level, there was a wide variability such that it would be difficult to predict an individual's cortical bone density based on any given fasting glucose assessment. This is perhaps not surprising as fasting glucose measurements provide only a snapshot of glycemic control and are highly variable in individuals over time. Unfortunately we did not have a more integrated measure of long-term glycemic control (such as HbA1c) available for analysis.

Although we detected a statistically significant difference in radius cortical porosity between women with DM2 and controls, it is unclear what the impact of a <1% absolute difference in cortical porosity has on overall mechanical strength and fracture risk. In combination with a decreased cortical tissue mineral density at the radius, these changes led to an overall lower cortical vBMD. Nevertheless, as in other studies [9, 10], estimated stiffness and failure load of the whole bone did not differ between the women with DM2 and controls. It may be that

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other factors that are unrelated to the density and structure of the bone may further contribute to increased skeletal fragility in women with DM2 [25]. For example, a recent study found that women with longstanding DM2 had decreased cortical "bone material strength (BMS)", as assessed by reference point indentation of the tibia diaphysis [18]. Furthermore, BMS was negatively associated with long-term glycemic control (assessed by HbA1c), again suggesting that hyperglycemia itself may contribute to impaired bone quality. Defects in BMS would not be captured in HR-pQCT-derived estimations of bone strength.

Our study has several limitations. First, our sample size was relatively small. Further, assessment of intracortical pores was limited by the resolution of the HR-pQCT machine, which is only able to detect macroscopic pores of > ~100 microns [26]. Therefore, assessment of differences in cortical porosity may be incomplete and measurement of cortical TMD may partially reflect differences in microscopic pores. Nevertheless, the contribution of microscopic pores that are below the limit of detection to bone strength remains controversial. As mentioned earlier, our finite element models were constrained by assumptions of homogenous material properties, and therefore could not account for differences in bone material properties that may exist between study groups. Lastly, although we found associations of cortical microarchitecture and fasting glucose levels, we were unable to detect an association with duration of DM2, and we did not have information on glycohemoglobin or other proxies of long-term glycemic control.

In conclusion, we found that DM2 was associated with increased cortical porosity and decreased cortical density at the distal radius in a cohort of African-American women. These cortical deficits may contribute in part to the higher fracture risk observed among adults with DM2. Further studies are required to determine whether hyperglycemia is directly involved in mechanisms of skeletal fragility associated with DM2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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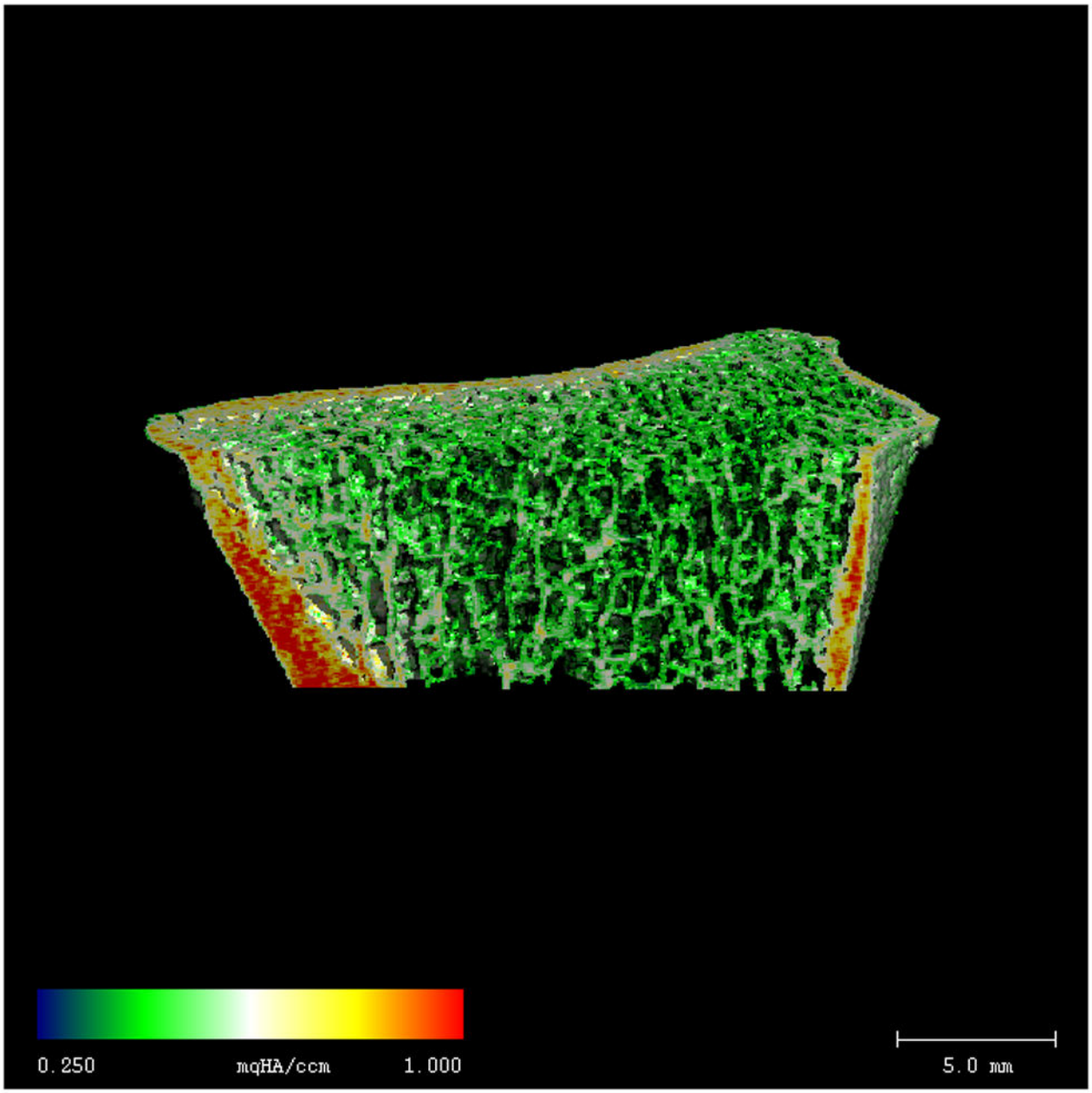

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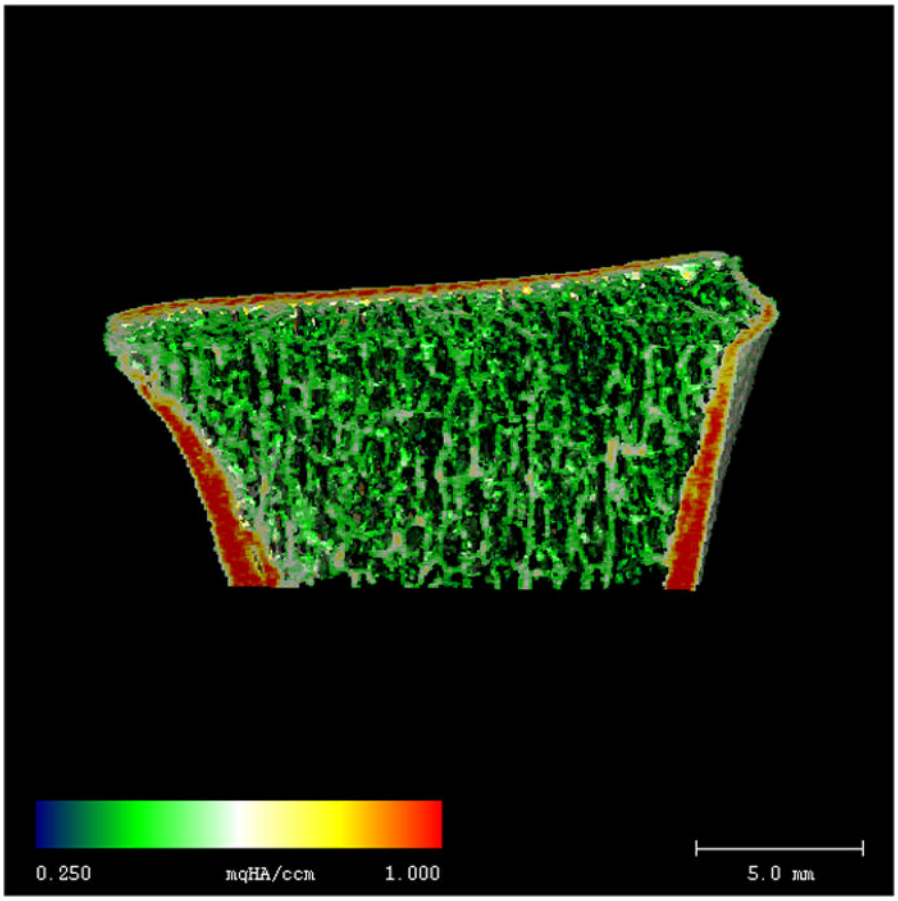

Figure 1.

Radius HR-pQCT images from representative African-American women with DM2 (A) and non-DM2 (B). Color shading indicates ranges of BMD (lowest BMD = blue, highest BMD = red). Despite similar cortical size and thickness, cortical BMD is lower in DM2, as indicated by a more heterogeneous pattern of red/yellow shading within the cortex. Trabecular density and microstructure are similar in the DM2 and non-DM2 subjects.

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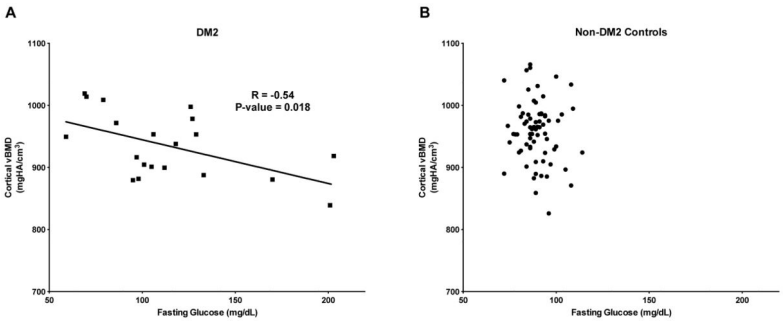

Figure 2.

Scatterplot of cortical vBMD at the radius versus fasting glucose among African-American women with DM2 (A) and non-DM2 controls (B). Among women with DM2, cortical vBMD is negatively associated with fasting glucose ($r = -0.54$, $p=0.018$).

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Table 1

Cohort characteristics, mean ± SD

	DM2 n=22	Non-DM2 n=78	p-value (t-test or chi-square)
Age, yr	60.1 ± 2.8	59.4 ± 2.5	0.26
Weight, kg	87 ± 20	84 ± 19	0.58
BMI, kg/m^2	32 ± 7	31 ± 7	0.58
Time since menopause, yr	8.7 ± 2.9	7.7 ± 3.7	0.28
Previous fracture, N (%)	4 (18%)	5 (6%)	0.10
Current smoking, N (%)	8 (36%)	10 (13%)	**0.02**
Current alcohol ≥1 drink/day, N (%)	14 (64%)	50 (64%)	0.20
Physical activity score*	7.2 ± 2.1	7.8 ± 1.8	0.18
Osteoporosis medication, N (%)	8 (36%)	29 (37%)	1.00
Glucocorticoid medication, N (%)	4 (18%)	9 (12%)	0.47
Fasting glucose, mg/dL	115 ± 41	91 ± 12	**0.02**
Fasting insulin, uIU/mL	23 ± 29	14 ± 17	0.11
HOMA-IR	6.3 ± 7.4	3.5 ± 6.6	0.11
Spine BMD, g/cm^2	1.079 ± 0.220	1.061 ± 0.155	0.67
Total hip BMD, g/cm^2	1.019 ± 0.172	1.002 ± 0.144	0.64
Femoral neck BMD, g/cm^2	0.896 ± 0.130	0.873 ± 0.144	0.51
Total body BMD, g/cm^2	1.170 ± 0.120	1.154 ± 0.126	0.60

*Scores range 3–9 with higher scores indicating increased physical activity(12)

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Table 2

Bone density, microarchitecture, and biomechanical parameters at the distal radius and tibia in African-American women with and without DM2 (mean ± SD)

	Radius			Tibia		
	DM2 (n=22)	**Controls (n=78)**	**p-value**	**DM2 (n=22)**	**Controls (n=78)**	**p-value**
Total BMD (mgHA/cm^3)	308.6 ± 60.9	325.5 ± 73.3	0.325	287.3 ± 68	289.4 ± 53.8	0.878
Geometry						
Total Area (mm^2)	284.6 ± 42.4	269.4 ± 52.7	0.216	717.8 ± 107.0	712.4 ± 120.5	0.849
Trabecular Area (mm^2)	227.4 ± 44.4	213.0 ± 53.6	0.254	599.9 ± 113.5	597.0 ± 124.0	0.921
Cortical Area (mm^2)	60.4 ± 7.0	59.2 ± 10.8	0.547	123.1 ± 21.4	120.3 ± 23.6	0.622
Cortical Area / Total area (%)	21.7 ± 4.2	22.8 ± 6.1	0.433	17.6 ± 4.5	17.4 ± 4.6	0.830
Cortical density and structure						
Cortical BMD (mgHA/cm^3)	**933.3 ± 52.7**	**957.7 ± 47.0**	**0.040**	878.6 ± 65.1	894.9 ± 64.9	0.304
Cortical Tissue Mineral Density (mgHA/cm^3)	**975.8 ± 40.3**	**993.9 ± 35.4**	**0.045**	975.3 ± 31.7	982.2 ± 35.3	0.450
Cortical Thickness (mm)	0.91 ± 0.14	0.93 ± 0.20	0.729	1.26 ± 0.26	1.23 ± 0.27	0.607
Cortical Porosity (%)	**2.9 ± 1.5**	**2.3 ± 1.1**	**0.025**	7.2 ± 2.8	6.3 ± 2.6	0.161
Cortical Pore Volume (mm^3)	**14.8 ± 7.5**	**11.5 ± 6.2**	**0.037**	74.0 ± 25.0	63.4 ± 26.8	0.102
Cortical Pore Diameter (mm)	0.17 ± 0.02	0.16 ± 0.02	0.319	0.19 ± 0.03	0.18 ± 0.03	0.169
Trabecular density and structure						
Trabecular BMD (mgHA/cm^3)	156.7 ± 44.9	160.4 ± 36.0	0.690	163.6 ± 41.7	165.9 ± 33.7	0.791
Trabecular Number (1/mm)	1.83 ± 0.4	1.89 ± 0.32	0.483	1.79 ± 0.43	1.87 ± 0.34	0.341
Trabecular Thickness (mm)	0.071 ± 0.014	0.071 ± 0.014	0.934	0.077 ± 0.012	0.075 ± 0.014	0.570
Trabecular Separation (mm)	0.519 ± 0.235	0.475 ± 0.101	0.208	0.514 ± 0.145	0.477 ± 0.097	0.274
Heterogeneity of Network (mm)	0.234 ± 0.146	0.211 ± 0.087	0.486	0.261 ± 0.137	0.22 ± 0.069	0.060
Biomechanics						
Strength (kN/mm)	75.5 ± 15.6	74.6 ± 14.6	0.792	201.4 ± 34.1	200.1 ± 43.8	0.882
Failure Load (N)	3774 ± 765	3744 ± 719	0.867	10193 ± 1678	10073 ± 2200	0.784

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