Bone 123 (2019) 260–264

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

Type 1 diabetes onset at young age is associated with compromised bone quality

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ARTICLE INFO

Keywords:
Type 1 diabetes
Postmenopausal women
Bone health
Bone mineral density
Peripheral quantitative computed tomography

ABSTRACT

Women with type 1 diabetes (T1D) are at increased risk for fracture. We studied the association of T1D and young age at T1D onset (T1D onset before 20 years) on bone structural quality.

24 postmenopausal women with T1D (mean age 60.9 years, mean T1D duration 41.7 years) and 22 age, sex- and body mass index (BMI)-matched controls underwent dual X-ray absorptiometry (DXA) measured areal bone mineral density (aBMD) at the lumbar spine, hip and distal radius. Bone mass, geometry and estimated bone strength were assessed at distal and shaft of non-dominant radius and tibia using peripheral quantitative computed tomography (pQCT).

Postmenopausal women with T1D had lower trabecular volumetric bone mineral density (vBMD) (LSM ± SEM; 166.1 ± 8.2 vs 195.9 ± 8.3 mg/cm^3, $p = 0.02$) and compressive bone strength (24.6 ± 1.8 vs 30.1 ± 1.9 mg$^{2/}$mm^4, $p = 0.04$) at the distal radius compared to controls adjusting for age, BMI and radius length. At the distal radius, patients with young onset T1D had lower total vBMD (258.7 ± 19.7 vs 350.8 ± 26.1 mg/cm^3, $p = 0.02$) and trabecular vBMD (141.4 ± 11.6 vs 213.6 ± 15.4 mg/cm^3, $p = 0.003$) compared to adult onset T1D patients adjusting for age, BMI and the radius length. At the tibial shaft, young onset T1D patients had larger endosteal circumference (39.1 ± 1.2 vs 32.1 ± 1.6 mm, $p = 0.005$) with similar periosteal circumference (67.1 ± 0.9 vs 65.1 ± 1.2 mm, $p = 0.2$) resulting in reduced cortical thickness (4.4 ± 0.1 vs 5.2 ± 0.1 mm, $p = 0.004$) compared to adult onset T1D patients adjusting for age, BMI and the tibia length. There was no difference in the lumbar spine, femoral neck, total hip and distal radius DXA-measured aBMD between subjects with T1D and controls.

T1D is associated with lower trabecular vBMD at the distal radius. T1D onset before age 20 is associated with cortical bone size deficits at the tibial shaft.

1. Introduction

People with type 1 diabetes (T1D) have a three-fold increase in risk for major osteoporotic fractures, and a four to six-fold increase in risk for hip fractures compared to subjects without diabetes [1,2]. Moreover, the elevated risk of hip fracture risk in women with T1D compared to subjects without diabetes [3] begins well before 50 years of age, fifteen years before screening is recommended.

A recent meta-analysis reported moderate reduction in femoral neck areal bone mineral density (aBMD) by dual x-ray absorptiometry (DXA) and minimal or no change in aBMD at the lumbar spine in adults with T1D compared to non-diabetic adults [4]. Sex differences in aBMD are well-known; women have lower aBMD compared to men. However, in a small cohort from the Fremantle Diabetes Study, modestly lower aBMD at the hip and femoral neck was reported in men with T1D compared to controls (n = 23 per group), whereas in women with T1D compared to controls (n = 11 per group), there was no significant difference in aBMD at any site [5]. In a study by Vestergaard, the observed fracture risk among patients with T1D was three times higher than calculated fracture risk based on DXA aBMD overall, with a four-fold higher fracture risk in women with T1D versus a two-fold higher fracture risk in men [6]. This suggests that aBMD by DXA underestimates the fracture risk, perhaps particularly so in women with T1D. Bone structural and/or tissue material quality, which is not reflected by DXA measures

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https://doi.org/10.1016/j.bone.2019.03.039
Received 19 November 2018; Received in revised form 19 March 2019; Accepted 28 March 2019
Available online 29 March 2019

of aBMD, may therefore be compromised among patients with T1D and may be responsible for the high fracture risk in this population.

Besides bone mass, the geometry and strength of the bone are important contributors to fracture risk [7]. However, bone structural quality is not well-studied in T1D. In addition, it is possible that age of onset of T1D influences bone geometry and strength. For example, metabolic perturbation due to hyperglycemia at a young age (age of diabetes onset ≤20 years) when bone is accruing may be more detrimental compared to hyperglycemia at adult onset (age of diabetes onset > 20 years). Data from the T1D Exchange registry demonstrated an increased rate of fractures in patients with T1D who were diagnosed before the age of 20 years compared to adult onset T1D [8]. However, little is known about how age of T1D onset influences bone mass, geometry and strength.

We hypothesize that bone structural quality will be compromised in women with T1D especially in those who were diagnosed with T1D before 20 years of age. Consistent with our hypothesis, the present study aimed to evaluate bone mass, bone geometry and estimated bone strength at the distal radius and tibia among postmenopausal women with T1D compared to age-, and BMI-matched postmenopausal women without diabetes. In addition, we also evaluated the association of age of T1D onset with measures of bone quality among women with T1D.

2. Materials and methods

2.1. Study population

This cross-sectional study was conducted at the Barbara Davis Center for Diabetes at the University of Colorado Anschutz Medical Campus. Postmenopausal women (aged 45 years and above) from the Bone and Vascular Health in Postmenopausal Women with Type 1 Diabetes study (NCT02693964); were invited to participate in the present study. T1D was defined as: 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. Based on age at T1D onset, postmenopausal women with T1D were divided in two groups; young onset T1D defined as T1D onset before the age 20 and adult onset T1D defined as T1D onset after age 20. Menopause was defined as no menstrual periods for at least 12 consecutive months or history of hysterectomy with bilateral oophorectomy or FSH values > 40 IU/L on at least two occasions in women with history of hysterectomy without oophorectomy. Postmenopausal women without diabetes (HbA1c ≤ 5.7% at screening) were frequency matched by age, sex, and body mass index (BMI) category to women with T1D. Diabetes other than T1D, use of osteoporotic medications, history of bone abnormalities that can preclude DXA aBMD measurements, use of oral steroid equivalent of prednisolone of 5 mg for at least 3 months, estimated glomerular filtration (eGFR) < 30 mL/min/1.73 m^2, history of parathyroid and rheumatologic disease, and medication or disease that can significantly affect bone density were exclusion criteria. All participants provided written informed consent and Colorado Multiple Institutional Review Board approved the study.

2.2. Study procedures

2.2.1. Anthropometry and questionnaires

Height, weight, and waist circumference (WC, measured at the smallest point between the 10th rib and the iliac crest over the bare skin) were measured as described previously and BMI (weight/height^2; kg/m^2) was calculated [9,10]. Hypertension was defined as current systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or current antihypertensive therapy. Participants completed questionnaires including diabetes and other medical history, medication inventory, history of smoking, and diabetes comorbidities as described previously [9,10]. Diabetic retinopathy was self-reported as requiring laser therapy and/or intraocular injection. A score ≥ 4 on the Michigan Neuropathy Screening Instrument (MNSI) was classified as diabetic neuropathy [11].

2.2.2. aBMD by DXA

Dual X-ray absorptiometry (DXA, Hologic Discovery W) scans were performed for body composition and aBMD measurement at the lumbar spine, hip and distal radius. All subjects underwent screening questions regarding recent radiocontrast administration, implants or devices in the measurement area before BMD testing. A single ISCD certified technician performed aBMD measurements. The coefficient of variation for total hip BMD, lumbar spine BMD, whole body fat mass and lean mass were 1.7%, 4.0%, 1.5% and 0.4%, respectively. DXA aBMD was reviewed by three authors (VNS, RS, JKS) for the accuracy of region of interest selection, scoliosis, spinal deformity, and any fractured and/or fused vertebrae.

2.2.3. pQCT at distal radius and tibia

A pQCT scanner XCT 3000 with software version 6.00 (Stratec Medizintechnik GmbH, Pforzheim, Germany) was used to measure and analyze total, cortical, and trabecular vBMD (mg/cm^3) and area (mm^2) of the non-dominant tibia at 4%, and 38% of tibia length and the nondominant forearm at 4% and 33% of ulna length, distal to proximal. Periosteal (mm) and endosteal circumferences (mm), and cortical thickness were used as further indicators of bone size and shape as described previously [12,13]. For the 4% sites, the total and trabecular bone analyses were performed using the Stratec Contour Mode 3 and Peel Mode 4, with an outer threshold of 169 mg/cm^3 and an inner threshold of 650 mg/cm^3 because of the thinner cortical shell at these sites. Sites 33, 38, and 66% used Contour Mode 1 and Peel Mode 2 with 710 mg/cm^3 as the inner and outer thresholds. The cortical bone analyses were performed using Cortical Mode 2 with a threshold of 710 mg/cm^3. The 480 mg/cm^3 threshold was used to measure polar strength strain index (pSSI). Bone strength index (BSI, mg/mm^4), a measure of compressive strength, was calculated as (total bone cross sectional area × total bone density) / 1,000,000. The principal axes of the bone slices were determined as previously described [12,13].

2.2.4. Laboratory measures

After an overnight fast, blood was collected and centrifuged, and separated plasma was stored at 4 °C until assayed. Total cholesterol (TC) and triglyceride (TG) 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 (A1c) (HPLC; BioRad variant). A complete metabolic panel including total serum calcium and phosphorus were obtained from fasting serum samples. Glomerular filtration rate (eGFR) was estimated from serum creatinine using the Modification of Diet in Renal Disease Study (MDRD) equation [14]. To reduce analytical variation, serum 25-OH-D, bone turnover markers and PTH were assayed in single batch, all analytes were measured in duplicate, and the average of two measures was reported. Serum 25-OH-D (Immunodiagnostics), CTX (Immunodiagnostics), P1NP (Aviva Systems Biology), IGF-1 (Mediagnost), and total osteocalcin (Meso Scale Discovery) concentrations were measured using Enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's instructions.

2.2.5. Statistical analysis

Variables were assessed for normality using the Kolmogorov-Smirnov test. Continuous variables were compared using *t*-tests or Kruskal-Wallis Rank Sum tests, and Fisher's exact tests were used for categorical variables. Groups (with vs. without T1D and young onset vs. adult onset T1D) were compared using linear regression models adjusted for age, BMI, and either the radius or the tibia length. Analyses were performed using R version 3.5.1 and descriptive statistics were

Table 1
Baseline characteristics of participants.

	Postmenopausal women with T1D (n = 24)	Postmenopausal women without diabetes (n = 22)	*p*-Value
Age (years)	60.8 (5.45)	63.2 (5.96)	0.15
Menopause duration, (years)	10.0 [7.00, 14.25]	13.5 [6.50, 21.75]	0.20
BMI (kg/m^2)	26.8 (5.03)	25.0 (4.04)	0.18
T1D duration (years)	41.7 (9.08)	NA	NA
A1c (%)	7.7 [7.25, 8.10]	5.50 [5.30, 5.70]	< 0.001
Insulin dose (units/kg)	0.4 [0.3, 0.5]	NA	NA
Total fat (%)	39.4 (5.7)	39.4 (6.7)	0.99
Total lean mass (kg)	39.7 (4.9)	36.2 (3.9)	0.02
Use of HRT, n (%)	11 (45.8)	11 (50.0)	1.00
History of fracture, n (%)	19 (79.2)	10 (45.5)	0.03
Calcium intake (mg/day)	1311.5 (661.0)	1285.9 (831.1)	0.92
eGFR (ml/min/1.73 m^2)	77.55[68.8, 90.4]	75.3 [66.4, 87.3]	0.34
Urinary calcium:creatinine ratio (mg/dl)	0.08 [0.03, 0.12]	0.08 [0.05, 0.12]	0.74
Urine albumin:creatinine ratio (mcg/mg)	5.2 [3.8, 11.7]	7.2 [4.5, 10.7]	0.60
Serum corrected calcium (mg/dl)	9.2 (0.2)	9.2 (0.3)	0.60
Serum phosphorus (mg/dl)	3.8 [3.5, 4.0]	3.8 [3.7, 4.0]	0.85
IGF1 (ng/ml)	43.7 (21.9)	57.6 (34.2)	0.12
PTH (pg/ml)	36.1 (10.7)	39.6 (17.0)	0.39
Total 25-OH-D (ng/ml)	25.36 [22.97, 32.45]	27.36 [20.73, 31.44]	0.88
Osteocalcin (ng/ml)	34.8 [26.6, 41.1]	39.3 [33.2, 46.3]	0.11
P1NP (mcg/l)	57.8 [22.7, 102.3]	43.2 [31.3, 68.7]	0.90
CTX1 (ng/ml)	0.30 [0.2, 0.5]	0.38 [0.3, 0.6]	0.06

Statistics presented are mean (SD) or median [IQR]. BMI; body mass index, T1D; type 1 diabetes, HRT; hormone replacement therapy, eGFR; estimated glomerular filtration rate by MDRD equation, IGF-1; insulin-like growth factor-1, P1NP; procollagen 1 intact N-terminal, CTX; C-telopeptide.

compared using the "table one" package. All tests performed were two-sided and a p-value < 0.05 was considered statistically significant.

3. Results

Of 100 subjects (47 T1D, 53 controls) enrolled in the 'Bone and Vascular Health in Postmenopausal Women with Type 1 Diabetes' study, 24 postmenopausal women with T1D and 22 postmenopausal women without diabetes (controls) who completed baseline pQCT measurements were included in this study. The baseline characteristics of patients with T1D and controls are provided in Table 1. There was no difference in age, BMI, menopausal duration, and use of hormone replacement therapy (Table 1). Renal function (eGFR), total calcium intake, and urinary excretion of calcium were also similar between the groups. Hypertension (58.3 vs 31.8%, $p = 0.1$) was similar but use of statin (50% vs 13.6%, $p = 0.01$) was more common among subjects with T1D compared to controls. Of 24 subjects with T1D, 4 (16.6%) had increased urinary albumin excretion, 11 (45.8%) reported diabetic retinopathy and 8 (38.1%) had peripheral neuropathy.

There were no differences in age adjusted DXA-measured aBMD at the lumbar spine (least square mean ± standard error of mean; 0.974 ± 0.03 vs 0.932 ± 0.03 g/cm^2, $p = 0.4$), femoral neck (0.676 ± 0.01 vs 0.693 ± 0.01 g/cm^2, $p = 0.5$), total hip (0.805 ± 0.02vs 0.809 ± 0.02 g/cm^2, $p = 0.9$) and the distal radius (0.635 ± 0.02 vs 0.667 ± 0.02 g/cm^2, $p = 0.2$) between postmenopausal women with T1D and controls.

There was no difference in the radius length (246.5 ± 14.5 vs 250.1 ± 11.8 mm, $p = 0.3$) but the tibia length was shorter (379.8 ± 25.6 vs 405 ± 28.3 mm, $p = 0.03$) among postmenopausal women with T1D compared to controls. At the distal radius, postmenopausal women with T1D had lower trabecular vBMD (166.1 ± 8.2 vs 195.9 ± 8.3 mg/cm^3, $p = 0.02$) and BSI (24.6 ± 1.8 vs 30.1 ± 1.9 mg$^{2/}$mm^4, $p = 0.04$) with similar total area and total vBMD compared to postmenopausal women without diabetes adjusting for age, BMI and the radius length (Table 2). At the radial shaft, there were no differences in bone mass, geometry or estimated pSSI between postmenopausal women with T1D and controls. There were no differences in total vBMD, endosteal circumference, periosteal circumference and estimated bone strength (BSI and pSSI) at the distal tibia or tibia shaft between postmenopausal women with T1D and controls. However, cortical vBMD at tibial shaft was higher among postmenopausal women with T1D compared to controls (1170.6 ± 6.8 vs 1141.3 ± 7.5 mg/cm^3, $p = 0.001$).

We also performed an analysis by the age of onset of T1D. The postmenopausal women with T1D were divided in two groups; young onset (T1D diagnosis at or before the age 20 years) and adult onset T1D (T1D onset after 20 years). The postmenopausal women with young onset T1D were younger, had higher BMI, and longer duration of diabetes (Supplementary Table). At the distal radius, women with young onset T1D had lower total vBMD (258.7 ± 19.7 vs 350.8 ± 26.1 mg/cm^3, $p = 0.02$) and trabecular vBMD (141.4 ± 11.6 vs 213.6 ± 15.4 mg/cm^3, $p = 0.003$) with similar total area, resulting in significantly reduced compressive bone strength (BSI) compared to women with adult onset T1D adjusting for age, BMI and the radius length (Table 3). Similar findings of low total vBMD (232.2 ± 12.5 vs 322.6 ± 17.0 mg/cm^3, $p = 0.001$) and trabecular vBMD (186.4 ± 11.3 vs 267.5 ± 15.4 mg/cm^3, $p = 0.001$) with similar total area were observed at the distal tibia among women with young onset T1D compared to women with adult onset T1D. At the radial shaft, there was a trend of larger endosteal circumference (18.2 ± 1.2 vs 14.3 ± 1.5 mm, $p = 0.09$) with similar periosteal circumference among women with young onset T1D compared to women with adult onset T1D. At the tibial shaft, women with young onset T1D had larger endosteal circumference (39.1 ± 1.2 vs 32.1 ± 1.6 mm, $p = 0.005$) with similar periosteal circumference (67.1 ± 0.9 vs 65.1 ± 1.2 mm, $p = 0.2$) resulting in reduced cortical thickness (4.4 ± 0.1 vs 5.2 ± 0.1 mm, $p = 0.004$) compared to adult onset T1D patients adjusting for age, BMI and the tibia length.

There were no differences in the bone mass and geometry between women with T1D who reported diabetic retinopathy compared women with T1D who did not have diabetic retinopathy (data not shown).

4. Discussion

Fracture risk in patients with T1D is high, which cannot be explained based on DXA-measured bone density alone [2,6]. As expected, there was no difference in DXA-measured aBMD between patients with T1D and controls in our study, despite the fact that 79% of women with T1D had a reported history of fractures. Most, but not all, studies in children and adolescents with T1D showed smaller bones despite

Table 2
Differences in bone mass and geometry at the radius and tibia between postmenopausal women with T1D and postmenopausal women without diabetes.

	Postmenopausal women with T1D (n = 24)	Postmenopausal women without diabetes (n = 22)	*p*-Value	Postmenopausal women with T1D (n = 24)	Postmenopausal women without diabetes (n = 22)	*p*-Value
Distal radius				Distal tibia		
Total area (mm^2)	298.2 ± 11.1	312.8 ± 11.3	0.4	947.9 ± 30.0	1005.9 ± 33.4	0.2
Total vBMD (mg/cm^3)	292.1 ± 13.1	307.1 ± 13.4	0.4	267.9 ± 10.1	262.1 ± 11.2	0.7
Trabecular vBMD (mg/cm^3)	166.1 ± 8.2	195.9 ± 8.3	0.02	216.3 ± 9.1	222.2 ± 10.1	0.7
BSI (mg^2/mm^4)	24.6 ± 1.8	30.1 ± 1.9	0.04	69.1 ± 4.7	69.1 ± 5.3	0.9
Radial shaft				Tibial shaft		
Total area (mm^2)	95.1 ± 2.5	97.3 ± 2.6	0.5	359.1 ± 7.7	359.0 ± 8.5	0.9
Cortical area (mm^2)	69.5 ± 2.3	72.9 ± 2.4	0.4	248.9 ± 5.8	241.3 ± 6.4	0.4
Total vBMD (mg/cm^3)	923.7 ± 25.3	940.5 ± 26.0	0.6	859.4 ± 17.7	825.3 ± 19.7	0.2
Cortical vBMD (mg/cm^3)	1181.2 ± 8.7	1178.7 ± 8.9	0.8	1170.6 ± 6.8	1141.3 ± 7.5	0.01
Endosteal circumference (mm)	17.4 ± 0.8	17.1 ± 0.8	0.8	36.5 ± 5.3	38.5 ± 4.9	0.4
Periosteal circumference (mm)	34.5 ± 0.5	34.9 ± 0.5	0.5	66.4 ± 3.1	67.9 ± 3.7	0.9
Cortical thickness (mm)	2.7 ± 0.1	2.8 ± 0.1	0.4	4.8 ± 0.1	4.5 ± 0.1	0.2
pSSI (mm^3)	221.7 ± 8.5	232.9 ± 8.7	0.4	1546.9 ± 44.1	1548.2 ± 49.1	0.9

Statistics presented are least square mean ± standard error of mean, T1D; type 1 diabetes, vBMD; volumetric bone mineral density, BSI; bone strength index, pSSI; polar strength-strain index. *p*-Values adjusted for age, BMI and radius or tibia length.

Table 3
Differences in bone mass and geometry at the radius and tibia between postmenopausal women with young onset type 1 diabetes compared to postmenopausal women with adult onset type 1 diabetes.

	Adult onset T1D (n = 9)	Young onset T1D (n = 11)	*p*-Value
Distal radius			
Total area (mm^2)	275.7 ± 27.0	311.3 ± 20.3	0.3
Total vBMD (mg/cm^3)	350.8 ± 26.1	258.7 ± 19.7	0.02
Trabecular vBMD (mg/cm^3)	213.6 ± 15.4	141.4 ± 11.6	0.003
BSI (mg^2/mm^4)	32.0 ± 2.4	20.6 ± 1.8	0.003
Radial shaft			
Total area (mm^2)	89.3 ± 4.8	97.0 ± 3.6	0.2
Cortical area (mm^2)	72.5 ± 4.4	68.5 ± 3.3	0.5
Total vBMD (mg/cm^3)	1012.9 ± 50.7	897.9 ± 38.2	0.1
Cortical vBMD (mg/cm^3)	1207.7 ± 14.2	1171.0 ± 10.7	0.08
Endosteal circumference (mm)	14.3 ± 1.5	18.2 ± 1.2	0.09
Periosteal circumference (mm)	33.0 ± 0.9	35.0 ± 0.7	0.1
Cortical thickness (mm)	2.9 ± 0.2	2.6 ± 0.1	0.2
pSSI (mm^3)	206.0 ± 15.3	228.5 ± 11.5	0.3
Distal tibia			
Total area (mm^2)	847.8 ± 47.6	1040.1 ± 34.8	0.008
Total vBMD (mg/cm^3)	322.6 ± 17.0	232.2 ± 12.5	0.001
Trabecular vBMD (mg/cm^3)	267.5 ± 15.4	186.4 ± 11.3	0.001
BSI (mg^2/mm^4)	89.8 ± 9.0	57.0 ± 6.6	0.01
Tibial shaft			
Total area (mm^2)	337.9 ± 13.3	359.9 ± 9.7	0.2
Cortical area (mm^2)	256.0 ± 9.1	235.7 ± 6.6	0.1
Total vBMD (mg/cm^3)	933.8 ± 25.1	812.1 ± 18.4	0.02
Cortical vBMD (mg/cm^3)	1184.2 ± 7.9	1163.1 ± 5.8	0.06
Endosteal circumference (mm)	32.1 ± 1.6	39.1 ± 1.2	0.005
Periosteal circumference (mm)	65.1 ± 1.2	67.1 ± 0.9	0.2
Cortical thickness (mm)	5.2 ± 0.1	4.4 ± 0.1	0.004
pSSI (mm^3)	1483.8 ± 76.0	1510.6 ± 55.7	0.7

Statistics presented are least square mean ± standard error of mean, T1D; type 1 diabetes, vBMD; volumetric bone mineral density, BSI; bone strength index, pSSI; polar strength-strain index. *p*-Values adjusted for age, BMI and radius or tibia length.

normal growth and lower total vBMD or trabecular vBMD at the distal radius [15–19]. Most studies evaluating bone health have been carried out in children and adolescents with shorter duration of T1D. In addition, differences in the characteristics of study populations such as age and Tanner staging makes comparison of study results difficult.

Our study shows reduced trabecular vBMD and compressive bone strength (BSI) at the distal radius. However, there were no differences in the bone mass and geometry at the radial shaft. Verroken et al. [20] reported lower trabecular vBMD at the distal radius in 64 adults with T1D compared to 63 adults without diabetes. They also reported lower total vBMD and increased cortical vBMD at the radial shaft. We did not find differences in bone mass at the radial shaft possibly due to our smaller sample size. Reduced trabecular vBMD at the distal radius, a finding of our study and previously published studies using pQCT, may be due to various reasons; a) trabecular changes are often more easily detected at the distal radius, which has much more surface area available for basic multicellular units to induce a net bone loss, b) pQCT has limited resolution to detect changes in cortical bone, and c) increased endosteal bone resorption due to increased advanced glycation endproducts in people with T1D resulting in reduced trabecular vBMD.

Another study by Shanbhogoue et al. [21] showed no differences in cortical or trabecular structure at the distal radius using high resolution peripheral quantitative computed tomography (HR-pQCT). However, the total density, trabecular area and cortical thickness were lower among patients with T1D those who had microvascular diabetes complications. We did not find any differences in the bone mass and geometry by diabetic retinopathy status despite the fact that nearly 50% of our study participants reported diabetic retinopathy requiring treatment.

Our results suggest significant impairment in the bone structural quality among patients who were diagnosed with T1D before the age of 20 years. Young onset T1D is characterized by lower trabecular vBMD at the distal radius and cortical bone size deficit at the radial and tibial shaft. This may be due to reduced periosteal apposition and increased endosteal resorption resulting in a cortical deficit among patients with T1D. Our data suggest that young onset of T1D may have a significant influence on bone accrual resulting in compromised bone mass and geometry despite normal DXA-measured aBMD. Studies in children and adults with T1D showed lower bone density during the initial period of T1D diagnosis [22,23]; however, most studies have reported normalization of bone density over time suggesting temporary halting of bone accrual among patients who are diagnosed with diabetes at a young age [19]. Our study suggests that temporary halting of bone accrual during young age may have a significant impact on bone geometry and quality. However, it is important to note that women with young onset T1D had longer duration of diabetes compared to adult onset T1D and therefore, influence of duration of T1D on bone structural quality cannot be ruled out. Contrary to the findings of our study, a study by Verroken et al. [20] did not find differences in bone mass and geometry by age at onset of diabetes. The difference between results of our study and those of

Verroken et al. may be due to differences in disease severity at T1D onset, sample size, and duration of diabetes.

A homogenous population of postmenopausal women with well characterized T1D and long-duration of T1D and the use of age, sex and BMI-matched controls are major strengths of this study. Diabetes complications were well defined in our cohort and metabolic control in our cohort was similar to that reported by the national T1D Exchange registry [24]. However, the cross-sectional study design, inclusion of only postmenopausal women, and small sample size are major limitations. Furthermore, the limited resolution of pQCT did not allow us to evaluate trabecular structure or cortical porosity in this study.

In summary, T1D is associated with lower trabecular vBMD at the distal radius. T1D onset at a young age is associated with cortical bone size deficits at the tibial shaft which is characterized by larger endosteal circumference and similar periosteal circumference compared to adult onset T1D.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.03.039.

Acknowledgements

This work was supported by the Center for Women' Health Research Seed Grant and CTRC microgrant (NIH-M01-RR00051) at the University of Colorado Denver.

Author statement

Viral N Shah: Conceptualization, Investigation, Resources, Writing-Original Draft, Review and Edits, Funding Acquisition. Prakriti Joshee: Investigation, Writing-Review and Edits, Rachel Sippl: Investigation, Writing-Review and Edits. Laura Pyle: Data Curation, analysis and Writing-Review and Edits. Tim Vigers: Data Curation, analysis, and Writing-Review and Edits. Dana Carpenter: Investigation, Writing-Review and Edits. Wendy Kohrt and Janet K Snell-Bergeon: Resources, Data Curation, analysis and Writing-Review and Edits.

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