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ORIGINAL ARTICLE

Trabecular bone quality is lower in adults with type 1 diabetes and is negatively associated with insulin resistance

V. N. Shah[1] · R. Sippl[1] · P. Joshee[1] · L. Pyle[1,2] · W. M. Kohrt[3,4,5,6] · I. E. Schauer[4,5,6] · J. K. Snell-Bergeon[1]

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Abstract

Summary We evaluated trabecular bone score (TBS) and factors affecting TBS in adults with type 1 diabetes (T1D) compared to age-, sex-, and body mass index (BMI)-matched adults without diabetes. Adults with T1D had lower TBS compared to controls. Abdominal obesity and insulin resistance are associated with lower TBS.

Introduction We evaluated TBS, a non-invasive method to evaluate trabecular bone quality at the lumbar spine, in adults with T1D compared to age-, sex-, and BMI-matched adults without diabetes.

Methods We calculated TBS from adults with T1D ($n = 47$) and controls ($n = 47$) who had a lumbar spine dual x-ray absorptiometry (DXA) at their third visit (2006–2009) of the ongoing "Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study." The linear relationships of TBS and bone mineral density (BMD) with hemoglobin A1c, blood pressure, lipids, and insulin resistance were evaluated using Pearson's correlation coefficient. Multiple linear regression was used to test the association of TBS with sex and diabetes while adjusting for other potential confounders.

Results TBS was significantly lower in adults with T1D compared to controls (1.42 ± 0.12 vs 1.44 ± 0.08, $p = 0.02$) after adjusting for age, sex, current smoking status, and lumbar spine BMD, despite no difference in lumbar spine BMD between the groups. Components of the metabolic syndrome, including diastolic blood pressure, BMI, triglycerides, and insulin resistance were negatively correlated with TBS among patients with T1D.

Conclusion Trabecular bone score, an indirect measurement of trabecular bone quality, was lower in adults with T1D compared to controls. Components of metabolic syndrome and insulin resistance were associated with lower TBS in adults with T1D.

Keywords Bone mineral density · Fracture · Insulin resistance and abdominal obesity · Osteoporosis · Trabecular bone score · Type 1 diabetes

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✉ V. N. Shah
viral.shah@ucdenver.edu

[1] Barbara Davis Center for Diabetes, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[2] Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[3] Division of Geriatric Medicine, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[4] Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, Anschutz Medical Campus, University of Colorado, Aurora, CO, USA

[5] Endocrinology Section, Department of Medicine, Denver VA Medical Center, Denver, CO, USA

[6] Eastern Colorado Geriatrics Research, Education, and Clinical Center, Denver, CO, USA

Introduction

Improvements in diabetes care have resulted in a reduction in life-threatening complications and increased longevity in people with type 1 diabetes (T1D) [1, 2]. Generally, osteoporosis is recognized as a disease of elderly postmenopausal women. However, in T1D, osteoporotic fractures are common in both men and women and increased risk is apparent at a relatively young age (~ 50 years) [3–8]. In a meta-analysis of 14 observational studies with 27,300 subjects with T1D and 4,364,125 subjects without diabetes, we reported a three-fold higher fracture risk in people with T1D compared to people without diabetes [4]. In addition, fracture risk at the spine and hip was higher in both men and women with T1D compared to people without diabetes.

The observed fracture risk is higher than expected based on bone mineral density (BMD) in adults with T1D, suggesting a detrimental effect of diabetes on bone quality [7, 8]. Bone histomorphometry and quantitative computed tomography (QCT) are standard research methods to evaluate bone microarchitecture. However, bone biopsy is invasive and QCT is associated with radiation exposure and high cost. Therefore, these tools are not widely used in clinical practice.

Trabecular bone score (TBS) is a non-invasive tool to measure trabecular microarchitecture from the lumbar spine dual x-ray absorptiometry (DXA) image [9]. Trabecular bone is metabolically more active than cortical bone. A population-based study showed that substantial bone loss starts earlier in the trabecular region compared to the cortical region at the lumbar spine, distal radius, and hip [10]. Trabecular bone quality measured by TBS has been shown to predict fracture risk independent of BMD [11, 12].

Patients with type 2 diabetes (T2D) have lower TBS despite higher BMD at the lumbar spine [13, 14]. In a study of patients with T1D, TBS was lower in those with prevalent fractures [15]. However, the study was limited by recruitment of younger subjects with T1D and shorter duration of diabetes. In addition, the factors affecting trabecular bone quality have not been studied in adults with T1D. Studies in patients with T2D suggest that higher body weight positively influences BMD [16, 17]. However, higher insulin resistance is associated with lower BMD and lower bone strength at the femoral neck, suggesting a detrimental role of high fat mass and insulin resistance on bone density and quality [18]. Studies have reported higher insulin resistance in patients with T1D as compared with controls without diabetes [19, 20]. However, the effects of body weight and insulin resistance on trabecular bone quality are unknown. The primary objective of the study was to compare TBS between adults with T1D and controls. The secondary objective was to examine the relationships of body mass index, waist circumference, lipids, and insulin resistance with lumbar spine BMD and TBS among adults with T1D.

Methods

Study design

This was a retrospective cross-sectional study of adults with T1D and non-diabetic controls who had a lumbar spine DXA ($n = 109$) at their third visit (2006–2009) of the ongoing "Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study" [21]. The inclusion criteria and patient selection were described in detail previously [21]. T1D was defined as follows: on insulin therapy within a year of diabetes diagnosis and currently on insulin therapy, diagnosed before age 30 or a clinical course consistent with T1D, and a diabetes duration of 4 years or greater. Adults without diabetes were frequency matched on age, sex, and body mass index (BMI) category as controls. All subjects provided informed consent and the study was approved by the Colorado Multiple Institutional Review Board.

Measures

Current height, weight, and waist circumference (WC, measured at the smallest point between the 10th rib and the iliac crest over the bare skin) were recorded, and BMI (weight/height^2; kg/m^2) was calculated. Resting systolic blood pressure (SBP) and fifth-phase diastolic blood pressure (DBP) were measured three times while the subjects were seated, and the second and the third measurements were averaged. Hypertension was defined as current SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or current antihypertensive therapy. Participants completed a standardized questionnaire including medical history and medication inventory and current and past smoking status as described previously [21–23].

After an overnight fast, blood was collected and centrifuged, and separated plasma was stored at 4 °C until assayed. Total cholesterol and triglyceride levels were measured using standard enzymatic methods. High density lipoprotein cholesterol (HDL-C) was separated using dextran sulfate, and low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. High-performance liquid chromatography was used to measure glycosylated hemoglobin (HbA1c) (HPLC; BioRad variant).

Dual X-ray absorptiometry (DXA, Hologic Discovery W) scans were performed for body composition and fat-free mass (FFM) and lumbar spine BMD just before the clamp study. All subjects underwent screening questions such as recent radiocontrast administration, implants, or devices in measurement area before BMD testing. A single well-trained technician performed BMD at the lumbar spine per the guidelines of the International Society for Clinical Densitometry (ISCD) [24]. The coefficient of variation for total hip BMD, lumbar spine BMD, whole body fat mass, and lean mass was 1.7, 4.0, 1.5, and 0.4%, respectively.

Trabecular bone score was measured at the lumbar spine using TBS iNsight software version 2.2.0.0 (TBS iNsight; Medimaps, Switzerland) per manufacturer instructions. TBS was calculated as the mean value of the individual measurements for vertebrae L1–L4, based on gray-level analysis of DXA images. All the DXA scans were reviewed by three authors (VNS, RS, JKS) for the accuracy of L1-L4 selection, scoliosis, spinal deformity, and any fractured and/or fused vertebrae before computation of TBS. Of the 109 subjects who had lumbar spine DXA done in the CACTI study, 15 subjects were excluded from the study due to inability to obtain TBS or to spinal pathologies.

Subjects ($n = 94$) also underwent a hyperinsulemic-euglycemic clamp for measurement of glucose infusion rate (a measure of insulin sensitivity) as described previously [21]. In brief, subjects were admitted to the inpatient clinical research unit before dinner the evening before their study. Subjects with T1D were instructed to take their last long-acting insulin injections at least 12 h before admission. Dinner was provided on the unit and subjects then fasted overnight and through the clamp. Subjects with T1D bolused for dinner per their usual regimen and were transitioned 3 h later to a continuous insulin infusion overnight to optimize glycemic control with short-acting insulin. After a baseline blood sample was collected for insulin, glucose, and C-peptide measurement, a primed continuous infusion of insulin was administered at 4, 8, and then 40 mU/m^2/min for 1.5 h each. A variable infusion of 20% dextrose was infused to maintain blood glucose of 90 mg/dl. Arterialized blood was sampled every 5 min for bedside determination of glucose concentration (Analox, Lunenberg, MA) and the dextrose infusion adjusted as necessary. A hyperinsulemic-euglycemic steady state was achieved during the last 30 min of the high insulin infusion stage and mean glucose infusion rate ([GIR], mg/kg fat-free mass/min) during this time was used as the measure of whole body insulin sensitivity. For example, the lower the GIR, the higher is the insulin resistance.

Statistical analysis

Descriptive statistics presented are mean ± standard deviation (SD), counts, and frequencies. Variables were tested for normality using the Shapiro-Wilk test. Non-normally distributed (TBS, triglycerides, HDL-C, waist circumference, lean mass, fat mass, GIR, and TBS) were log transformed before analysis. Continuous variables were compared using unpaired *t* tests. Pearson's correlation coefficient was used to evaluate the linear relationships of TBS and BMD with other clinical variables. Multiple linear regression was used to test the association of TBS with sex and diabetes while adjusting for other potential confounders. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). All tests performed were two-sided, and a p value < 0.05 was considered statistically significant.

Results

A total of 47 adults with T1D and 47 non-diabetic controls were included in this study. Characteristics of the study population are shown in Table 1 by diabetes status. Since there are well-recognized gender differences in lipids, waist circumference, fat and lean mass, insulin resistance, and bone density, the differences in these variables by diabetes status and sex are provided in Supplementary Table 1.

There were no differences in BMI, WC, systolic, or diastolic blood pressure between adults with and without diabetes (Table 1). Only eight adults with T1D had some form of microvascular complications (nephropathy, proliferative retinopathy, and/or diabetic neuropathy). The frequency of current smoking did not differ by diabetes status among either men or women. Statin use was more common among participants with T1D for both men and women. Total cholesterol, LDL-C, and triglyceride levels were lower in adults with T1D compared to controls, and GIR was significantly lower among T1D participants in both men and women. In a sensitivity analysis excluding participants on statin therapy, adults with T1D still had significantly lower total cholesterol ($p = 0.003$) and LDL-C ($p = 0.01$), triglycerides ($p = 0.008$), and GIR ($p = 0.003$).

Correlations between clinical measures and both TBS and lumbar spine BMD are shown in Table 2, by diabetes status. HbA1c was not correlated with either TBS or lumbar spine BMD in either group, but among participants with T1D, a higher insulin dose was significantly correlated with lower TBS and lower lumbar spine BMD. Components of the metabolic syndrome such as diastolic blood pressure, BMI, and triglycerides were all negatively correlated with TBS but not with lumbar spine BMD among adults with T1D. WC and triglycerides were negatively correlated with TBS in non-diabetics. GIR, a measure of skeletal muscle insulin sensitivity, was positively correlated with TBS in participants with and without T1D; insulin resistance (low GIR) was associated with lower TBS in participants irrespective of diabetes status. BMI was the only factor associated with lumbar spine BMD and was positively correlated among non-diabetic participants.

As shown in Table 1, there were no differences in BMD at the lumbar spine in adults with T1D and controls. In multiple linear regression, TBS at the lumbar spine was significantly lower in adults with T1D compared to controls (1.4 ± 0.12 vs 1.44 ± 0.08, $p = 0.02$) after adjusting for age, sex, current smoking status, and lumbar spine BMD. TBS, though within normal range, was lower in adults with T1D compared to controls at any age, even in T1D patients as young as 30 years

Table 1 Baseline characteristics of the participants with T1D and controls without diabetes

Variables	Type 1 diabetes ($n = 47$)	Controls without diabetes ($n = 47$)
Age (years)	43.4 ± 8.7	44.7 ± 6.9
Duration of diabetes (years)	28.7 ± 7.5	NA
HbA1c (%)	7.7 ± 1.0	5.4 ± 0.3
Insulin dose (units/kg/day)	0.6 ± 0.2	NA
BMI (kg/m^2)	26.1 ± 4.0	25.7 ± 4.1
Waist circumference (cm)	87.1 ± 12.6	85.8 ± 12.8
Total fat mass (kg)	21.8 ± 8.2	22.6 ± 7.9
Lean body mass (kg)	54.8 ± 12.1	51.3 ± 13.1
GIR (mg/kg FFM/min)	5.7 ± 3.7	13.2 ± 5.9
SBP (mmHg)	113.5 ± 10.4	113.0 ± 11.8
DBP (mmHg)	76.1 ± 7.5	76.1 ± 7.9
Total cholesterol (mg/dl)	158.1 ± 31.5	189.1 ± 30.2
HDL-C (mg/dl)		
LDL-C (mg/dl)	84.4 ± 28.5	110.0 ± 28.1
Triglyceride (mg/dl)		
Total hip BMD (g/cm^2)	0.99 ± 0.14	0.97 ± 0.15
Lumbar spine BMD L1-L4 (g/cm^2)	1.04 ± 0.15	1.02 ± 0.14
TBS	1.42 ± 0.12	1.44 ± 0.08

Statistics are mean ± SD unless specified

T1D type 1 diabetes, *HbA1c* glycated hemoglobin A1c, *BMI* body mass index, *GIR* glucose infusion rate, *FFM* fat-free mass, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HDL* high density lipoprotein cholesterol, *LDL* low density lipoprotein cholesterol, *BMD* bone mineral density

of age (Fig. 1). In this analysis, men had a lower TBS than women ($p < 0.0001$) when adjusted for age, diabetes status, smoking, and lumbar spine BMD. Smoking status ($p = 0.44$) and age ($p = 0.11$) were not significantly associated with TBS, but higher BMD at the lumbar spine was significantly associated with higher TBS ($p < 0.0001$).

Table 2 Correlations of trabecular bone score with clinical markers by diabetes status

	Participants with T1D		Non-diabetic controls	
	LogTBS	Lumbar BMD	Log TBS	Lumbar BMD
HbA1c	0.001	0.1	0.05	− 0.05
Insulin dose	− 0.4*	− 0.3*	–	–
DBP	− 0.3*	− 0.06	− 0.2	0.01
SBP	− 0.2	0.1	− 0.3	− 0.03
BMI	− 0.3*	0.1	− 0.2	0.3*
WC	− 0.6	− 0.0	− 0.4*	0.2
Total cholesterol	− 0.05	− 0.02	− 0.2	− 0.08
Log LDL-C	− 0.1	0.1	− 0.2	0.01
Log HDL-C	0.2	− 0.1	0.3*	− 0.03
Log triglyceride	− 0.4*	− 0.1	− 0.5*	− 0.1
Log GIR	0.3*	0.1	0.4*	0.2

*$p < 0.05$

T1D type 1 diabetes, *HbA1c* glycated hemoglobin A1c, *TBS* trabecular bone score, *WC* waist circumference, *BMI* body mass index, *GIR* glucose infusion rate, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HDL* high density lipoprotein cholesterol, *LDL* low density lipoprotein cholesterol, *BMD* bone mineral density

Shown in Table 3 are least-squares (LS) means for TBS by diabetes status in the multiple linear regression model adjusted for age, sex, smoking status and lumbar spine BMD, and then in subsequent models adjusted for each of the clinical factors correlated with TBS individually. TBS remained significantly lower in adults with T1D even when further adjusted for BMI, WC, HDL-C, triglycerides, systolic, and diastolic blood pressure, but was attenuated and no longer significantly different by diabetes status when adjusted for GIR.

Discussion

Our study showed that TBS, an indirect measure of trabecular bone quality, at lumbar spine was lower in adults with T1D compared to age-, BMI-, and sex-matched subjects without diabetes, despite similar lumbar spine BMD. BMI, triglyceride levels, and diastolic blood pressure were associated with lower TBS among adults with T1D. Insulin resistance was independently associated with lower TBS in adults with and without T1D, and adjustment for insulin resistance as measured using a hyperinsulinemic euglycemic clamp study attenuated the difference in TBS by diabetes status.

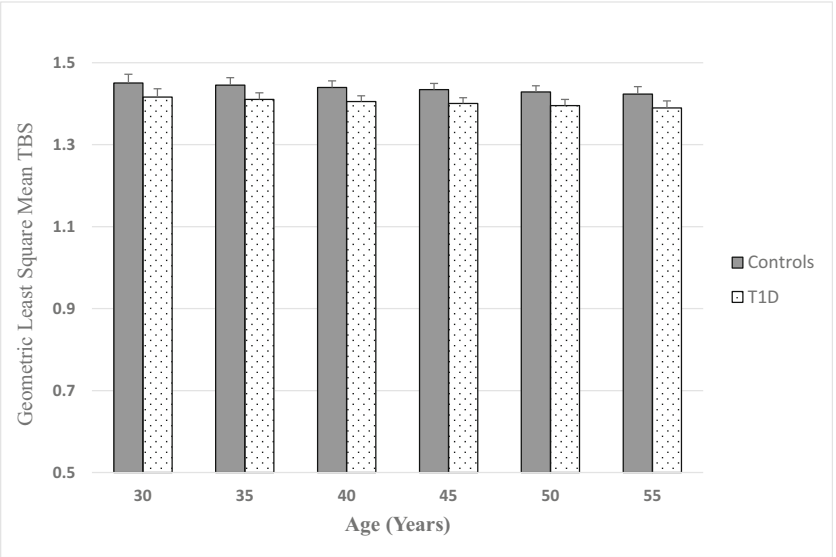

Fig. 1 Geometric least square mean trabecular bone score at lumbar spine in adults with T1D and controls

In this study, we did not find differences in lumbar spine or total hip BMD between adults with T1D and controls. This is in agreement with a recent meta-analysis reporting no differences in lumbar spine BMD between T1D and controls, after adjusting for age, sex, and DXA instrument [8]. Similarly, higher BMD does not protect patients with type 2 diabetes from osteoporotic fractures [7]. Mechanisms associated with skeletal fragility in diabetes are therefore recognized as not directly associated with bone loss but rather with impaired bone quality. Studies in patients with T2D consistently showed lower TBS compared to controls and TBS adjusted FRAX improved fracture prediction in this population [13, 14]. In a study by Neumann et al., there were no differences in TBS between adults with T1D and controls; however, TBS was lower in patients with T1D with a prior history of fractures [15]. The fact that participants with T1D in our study had longer duration of diabetes compared to the study by Neumann et al. [15] may explain the differences in our results.

Little is known about factors affecting bone quality in patients with diabetes. It is generally accepted that obesity has a protective effect on bone tissue [25]. However, many studies have shown higher fractures among obese patients [26]. The relationship between obesity and osteoporosis varies depending on how obesity is defined. Obesity defined on the basis of BMI or body weight appears to be a protective factor against bone mineral loss or vertebral fractures. However, obesity based on the percentage body fat may be a risk factor for osteoporosis [27]. Our study did show a positive relation between BMI as a measure of obesity and lumbar spine BMD in adults without diabetes; however, BMI was negatively related with TBS. This suggests that excess overall and central adiposity affects bone quality at the lumbar spine adversely despite normal BMD, whereas mechanical loading by higher weight may explain the positive association between BMI and BMD.

Table 3 Least square mean TBS and 95% CI by diabetes status in multivariable linear regression models

	T1D	Controls	*p* value
Model 1: age, sex, smoking status, lumbar BMD	1.40 (1.38–1.43)	1.44 (1.41–1.47)	0.0394
Model 1 + BMI	1.40 (1.38–1.43)	1.44 (1.41–1.46)	0.0295
Model 1 + WC	1.40 (1.38–1.43)	1.44 (1.41–1.46)	0.0106
Model 1 + HDL	1.40 (1.38–1.43)	1.44 (1.41–1.47)	0.0198
Model 1 + Triglycerides	1.40 (1.37–1.43)	1.45 (1.42–1.48)	0.0048
Model 1 + SBP	1.41 (1.38–1.43)	1.44 (1.41–1.47)	0.0354
Model 1 + DBP	1.41 (1.38–1.44)	1.44 (1.41–1.48)	0.0297
Model 1 + GIR	1.41 (1.37–1.44)	1.43 (1.40–1.47)	0.2090

T1D type 1 diabetes, *HbA1c* glycated hemoglobin A1c, *TBS* trabecular bone score, *BMI* body mass index, *WC* waist circumference, *GIR* glucose infusion rate, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *HDL* high density lipoprotein cholesterol, *LDL* low density lipoprotein cholesterol, *BMD* bone mineral density

In our study, adults with T1D were more insulin resistant than controls as measured using the gold standard clamp technique, and greater insulin resistance was associated with lower TBS. Similar to previous studies [19, 20], our study highlights that T1D is a highly insulin resistant state. Insulin resistance in patients with T1D is one of the potential explanations for compromised bone quality in patients with T1D.

Abdominal obesity is associated with higher triglyceride levels and insulin resistance [28]. In our study, diastolic blood pressure and triglyceride levels were negatively associated with TBS among adults with T1D. The findings from our study provide further evidence that abdominal obesity and related metabolic consequences are associated with compromised bone quality despite normal BMD at the lumbar spine. Abdominal obesity is associated with higher inflammatory markers such as IL-6 and TNF-α [29] that might result in increased bone resorption from the trabecular structure in the spine resulting in lower TBS.

To our knowledge, this was the first study to evaluate the effects of central obesity and insulin resistance on trabecular bone quality at the lumbar spine in adults with T1D. The well-characterized cohort of adults with long-standing T1D and non-diabetic controls with similar levels of obesity from the ongoing CACTI study was a major strength of this study. Small sample size, relatively young age of subjects, variable duration of diabetes, and single time point measurement of insulin resistance were some of the limitations of the study. In addition, participants with T1D were well controlled, and only a small number of participants with T1D ($n = 8$) had microvascular complications, limiting the generalization of our findings.

In conclusion, our study showed that trabecular bone score, an indirect measure of trabecular bone quality at the lumbar spine, was lower in adults with T1D compared to non-diabetic controls after adjusting for age, sex, smoking status, and lumbar spine BMD. Components of metabolic syndrome such as body weight, triglyceride levels, diastolic blood pressure, and insulin resistance were associated with lower TBS in adults with T1D. Further studies are needed to clarify the relationship between the components of metabolic syndrome, insulin resistance, and trabecular bone quality.

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Compliance with ethical standards All subjects provided informed consent and the study was approved by the Colorado Multiple Institutional Review Board.

Conflict of interest VNS, RS, PJ, LP, PJ, WMK, IES, and JKS declare no conflict of interest related to this work. JKS is the guarantor of this work.

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