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ORIGINAL ARTICLE

Bone material strength in normoglycemic and hyperglycemic black and white older adults

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Abstract

Summary This cross-sectional study assessed cortical bone properties via impact microindentation in adults with normoglycemia, prediabetes, and early-stage T2D. Bone material strength index was stable across the glycemia categories in whites but it declined in blacks. Blacks may be more susceptible than whites to impaired cortical bone properties in early diabetes.

Introduction Individuals with long-standing type 2 diabetes (T2D) have altered cortical bone material properties as determined by impact microindentation. This cross-sectional study was done to determine whether altered cortical bone material properties could be detected in adults with prediabetes or early-stage T2D.

Methods Men and postmenopausal women aged ≥ 50 years with no diabetes (50 white, 6 black), prediabetes (75 white, 13 black), and T2D of ≤ 5 years duration (24 white and 16 black) had assessments of bone material strength index (BMSi) by impact microindentation, trabecular bone score (TBS), and bone mineral density (BMD) by DXA and the advanced glycation end product, urine pentosidine.

Results The association between glycemia category and BMSi differed by race (interaction $p = 0.037$). In the whites, BMSi did not differ across the glycemia categories, after adjustment for age, sex, and BMI (no diabetes 76.3 ± 1.6 (SEM), prediabetes 77.2 ± 1.3, T2D 76.2 ± 2.5, ANCOVA $p = 0.887$). In contrast, in the blacks, BMSi differed (ANCOVA $p = 0.020$) and was significantly lower in subjects with T2D than in those with prediabetes ($p < 0.05$) and no diabetes ($p < 0.05$) (mean ± SEM BMSi in no diabetes 86.0 ± 4.3, prediabetes 91.0 ± 3.2, and T2D 71.6 ± 2.9). Neither TBS nor urine pentosidine differed significantly across the glycemia categories in either whites or blacks.

Conclusions These findings suggest different associations of glycemia with cortical bone material properties in blacks and whites, with blacks possibly being more susceptible to impaired cortical bone properties than whites in early diabetes. A larger study is needed to verify these observations.

Keywords Blacks · Bone material strength · Bone mineral density · Micro indentation · Trabecular bone score

Introduction

Individuals with type 2 diabetes (T2D) have 2- to 3-fold greater risk of hip fracture [1] and a higher mortality rate after hip fracture than individuals with no diabetes [2]. The increased fracture risk is not explained by lower bone mineral density (BMD) and in fact BMD tends to be higher in individuals with T2D than in those without diabetes [3]. These findings implicate reduced bone quality in diabetic skeletal fragility. The specific features of bone quality that differ in diabetics and non-diabetics have not been thoroughly delineated.

Measures currently being evaluated as clinically relevant indicators of bone quality include bone material strength index (BMSi) and trabecular bone score (TBS). BMSi, assessed by impact microindentation at the midshaft of the tibia, measures

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the resistance to microfracture at a cortical site. Lower BMSi has been linked to higher fracture risk in some [4, 5], but not all [6], studies of older predominantly Caucasian women. Information linking BMSi to fracture risk in other race/ethnic groups and men is lacking. TBS, determined by analysis of DXA spine scans, measures the spatial heterogeneity of DXA gray scale image and has been associated with trabecular architecture in in vitro studies [7]. In an analysis of six prospective studies, Silva et al. found low TBS to be linked to fragility fractures independently of BMD [8]. In a subsequent meta-analysis of individual-level data from 14 prospective, population-based cohorts, TBS was a significant predictor of fracture risk [9]. Both BMSi [10–12] and TBS [7] are lower in adults with established, long-standing T2D compared with non-diabetics. However, little is known about the stage at which bone quality, assessed by BMSi and TBS, begins to decline in the progression from normoglycemia to prediabetes to T2D.

The mechanisms by which diabetes alters bone quality may include the non-enzymatic glycosylation of collagen leading to formation of advanced glycosylation end products (AGEs). Non-enzymatic glycosylation is a spontaneous biochemical reaction between amino acid residues on collagen fibers and extracellular sugars [13, 14]. AGEs accumulate in bone, stiffen the collagen matrix, and impair bone's mechanical properties [15–18]. The AGE, pentosidine, measured in urine, was strongly associated with incident vertebral fracture in older adults with T2D in the Health ABC study [19]; similar findings for serum pentosidine were reported in a small Japanese cohort [20]. Whether AGE accumulation influences bone properties, as measured by BMSi and TBS, is unknown.

The overall objective of the proposed cross-sectional study is to obtain preliminary information on how two low-cost measures of bone, BMSi and TBS, vary across the spectrum of glycemic states of normoglycemia, prediabetes, and recently established (≤ 5 years) diabetes. We also examined urine pentosidine, an AGE, as a potential mediator of any bone quality differences that are observed. This study is the logical next step in assessing whether BMS and TBS warrant further evaluation as potential biomarkers of bone disease in individuals with prediabetes and recently diagnosed T2D. Currently, there is no effective way to determine which individuals with prediabetes and early-stage T2D should be monitored for increased risk for fracture.

Materials and methods

Subjects

In this study, 450 candidates were prescreened by telephone and of these 216 were eligible. Of the 216 who were eligible, 200 were enrolled in the study. The participants, adult men and women aged 55 years and older, were categorized as (1) normoglycemic, defined as fasting plasma glucose (FPG) < 100 mg/dl and HbA1e ≤ 5.6%; (2) prediabetes, defined as FPG 100–125 mg/dl and/or HbA1c 5.7–6.4%; or (3) T2D defined as a self-reported history of diabetes for ≤ 5 years or a FPG > 125 mg/dl or HbA1c > 6.4%, in accordance with the American Diabetes Association guidelines [21]. By definition, the normoglycemia and prediabetes groups contained no oral glycemic medication users. Women were at least 5 years since last menses. Exclusion criteria included any history of insulin use, allergy to lidocaine, signs of diabetic neuropathy, poor vascular flow, skin lesions or infection or edema in the pretibial region, cardiovascular disease, clotting disorder, fracture in the last 6 months or cancer treatment in the last year, and use of the following medications: insulin, prescription drugs for osteoporosis in the last 2 years, corticosteroids for over 3 weeks in the last 6 months, or anti-coagulants. Participants with rheumatoid arthritis were excluded and no participant was being treated for any inflammatory disease. The study was carried out from January 31, 2017, through May 24, 2018.

Cortical bone tissue properties by impact microindentation

Bone material strength index (BMSi) was measured at the non-dominant mid-tibia with the handheld Osteoprobe RUO device (Active Life Scientific, Santa Barbara, CA, USA), as described in detail by Rozental et al. [5]. Briefly, with the subject supine and the non-dominant leg rotated externally to provide access to the anteromedial surface of the tibia, the region of interest was defined as the midpoint between the medial malleolus and medial tibial plateau. Following sterile preparation of the measurement site with Betadine, the skin and periosteum were numbed with 2% lidocaine. The test probe was then inserted through the skin and periosteum to rest on the bone surface. With the probe assembly perpendicular to the tibia surface, the operator initiated the measurement whereby a 40-N impact force was applied to the bone. The distance that the probe descended into the bone was recorded. The probe was then moved ~ 2 mm along the bone surface (without coming out of the skin) and the measurement was repeated until 8 to 10 measurements were made. The operator at the computer classified each measurement as "acceptable" or "poorly performed" (e.g., due to probe not being perpendicular, probe slipping, or leg movement). Measurements classified as "poorly performed" were excluded, and an additional measurement was acquired. After the indentations were acquired in the subject, the operator then performed five indentations on a polymethylmethacrylate (PMMA) calibration phantom. The bone material strength index (BMSi) was computed as 100 times the harmonic mean of the indentation distance into the PMMA divided by the average indentation

distance into the bone. Thus, a higher indentation distance into the bone will result in a lower BMSi measurement, reflecting worse bone material properties. All BMSi measurements were carried out by one registered nurse (SM) and the determination of "poorly performed" measurements was made by one investigator (BD-H). The short-term precision of BMSi is reported to be 1.7 to 3.2% [10].

BMD and TBS by DXA

A GE Lunar Prodigy DXA Scanner (Madison, WI) was used to measure non-dominant hip BMD and spine BMD with precision of < 1% [22]. The non-dominant mid-tibial shaft BMD scan was performed by a modification of the AP spine scan DXA specifications. Precision of BMD at a neighboring segment of the tibia in our laboratory is 1.01% [23]. Trabecular bone score was extracted from spine anterior-posterior DXA images with use of TBS iNsight software provided by GE Lunar for our Prodigy scanner. TBS was evaluated based on gray-level analysis of the DXA images as the slope at the origin of the log-log representation of the experimental variogram [24]. The precision of TBS measurements is 1.5 to 1.9% [8].

Biochemical measures

Blood was drawn in the morning after the subjects had fasted for 12 h. HbA1c was measured in whole blood hemolysate by immunoturbimetric assay on a Cobas Fara centrifugal analyzer; plasma glucose was measured by an enzymatic couple method using the Olympus AU400 clinical chemistry analyzer (Olympus America Inc., Melville, NY 11747), with intra- and inter-assay coefficient of variations (CVs) are 1.0% and 2.0%, respectively. Serum insulin was measured by a competitive binding radioimmunoassay commercial kit (HI-14K Human Insulin Specific Kit, Linco Research, Inc., St Charles, MO) with intra- and inter-assay CVs of 5.0 and 6.0%, respectively. Pentosidine was measured in a fasting spot urine specimen by a double-antibody sandwich enzyme-linked immunosorbent (ELISA) kit procedure from Antibody Research Corporation (St.Charles, MO 63304) within intra-assay CVs at < 10% and inter-assay CVs of < 12%. Creatinine in the spot urine was measured on an automated clinical chemistry analyzer (Olympus AU400, Olympus America, Inc., Melville, NY).

Other clinical measures

Medical history was assessed by a questionnaire. Dietary calcium and vitamin D intake and supplement use was assessed with use of the web-based Diet History Questionnaire II (DHQ II) (past month) developed by the Risk Factor Monitoring and Methods Branch of the National Cancer Institute. The Diet × Calc Analysis Program (Version 1.5.0. National Cancer Institute) was used to interpret the DHQ II data to provide nutrient, food group, and diet quality estimates.

Leisure, household, and occupational activity was estimated with use of the Physical Activity Scale for the Elderly (PASE) questionnaire [25]. This questionnaire was designed to capture activities commonly carried out by older adults.

Statistical analyses

The associations of glycemia category with bone properties, assessed by BMSi and TBS (the primary aim), were examined by an analysis of covariance (ANCOVA). These analyses included the computation of means by glycemia category adjusted for age, sex, and BMI. In consideration of two primary outcomes, p values of < 0.025 (Bonferroni adjusted) were considered to indicate statistical significance. Associations of glycemia category with BMD of the spine, hip and mid-tibia (secondary aims) were examined similarly and P values < 0.017 (Bonferroni adjusted) were considered to indicate statistical significance. Effect modification by sex and race were evaluated using product terms (i.e., race × glycemic status category). SAS v 9.4 (Cary, NC) was used for all statistical analyses.

Results

Of the 197 subjects with complete data, 149 were self-identified as white, 35 as black, 8 as Asian, 4 as Hispanic, and 1 as other. We detected a significant interaction (interaction $p = 0.037$) between glycemic status category and race (black-white) with respect to BMSi, so we analyzed blacks and whites separately. The other race/ethnic groups were too small to analyze and were omitted from further analyses. Their distributions across the glycemia categories are shown in Supplemental Table 1. There were no significant interactions between glycemic status and sex with respect to any outcome detected (all interaction $p > 0.30$), so men and women were analyzed together.

Clinical characteristics

The clinical characteristics of the white and black subjects by glycemia category are shown in Table 1. As expected, fasting glucose, insulin, and HbA1c levels increased progressively across the glycemia categories in the whites and the blacks. In contrast, age, BMI, urine pentosidine, and physical activity levels did not differ significantly across these categories in either race group. In each glycemia category, the black participants were younger and had higher BMI levels than the white subjects. In the diabetes category, there was 1 black

Table 1 Clinical characteristics of white and black participants according to glycemic status. Data are presented as mean (SD), unless indicated otherwise

	No diabetes	Prediabetes	Diabetes
Race[a], *n*			
White	50	75	24
Black	6	13	16
Female, *n*			
White[a]	31	37	5
Black[a]	2	8	7
Age (year)			
White	67.3 (6.2)	66.6 (6.2)	68.0 (7.9)
Black	62.0 (4.8)	62.2 (6.2)	62.9 (7.1)
BMI (kg/m$^{2)}$			
White	27.1 (4.7)	28.4 (6.7)	28.7 (5.1)
Black	31.2 (7.5)	30.1 (5.3)	33.3 (6.0)
PASE score[b]			
White	106 (71)	86 (67)	90 (75)
Black	140 (98)	85 (51)	73 (44)
Fasting plasma glucose (mg/dl)			
White[a]	89 (6)	98 (10)	130 (32)
Black[a]	88 (4)	92 (8)	112 (21)
Fasting plasma insulin (UIU/ml)			
White[a]	8.5 (4.8)	11.4 (7.7)	18.8 (8.0)
Black[a]	10.2 (9.0)	10.5 (6.2)	18.7 (10.1)
HbA1c (%)			
White[a]	5.3 (0.3)	5.8 (0.3)	7.1 (1.1)
Black[a]	5.4 (0.2)	5.9 (0.2)	7.0 (0.9)
Serum creatinine[b] (mg/dl)			
White[c]	0.82 (0.25)	0.82 (0.22)	0.96 (0.20)
Black	0.90 (0.23)	0.86 (0.16)	0.78 (0.26)
Urine creatinine[b] (mg/dl)			
White	126 (99)	139 (100)	145 (84)
Black	120 (103)	148 (151)	148 (70)
Urine pentosidine[b] (ng/ml)			
White	110 (144)	121 (197)	179 (221)
Black	127 (241)	228 (323)	153 (195)
Vitamin D intake[b,d] (mcg/d)			
White	8.4 (0.5)	10.3 (1.0)	6.6 (1.5)
Black	6.3 (2.9)	6.5 (5.6)	7.4 (0.3)
Calcium intake[b,d] (mg/d)			
White	959 (205)	1066 (244)	1032 (252)
Black	977 (407)	558 (246)	787 (160)
On hypertension meds, *n*			
White	7 (14%)	19 (25%)	7 (29%)
Black	1 (17%)	3 (23%)	6 (38%)

[a] Glycemic status groups differ overall based on one-way analysis of variance (continuous measures) or Fisher's Exact Test (categorical measures), $p \le 0.003$

[b] Values presented are median (interquartile range), significance tested using the Kruskall-Wallis test, all $p \ge 0.135$ unless indicated otherwise

[c] $p = 0.033$, based on the Kruskall-Wallis test

[d] Includes from diet and supplements

saxagliptin user and there were 17 white and 9 black metformin users. There was no significant difference in BMSi, BMD, or TBS according to metformin use.

Bone measures and urine pentosidine

BMSi

There were no minor or serious adverse events associated with the measurements. Mean BMSi, adjusted for age, sex, and BMI, did not differ significantly by glycemia category in the whites ($p = 0.887$; Table 2). In the blacks, mean levels of BMSi (adjusted for age, sex, and BMI) differed significantly across the glycemia categories ($p = 0.02$), with mean BMSi significantly lower in the diabetics than in the other two categories (Table 2). The significantly lower BMSi in the blacks with diabetes persisted after adjustment for urine pentosidine (adjusted mean values 85.8 ± 5.0 SEM, 80.6 ± 3.5, and 71.8 ± 3.0; $P = 0.04$). Mean BMSi did not differ significantly between blacks and whites with no diabetes and prediabetes, but among subjects with diabetes, BMSi was significantly lower in blacks than in whites ($p = 0.011$; Fig. 1a).

TBS

TBS did not differ significantly across the glycemia categories in either the white or the black subjects (Table 2). Moreover, TBS did not differ significantly between blacks and whites (Fig. 1b).

BMD

BMD of the femoral neck increased significantly across the glycemia categories in the whites but not in the

Table 2. Least-square mean ± SEM BMSi, TBS, and BMD in whites and blacks according to glycemic status[a]

	No diabetes	Prediabetes	Diabetes	*p* value [b]
BMSi				
White	76.3 ± 1.6	77.2 ± 1.3	76.2 ± 2.5	0.887
Black	86.0 ± 4.3[c]	91.0 ± 3.2[c]	71.6 ± 2.9[d]	0.020
TBS				
White	1.32 ± 0.02	1.33 ± 0.02	1.33 ± 0.03	0.901
Black	1.29 ± 0.05	1.38 ± 0.04	1.33 ± 0.03	0.393
Femoral neck BMD (g/cm^2)				
White	0.88 ± 0.02[c]	0.89 ± 0.02[c]	0.97 ± 0.02[d]	0.004
Black	1.12 ± 0.06	1.02 ± 0.04	1.02 ± 0.04	0.317
Lumbar spine BMD (g/cm^2)				
White	1.25 ± 0.03	1.23 ± 0.02	1.25 ± 0.04	0.762
Black	1.35 ± 0.09	1.33 ± 0.06	1.32 ± 0.05	0.949
Mid-tibia BMD (g/cm^2)				
White	1.17 ± 0.03	1.16 ± 0.02	1.24 ± 0.04	0.245
Black	1.31 ± 0.12	1.36 ± 0.08	1.32 ± 0.08	0.931

[a] Least-square means ± SEM are adjusted for age, sex, and BMI

[b] Based on general linear regression, adjusted for age, sex, and BMI

[c,d] Groups with different superscripts differ, $p < 0.05$

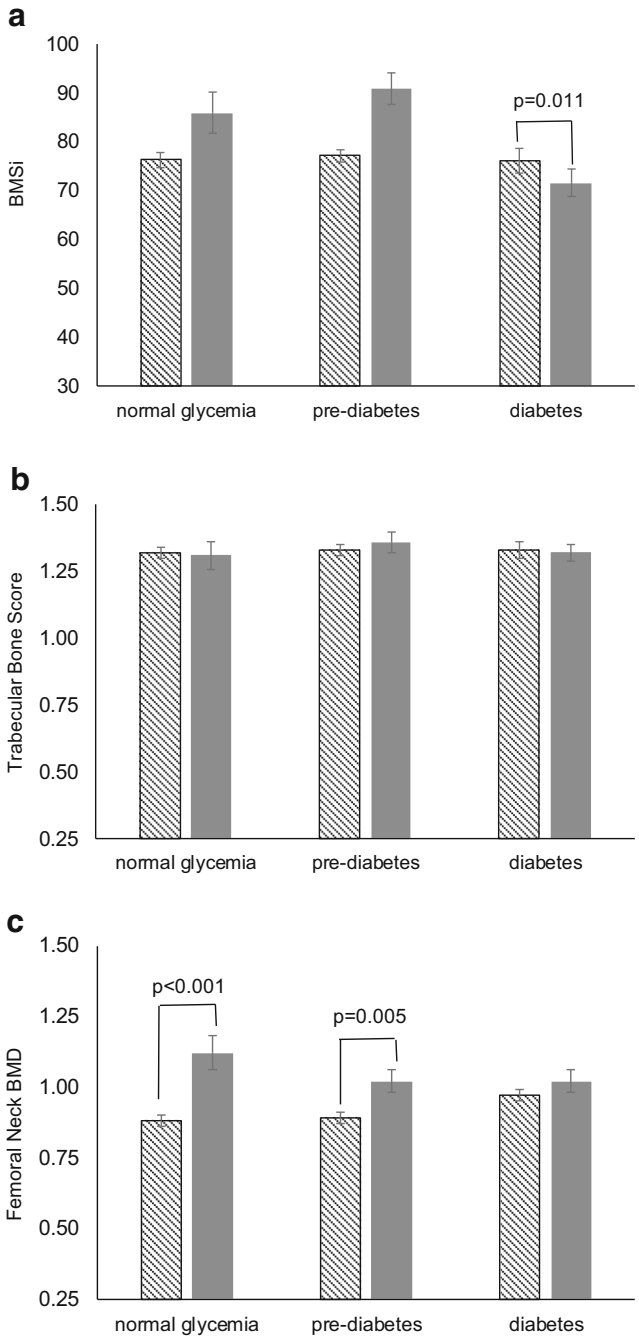

Fig. 1 Bone material strength (**a**), trabecular bone score (**b**), and femoral neck BMD (**c**) in whites (hatched bars) and blacks (solid bars) according to glycemic status. Within glycemia status group, whites and blacks were compared using general linear regression adjusted for age, sex, and BMI

blacks. BMD of the spine and mid-tibia were stable across the glycemia categories in both whites and blacks. In the no diabetes and prediabetes categories, femoral neck BMD was significantly higher in the blacks than in the whites, whereas femoral neck BMD did not differ significantly in the diabetes category (Fig. 1c). Tibia BMD and BMSi were not significantly correlated in either the whites or the blacks.

Urine pentosidine

Urine pentosidine did not differ significantly across glycemia categories in either the whites or the blacks and it did not differ significantly between the whites and the blacks. Urine pentosidine/creatinine levels were not significantly correlated with either TBS or BMSi in the blacks or the whites.

Discussion

BMSi, an indicator of the resistance of cortical bone to microfracture, is known to be lower in white individuals with long-standing diabetes, of 10 years or more duration, compared with non-diabetic controls [10–12]. We did not detect a downward trend in BMSi across normoglycemia, prediabetes, and early-stage diabetes (for ≤ 5 years) spectrum in whites in this study. This observation indicates that BMSi is not a promising tool for detection of impaired bone properties in whites with recent onset diabetes. And our null BMSi finding in whites suggests indirectly that skeletal fragility in diabetes may involve degradation of other bone material properties [18]. In contrast, in the black participants, BMSi declined across the glycemia spectrum and was 17 to 21% lower in the early diabetic subjects than in the normoglycemic and prediabetic subjects. There have been no previous reports of BMSi measurements in relation to glycemia in blacks for comparison; however, several other skeletal assessments tend to corroborate this observation. In a cross-sectional analysis of African-American women participating in the Study of Women across the Nation (SWAN), including 22 with diabetes (for a mean of 11 years) and 78 without diabetes, cortical porosity at the radius, measured by HR-pQCT, was 26% greater in the women with diabetes than in the women without diabetes [26]. Cortical porosity at the tibia did not differ significantly in the two groups but was numerically 14% higher in the women with diabetes [26]. Unfavorable cortical microarchitecture observed in these black diabetic women is consistent with our finding of lower BMSi in the blacks with diabetes. Moreover, in a sample of cadaveric bones extracted from 10 elderly donors, local cortical porosity explained over half of the variance in BMSi at the proximal humerus and distal radius, although the association was not statistically significant at the mid-tibia [27]. Another potentially relevant observation is that in NHANES, among participants aged 65 years and older with no diabetes, fracture rates were lower in blacks than in whites; however, among the subset of participants with diabetes, fractures rates were higher in blacks than in whites [28]. Diabetes appears to have a more damaging effect on bone in black than in white adults. This could potentially be due to poorer glucose control, but there was no evidence of that in our study, as neither HbA1c, nor glucose, nor pentosidine levels was higher in the black compared with the

white subjects with early diabetes. These findings suggest that the minimally invasive BMSi measurement is a potentially useful predictor of poor skeletal health in blacks with early-stage diabetes. Our sample of blacks was quite small, however, and a larger study is needed to verify this.

We assessed TBS because a large cohort study indicated that TBS was 6% lower in women with T2D compared with no diabetes [7]. Based on the lack of difference in TBS levels across the glycemia spectrum in whites or blacks in our study, TBS does not appear to be a useful tool for detecting deterioration in bone strength in early-stage diabetes.

Our finding that femoral neck BMD in whites increased across the glycemia spectrum is consistent with previous observations. A meta-analysis demonstrated that patients with T2D when compared with no diabetes had higher BMD at the hip; but despite this, the diabetic patients had increased risk of fracture [2]. Higher BMD in patients with diabetes was confirmed in a 2012 meta-analysis [29]. Spine BMD was stable across the glycemic spectrum in our subjects in contrast to these meta-analyses in which it, like femoral neck BMD, increased. We measured mid-tibial BMD because it is the site where BMSi is measured and identified no difference in mid-tibial BMD across the glycemia spectrum in either the whites or the black subjects. There are no previous reports of mid-tibial BMD available for comparison.

AGE accumulation reduces bone toughness, which may ultimately contribute to increased skeletal fragility [18, 20, 21]. In the Health ABC study, urine pentosidine, an AGE, was strongly associated with incident vertebral fracture in older adults with T2D, suggesting that it could be a marker of poor bone quality [24]. In our study, the fasting spot urine pentosidine levels did not differ across the glycemia categories or between the blacks and the whites. This null finding may relate to the fact that our study did not include individuals with long-standing T2D and/or to the high between-subject variability of the measurement.

This study has limitations, including that the design is cross-sectional, we lack HR-pQCT, and other measures of bone material properties, we did not have extensive prior history of fractures and other conditions that could have influenced bone strength, and, importantly, the number of blacks, while representative of our local population, was small.

In conclusion, BMSi levels were stable across the spectrum of normal, prediabetes, and T2D of ≤ 5 years duration in whites and BMSi therefore does not show promise as an indicator of impaired bone quality in whites with early T2D. This observation suggests that changes in material properties of bone other than those measured by impact microindentation may account for the increased fracture risk in diabetes in whites. In contrast, the blacks with T2D in this study had lower BMSi levels, raising the possibility that this test could be clinically useful in blacks; however, a larger study is needed to verify this. TBS levels did not vary across the glycemia categories in blacks or whites and its usefulness as a marker of bone disease in recent onset diabetes is questionable.

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Compliance with ethical standards

Disclaimer Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the National Institutes of Health or the U.S. Department of Agriculture.

Conflicts of interest Mary Bouxsein serves on the Scientific Advisory Board of ActiveLife Scientific. The other authors have no conflicts to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The protocol was approved by the Tufts Medical Center-Tufts University Institutional Review Board, and written informed consent was obtained from each subject.

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