Impact of Type 1 Diabetes Mellitus on Skeletal Integrity and Strength in Adolescents as Assessed by HRpQCT

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ABSTRACT

Adults with type 1 diabetes mellitus (T1DM) are at risk of premature osteoporosis and fractures. The onset of T1DM typically starts during childhood and adolescence. Thus, the effects of DM on the skeleton may be established during this period. Studies in children with T1DM primarily use DXA with conflicting results. We present the first study in adolescents assessing the impact of T1DM on skeletal microstructure and strength using HRpQCT. We recruited 22 patients aged 12 to 16 years with T1DM who were matched by age, gender, and pubertal stage with healthy controls. Paired t-tests were applied to assess differences in cortical and trabecular microarchitecture measurements from HRpQCT, and skeletal strength from HRpQCT-derived microfinite element analysis. Subtotal body, lumbar, and pelvic parameters were assessed using DXA. There was no significant difference in subtotal body, lumbar spine, and pelvic BMD between T1DM and control pairs. However, tibial trabecular thickness was lower (−0.005 mm; 95% CI, −0.01 to −0.001; p = 0.029) and trabecular loading was lower at the distal radius (ratio of the load taken by the trabecular bone in relation to the total load at the distal end (Tb.B/TF) distal: −6.2; 95% CI, −12.4 to −0.03; p = 0.049), and distal and proximal tibia (Tb.B/TF distal: −5.2, 95% CI, −9.2 to −1.2; p = 0.013; and Tb.B/TF proximal: −5.0, 95% CI, −9.8 to −0.1; p = 0.047) in T1DM patients. A subanalysis of radial data of participants with duration of T1DM of at least 2 years and their matched controls demonstrated a reduced trabecular bone number (−0.15, 95% CI, −0.26 to −0.04; p = 0.012), increased trabecular separation (0.041 mm, 95% CI, 0.009–0.072; p = 0.015), an increased trabecular inhomogeneity (0.018, 95% CI, 0.003–0.034; p = 0.021). Regression models demonstrated a reduction in tibial stiffness (−0.877 kN/mm; p = 0.03) and tibial failure load (−0.044 kN; p = 0.03) with higher HbA1C. Thus, in adolescents with T1DM, detrimental changes are seen in tibial and radial microarchitecture and tibial and radial strength before changes in DXA occur and may result from poor diabetic control. © 2020 The Authors. JBMR Plus published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research.

KEY WORDS: DXA; OTHER; RADIOLoGY; FRACTURE RISK ASSESSMENT

Introduction

Adults with type 1 diabetes mellitus (T1DM) have an increased risk of osteoporosis and fractures.1-3 The pooled relative risk for any fracture is 3.16,4 the risk of hip fractures is between 3.78 to 6.94 times higher than the normal adult population.1,5 Previous studies have shown that adults with T1DM have reduced BMD,1,3-6 and fracture risk is compounded by poor diabetic control or coexistent diabetic complications.3,7,8

The onset of T1DM is typically in childhood, with the peak age of onset between 10 to 14 years,1 leading to a long exposure to the effects of hyperglycemia and hyperinsulinism. Significant bone growth and remodeling occurs in childhood and adolescence with 25% of peak bone mass attained in adolescence.9,10 Optimizing peak bone mass in childhood and adolescence reduces fracture risk.10 It is thus plausible that the impact of T1DM on skeletal health begins from diagnosis in childhood and adolescence, leading to skeletal changes and inadequate bone mass accrual. This may subsequently lead to an increased risk of osteoporosis and fractures in adults with T1DM.7

One of the earliest studies looking at the impact of T1DM on skeletal health in children dates back to 1948 where a loss of bone “content” was demonstrated through evaluation of conventional X-rays.11 Since then, there have been multiple studies looking at DXA-derived BMD in children with T1DM with conflicting results; some showing reduced BMD,5,6,10,11 and others showing no difference in BMD compared with controls.12-14 The inconsistencies in BMD seen between studies of children
with T1DM may be related to the age of the patient, time from diagnosis, and diabetic control. Despite this, studies showing no reduction in BMD have shown changes in the bone markers such as osteocalcin, PINP, and urinary pyridinoline and deoxypyridinoline, reflecting lower bone formation and an increased bone turnover.

Changes in bone markers can be seen within a year of onset of T1DM, suggesting that skeletal alterations may be taking place at a microarchitectural level. BMD may also be considered an inadequate predictor of fracture risk in DM. In a previous meta-analysis, lower BMD was demonstrated in adults with T1DM but higher BMD in adults with T2DM. Yet an increased fracture risk was observed in both conditions. Moreover, the fracture risk in T1DM is also higher than the calculated risk if it is solely based on BMD. Patients with T1DM can also still develop fractures even with a normal BMD, suggesting that fracture risk may also be driven by more subtle detrimental microstructural skeletal alterations.

Changes in bone microarchitecture that influence bone quality and strength may precede observable changes in DXA-derived bone mass in children. Comparable studies using pQCT in children have demonstrated detrimental changes in the cortical compartment in children and adolescents with T1DM. In participants with T1DM, Bechtold and colleagues demonstrated a reduction in total and cortical cross-sectional area in prepubertal participants and reduction in total cross-sectional area in participants in early puberty at the radius compared with healthy controls. Thus our objectives were to determine: (i) whether T1DM causes changes in cortical and trabecular bone microarchitecture and proxies of bone strength calculated using finite element analysis. HRpQCT was therefore used in this study as it provides high-resolution images of the cortical and trabecular microarchitecture to a resolution of 82 micrometers and estimated bone strength parameters.

We hypothesized that detrimental changes in bone mass and the cortical and trabecular bone microarchitecture, and proxies in bone strength will be seen in adolescents with T1DM compared with healthy controls. In all postpubertal participants with fused tibial and radial growth plates, a reference line was placed on the scan image at the endplate of the distal tibia and on the notch on the articular surface of the distal radius to indicate the position of the first measurement slice (22.5 and 9.5 mm proximal from the reference line for the tibia and radius, respectively). In prepubertal participants and in those participants with open tibial and radial growth plates, the reference line was placed on the scan image at the proximal end of the growth plate to indicate the position of the first measurement slice (1 mm proximal from the reference line). A single stack of parallel CT slices (110 slices = 9.02 mm) for each site was acquired in the high-resolution mode (image matrix = 1536 × 1536). Daily measurements of the manufacturer device-specific phantom (Scanco Medical AG) were performed to monitor the stability of the XtremeCT. Assessment of bone strength was determined using microfinite element analysis (mFEA) and a built-in software of HRpQCT.

HRpQCT densitometric measurements included total density (mg/cm³), trabecular density (mg/cm³), and cortical density (mg/cm³). Measures of microarchitectural properties included trabecular number (1/mm), trabecular thickness (mm), trabecular separation (mm), bone volume fraction (%), endosteal and periosteal perimeter (mm) and cortical thickness (mm). Extended cortical analysis techniques were applied to the segmented scans using specialist software provided by Scanco Medical AG (version 6.0, Scanco Medical AG, Brüttisellen, Switzerland). The scanning methodology has previously been described. In all postpubertal participants with fused tibial and radial growth plates, a reference line was placed on the scan image at the endplate of the distal tibia and on the notch on the articular surface of the distal radius to indicate the position of the first measurement slice (22.5 and 9.5 mm proximal from the reference line for the tibia and radius, respectively). In prepubertal participants and in those participants with open tibial and radial growth plates, the reference line was placed on the scan image at the proximal end of the growth plate to indicate the position of the first measurement slice (1 mm proximal from the reference line). A single stack of parallel CT slices (110 slices = 9.02 mm) for each site was acquired in the high-resolution mode (image matrix = 1536 × 1536). Daily measurements of the manufacturer device-specific phantom (Scanco Medical AG) were performed to monitor the stability of the XtremeCT. Assessment of bone strength was determined using microfinite element analysis (mFEA), and a built-in software of HRpQCT.

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**Table 1.** Types of images obtained from HRpQCT for a participant with type 1 diabetes mellitus (A) and an age-, pubertal stage-, and gender-matched control (B).
Participants with T1DM were matched to controls according to gender, age, and pubertal status. Comparisons between groups for age, anthropometry, and bone parameters (DXA, HRpQCT, and mFEA) were made using paired t-tests. Paired differences in bone parameters are presented as unadjusted data and data adjusted for height and weight using mixed effects linear model with pair as random intercept. Linear regression analysis was used to determine impact of glycemic control (as assessed by average HbA1c) and duration of T1DM on the skeletal parameters as assessed by HRpQCT with age and gender included in the model as independent variables. Significance was determined at a p value of ≤0.05. The analysis was done using the R Project for Statistical Computing.\(^{(23)}\)

### Results

From the adolescents contacted through the pediatric outpatient diabetic clinics, 29 adolescents with T1DM were eligible and consented to be part of the study. From these, 22 adolescents participated in the study. Thirty healthy controls were contacted and 25 adolescents participated in the study. Thirty healthy controls were consented to be part of the study. From these, 22 adolescents participated in the study. Data from three healthy controls were excluded from the study because they could not be matched to the existing participants with T1DM (three male participants).

Twenty-two participants with T1DM were age-, pubertal stage-, and gender-matched with healthy controls. At the time of analysis, HRpQCT data could not be obtained from two participants with T1DM (because of movement artifacts); hence, analyses of these data were from 40 participants (20 matched pairs). DXA data were obtained from all participants (22 matched pairs). Demographics of the cohort are presented in Table 1. There were 13 female matched pairs (n = 26) in this study. Participants with T1DM were significantly heavier (8.3 kg = paired difference and 95% CI is 2.9–13.8, p = 0.005) and had a higher BMI (3.0 is the paired difference with 95% CI 1.0–5.1, p = 0.006) than controls.

Eight participants with T1DM previously had fractures; six participants sustained one fracture, and two participants had two previous fractures. Ten healthy controls previously had fractures; seven participants had sustained one fracture and three participants had two fractures.

Among the participants with T1DM, the average age of onset of diagnosis was 9.25 ± 1.62 years. The duration of DM among participants ranged from 2 months (participant was 13.1 years at time of study) to 14.5 years (participant was 15.5 years at time of study). The average HbA1C was 62.4 ± 5.38 mmol (excluding one participant who did not have a HbA1C measurement as the duration of DM was <3 months).

There were no significant differences in BA, BMC, and BMD for total body less head, lumbar spine, and pelvic sites between participants with T1DM and matched controls (Table 2). After adjusting for differences in height and weight, there were no significant differences in fat and lean mass between both groups. A further subanalysis was done by excluding participants with a short T1DM duration (<2 years) and their paired healthy controls (Table 3), and there remained no difference in bone densitometry parameters.

HRpQCT comparisons of the radius are presented in Table 4. Participants with T1DM carried on average 6.2% less load at the distal surface of the trabecular bone (95% CI, −12.4 to −0.03; \(p = 0.049\)) compared with controls. However, when T1DM participants of <2 years DM duration and their paired controls were excluded in a further subanalysis (Table 5), further significant changes in the trabecular bone were found. At the radius, participants with T1DM had a reduced trabecular bone number by 0.15 (95% CI, −0.26 to −0.04; \(p = 0.012\)), increased trabecular separation by 0.041 mm (95% CI, 0.009–0.072; \(p = 0.015\)), an increased trabecular inhomogeneity by 0.018 (95% CI, 0.003–0.034; \(p = 0.021\)) and carried 9.7% less load at the distal surface of the trabecular bone (95% CI, −17.3 to −21; \(p = 0.017\)) compared with controls.

HRpQCT analyses of the tibia are presented in Table 6. Participants with T1DM had a lower mean trabecular thickness (−0.005 mm; 95% CI, −0.01 to −0.001; \(p = 0.029\)) and had a 5.2% mean reduction in load (95% CI, −9.2 to −1.2; \(p = 0.013\)) on the distal surface and 5.0% decreased load (95% CI, −9.8 to −0.1; \(p = 0.047\)) on the proximal surface of the tibial trabecular bone compared with controls. When T1DM participants of <2 years DM duration and their paired controls were excluded in a further subanalysis (Table 7), lower trabecular thickness remained a consistent finding in children with T1DM (−0.007 mm; 95% CI, −0.013 to −0.001; \(p = 0.029\)) compared with controls; however, changes in load carried by the trabecular bone were no longer significant.

Linear regression analysis was used to determine the relationship between HbA1C and duration of T1DM on skeletal parameters as assessed by HRpQCT. The regression models were adjusted for age and gender because this analysis was only performed for the group of T1DM patients. There was no correlation between HbA1C or duration of T1DM and radial skeletal parameters once adjusted for age and gender. In contrast, an increase in one unit of HbA1C was associated with a reduction in the estimated failure load by 0.044

### Table 1. Comparison of Anthropometry in T1DM and Control Groups and Mean Difference (95% CI) Matched by Age, Gender, and Pubertal Stage

| Variable          | T1DM  | Control | Paired difference (T1DM – control) |
|-------------------|-------|---------|-----------------------------------|
|                   | Mean  | SD      | Mean  | SD      | Mean (95% CI) | \(p\) Value |
| Age (years)       | 13.8  | 1.2     | 13.6  | 1.2     | 0.1 (−0.03 to 0.24) | 0.130 |
| Tanner stage      | 3.4   | 0.9     | 2.9   | 1.2     | 0.5 (−0.1 to 1.0)  | 0.091 |
| Height (cm)       | 160.6 | 9.4     | 159.7 | 10.2    | 0.9 (−3.9 to 5.8)  | 0.693 |
| Weight (kg)       | 58.1  | 14.6    | 49.8  | 10.2    | 8.3 (2.9 to 13.8)  | 0.005 |
| BMI               | 22.4  | 4.4     | 19.3  | 2.5     | 3.0 (1.0 to 5.1)   | 0.006 |

Significance is reached at \(p \leq 0.05\). T1DM = type 1 diabetes mellitus.
Table 2. Comparison of DXA Data for Total Body Less Head, Lumbar Spine, and Pelvis in T1DM and Control Groups and Mean Difference (95% CI) Matched by Age, Gender, and Pubertal Stage

|                      | T1DM Mean (SD) | Control Mean (SD) | Paired difference<sup>a</sup> (T1DM – control) | Paired difference<sup>b</sup> (T1DM – control) |
|----------------------|----------------|------------------|-----------------------------------------------|-----------------------------------------------|
|                      | N              |                  | Mean (95% CI)                                 | p Value                                      |
|                      |                |                  | Mean (95% CI)                                 | p Value                                      |
| Subtotal body area (cm<sup>2</sup>) | 22 1570.1 (203.3) | 1533.5 (213.8) | 36.6 (–64.4 to 137.6) 0.459 | –53.6 (–119.0 to 11.8) 0.103 |
| Subtotal body BMC (g) | 22 1328.5 (235.7) | 1308.4 (298.3) | 20.1 (–124.6 to 164.7) 0.776 | –89.0 (–186.9 to 8.8) 0.072 |
| Subtotal body BMD (g/cm<sup>2</sup>) | 22 0.841 (0.049) | 0.844 (0.089) | –0.002 (–0.048 to 0.043) 0.913 | –0.024 (–0.062 to 0.014) 0.209 |
| Lumbar spine area (cm<sup>2</sup>) | 22 45.9 (6.9) | 45.6 (8.6) | 0.3 (–4.9 to 5.4) 0.918 | –1.3 (–5.9 to 3.4) 0.579 |
| Lumbar spine BMC (g) | 22 40.7 (9.8) | 40.7 (12.2) | –0.1 (–6.4 to 6.3) 0.980 | –2.4 (–8.8 to 3.9) 0.438 |
| Lumbar spine BMD (g/cm<sup>2</sup>) | 22 0.879 (0.125) | 0.880 (0.144) | –0.001 (–0.064 to 0.063) 0.983 | –0.027 (–0.098 to 0.043) 0.425 |
| Pelvic area (cm<sup>2</sup>) | 22 189.6 (28.6) | 192.5 (39.4) | –2.9 (–23.0 to 17.1) 0.763 | –11.5 (–29.7 to 6.6) 0.200 |
| Pelvic BMC (g) | 22 208.6 (47.1) | 207.4 (62.4) | 1.2 (–29.3 to 31.8) 0.934 | –17.9 (–43.7 to 8.0) 0.164 |
| Pelvic BMD (g/cm<sup>2</sup>) | 22 1.094 (0.140) | 1.059 (0.140) | 0.034 (–0.048 to 0.116) 0.393 | –0.017 (–0.090 to 0.057) 0.637 |
| Whole-body fat (g) | 22 16842.0 (7360.9) | 12552.5 (4378.8) | 429.6 (1221.7–7357.5) 0.008 | 350.6 (1734.1–2435.3) 0.729 |
| Whole-body lean (g) | 22 41513.3 (8325.9) | 37276.4 (7729.6) | 4236.9 (4192.8–8054.7) 0.031 | –178.0 (–2279.5 to 1923.5) 0.861 |
| Whole-body percentage fat (%) | 22 27.7 (7.1) | 25.0 (6.2) | 2.8 (–1.3 to 6.9) 0.175 | –0.2 (–4.1 to 3.8) 0.932 |

Significance is reached at p ≤ 0.05. T1DM = type 1 diabetes mellitus.
<sup>a</sup>Unadjusted analysis using paired samples t test.
<sup>b</sup>Adjusted for height and weight using mixed effects linear model with pair as random intercept.

Table 3. Comparison of DXA Data for Total Body Less Head, Lumbar Spine, and Pelvis in T1DM and Control Groups and Mean Difference (95% CI) Matched by Age, Gender, and Pubertal Stage After Participants With T1DM <2 years and the Paired Controls Were Excluded

|                      | T1DM Mean (SD) | Control Mean (SD) | Paired difference<sup>a</sup> (T1DM – control) | Paired difference<sup>b</sup> (T1DM – control) |
|----------------------|----------------|------------------|-----------------------------------------------|-----------------------------------------------|
|                      | N              |                  | Mean (95% CI)                                 | p Value                                      |
|                      |                |                  | Mean (95% CI)                                 | p Value                                      |
| Subtotal body Area (cm<sup>2</sup>) | 14 1607.1 (193.9) | 1521.9 (233.5) | 85.2 (–58.0 to 228.4) 0.221 | –57.4 (–153.5 to 38.7) 0.215 |
| Subtotal body BMC (g) | 14 1367.9 (240.2) | 1300.9 (334.5) | 67.0 (–151.8 to 285.8) 0.520 | –112.5 (–266.3 to 41.3) 0.136 |
| Subtotal body BMD (g/cm<sup>2</sup>) | 14 0.846 (0.053) | 0.843 (0.104) | 0.003 (–0.068 to 0.075) 0.919 | –0.033 (–0.094 to 0.027) 0.253 |
| Lumbar spine area (cm<sup>2</sup>) | 14 45.8 (6.7) | 46.5 (8.5) | –0.6 (–7.1 to 5.9) 0.842 | –3.9 (–9.9 to 2.2) 0.191 |
| Lumbar spine BMC (g) | 14 41.9 (10.0) | 41.5 (12.6) | 0.3 (–8.4 to 9.1) 0.932 | –3.9 (–13.1 to 5.2) 0.365 |
| Lumbar spine BMD (g/cm<sup>2</sup>) | 14 0.907 (0.139) | 0.881 (0.161) | 0.025 (–0.073 to 0.123) 0.586 | –0.017 (–0.134 to 0.099) 0.752 |
| Pelvic area (cm<sup>2</sup>) | 14 196.9 (22.8) | 191.6 (44.9) | 5.3 (–21.9 to 32.5) 0.679 | –10.8 (–37.3 to 15.7) 0.390 |
| Pelvic BMC (g) | 14 220.3 (47.0) | 207.6 (70.6) | 12.7 (–31.5 to 57.0) 0.545 | –20.7 (–60.5 to 19.2) 0.279 |
| Pelvic BMD (g/cm<sup>2</sup>) | 14 1.112 (0.160) | 1.062 (0.159) | 0.051 (–0.075 to 0.176) 0.399 | –0.034 (–0.150 to 0.083) 0.538 |
| Whole-body fat (g) | 14 18053.5 (7892.9) | 11701.98 (4528.6) | 6351.5 (2285.8–10417.2) 0.005 | 1178.3 (–2124.0 to 4480.6) 0.449 |
| Whole-body lean (g) | 14 42833.6 (9367.3) | 36803.3 (9159.2) | 6030.3 (4386.6–11622.0) 0.037 | –984.0 (–4313.4 to 2345.4) 0.529 |
| Whole-body percentage fat (%) | 14 28.6 (7.2) | 24.0 (6.9) | 4.6 (–1.0 to 10.2) 0.101 | 1.5 (–4.6 to 7.7) 0.595 |

Significance is reached at p ≤ 0.05. N = Number of matched pairs; T1DM = type 1 diabetes mellitus.
<sup>a</sup>Unadjusted analysis using paired samples t test.
<sup>b</sup>Adjusted for height and weight using mixed effects linear model with pair as random intercept.
Trabecular Von Mises stress (MPa)  20 5.22 1.04 5.43 0.74

Endosteal perimeter (mm)  20 60.3 7.2 63.3 8.5

Stiffness (kN/mm)  20 71.3 44.5 67.2 19.9 4.2

Cortical porosity  20 0.036 0.018 0.043 0.019

Trabecular bone number (1/mm)  20 2.14 0.23 2.21 0.17

Trabecular BV/TV  19 0.140 0.027 0.157 0.032

Total bone area (cm²)  20 27.0 12.0 24.3 12.9 2.7

Trabecular bone density (mg/cm³)  20 3.58 1.85 3.46 0.95 0.12

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Mean SD Mean SD Mean (95% CI)  p Value

Discussion

We hypothesized that changes in bone microarchitecture and strength occur in adolescents with T1DM, and these changes precede changes in DXA-derived bone parameters.

In our study, we compared adolescents with T1DM with age-, sex-, and pubertal stage-matched controls, thus accounting for differences in physiological maturity at the same age. We did not observe differences in BA, BMC, and BMD at the total body (less head), lumbar spine, and pelvic sites. Our results thus support other studies that have shown no differences in total body and regional BMD in patients with T1DM compared with healthy controls. However, in contrast, some studies have shown a reduction in BMD. Inconsistencies between studies using DXA are related to the age of the population and the challenges with using areal bone density to assess bone mass and fracture risk, which inherently under- and overestimate bone mass in smaller and taller children, respectively.

To our knowledge, this is the first study using HRpQCT to look at skeletal microarchitecture in adolescents with T1DM. HRpQCT provides high-resolution in vivo bone biopsy, giving insight into the microarchitectural parameters and integrity of cortical and trabecular compartments. Moreover, HRpQCT provides relevant information about skeletal integrity and strength, albeit at the distal appendicular skeleton. We provide evidence for reduced bone strength at the distal radius and tibia of adolescents with T1DM, demonstrating a 6.2% mean reduction in load-bearing at the distal surface of trabecular bone in the radius and 5.2% and 5.0% mean reduction in load-bearing on the distal and proximal surface of tibial trabecular bone respectively, compared with healthy controls. Following subanalysis in children who had T1DM for >2 years, the reduction in load-bearing at the distal surface of tibial trabecular load in the T1DM group was no longer present. Conversely, in the same subanalysis, a reduced trabecular bone number, increased trabecular separation, and increased trabecular inhomogeneity was observed at the radius with a 9.7% reduction in the trabecular load at the distal surface of tibial trabecular bone respectively, compared with healthy controls. Following subanalysis in children who had T1DM for >2 years, the reduction in load-bearing at the distal surface of tibial trabecular load in the T1DM group was no longer present. Conversely, in the same subanalysis, a reduced trabecular bone number, increased trabecular separation, and increased trabecular inhomogeneity was observed at the radius with a 9.7% reduction in the trabecular load at the distal surface of tibial trabecular bone respectively, compared with healthy controls. Following subanalysis in children who had T1DM for >2 years, the reduction in load-bearing at the distal surface of tibial trabecular load in the T1DM group was no longer present. Conversely, in the same subanalysis, a reduced trabecular bone number, increased trabecular separation, and increased trabecular inhomogeneity was observed at the radius with a 9.7% reduction in the trabecular load at the distal surface of tibial trabecular bone respectively, compared with healthy controls. Following subanalysis in children who had T1DM for >2 years, the reduction in load-bearing at the distal surface of tibial trabecular load in the T1DM group was no longer present. Conversely, in the same subanalysis, a reduced trabecular bone number, increased trabecular separation, and increased trabecular inhomogeneity was observed at the radius with a 9.7% reduction in the trabecular load at the distal surface of tibial trabecular bone respectively, compared with healthy controls. Following subanalysis in children who had T1DM for >2 years, the reduction in load-bearing at the distal surface of tibial trabecular load in the T1DM group was no longer present. Conversely, in the same subanalysis, a reduced trabecular bone number, increased trabecular separation, and increased trabecular inhomogeneity was observed at the radius with a 9.7% reduction in the trabecular load at the distal surface of tibial trabecular bone respectively, compared with healthy controls.
The variability of the bone were thus identified in bone turnover markers in children with T1DM, despite architectural changes in childhood. Previously observed alterations in bone mass and increased fracture risk observed in adults with T1DM. We speculate that the consistently observed reduction in bone mass, despite no observable change in total body or regional BMD.

Physiologically significant. T1DM may have a more profound impact on the radius and thus, nonload-bearing bone and this finding may in part explain the increased fracture risk observed in adults with T1DM. Moreover, radial and tibial bone and bone area were lower in children with T1DM, although these differences were not significant in the analysis.

Alterations in the bone microarchitecture and loading properties of the bone were thus identified in adolescents with T1DM despite no observable change in total body or regional BMD. We speculate that the consistently observed reduction in bone mass and increased fracture risk, observed in adults with T1DM may be preceded and explained by more subtle skeletal microarchitectural changes in childhood. Previously observed alterations in bone turnover markers in children with T1DM, despite no significant differences in bone density, appear to support this finding, and with our data collectively suggest that the decline in skeletal quality in children with T1DM may begin in childhood.

To ensure that the significant changes in bone parameters identified between the two groups were not caused by changes in body composition, we assessed the impact of whole-body fat mass and lean mass on HRpQCT and mFEA parameters that were significantly different between the two groups to determine the effect of body composition on these differences (data not included). We analyzed the effect of an increase per 100 grams of fat and lean mass and an increase in 1% fat mass and lean mass on each of the parameters for the diabetic group, and then adjusted the data for age and sex. Moreover, we performed a sensitivity analysis to ensure outliers did not skew the results. We found that in children with T1DM, whole-body fat mass, percentage fat mass, and percentage lean mass were positively correlated with trabecular thickness at the radius following adjustment for age and sex. Further, an increase in percentage fat mass was also correlated with an increase in trabecular load at the distal radius. Body composition was not correlated with the relevant bone parameters at the tibia. In addition, as there was no difference in fat and lean mass observed between our cohorts, we surmise that the differences in bone parameters observed between the two groups are unlikely to be caused by changes in body composition in patients with T1DM.

In our study, at least at the tibia, a reduction in bone strength may be related to glycemic control. This concurs with other studies showing the negative impact of poor glycemic control on bone.

Our initial logistic regression analysis suggested that the duration of DM may be related to changes in tibial microarchitectural properties; however, this relationship disappeared after adjusting for age and gender. This is in agreement with other studies.

In adult patients with T1DM, no differences in HRpQCT parameters were identified between T1DM patients without the presence of microvascular disease and healthy controls. However, T1DM patients with established microvascular changes showed lower total, trabecular, and cortical volumetric BMD, thinner radial cortex, and lower total and trabecular vBMD
Table 6. Comparison of HRpQCT Cortical, Trabecular, and mFEA Tibial Parameters Between T1DM and Control Children Matched for Age, Pubertal Stage, and Gender Calculated by Paired t Tests—Mean Difference (95% CI)

| Tibial HRpQCT parameters | T1DM                | Control              | Paired difference (T1DM – control) |
|--------------------------|---------------------|----------------------|-------------------------------------|
| N                        | Mean    | SD     | Mean    | SD     | Mean (95% CI) | p Value |
| Total bone area (cm³)    | 20      | 838.5  | 175.3   | 906.0  | 147.9          | -67.5 (-149.0 to 14.1) | 0.100 |
| Total bone density (mg/cm³) | 20     | 240.5  | 45.7    | 237.3  | 33.1           | 3.2 (–20.1 to 26.6)   | 0.777 |
| Cortical bone area (cm³) | 20      | 58.2   | 43.9    | 47.1   | 29.3           | 11.1 (–4.8 to 27.1)   | 0.160 |
| Cortical bone density (mg/cm³) | 20    | 680.2  | 123.2   | 650.5  | 105.7          | 29.7 (–9.9 to 69.4)   | 0.133 |
| Cortical bone thickness (mm) | 20    | 0.550  | 0.451   | 0.413  | 0.292          | 0.137 (–0.022 to 0.295) | 0.088 |
| Cortical bone perimeter (mm) | 20    | 114.3  | 13.8    | 119.3  | 11.3           | –4.9 (–10.9 to 1.1)   | 0.101 |
| Cortical porosity | 20      | 0.045  | 0.021   | 0.048  | 0.019          | –0.003 (–0.014 to 0.007) | 0.473 |
| Periosteal perimeter (mm) | 20     | 120.6  | 19.2    | 125.8  | 16.0           | –5.2 (–12.5 to 2.0)   | 0.146 |
| Endosteal perimeter (mm)  | 20      | 108.7  | 14.1    | 114.0  | 12.0           | –5.4 (–11.4 to 0.6)   | 0.077 |
| Trabecular bone area (cm³) | 20     | 761.1  | 195.1   | 836.4  | 155.6          | –75.3 (–161.5 to 10.8) | 0.083 |
| Trabecular bone density (mg/cm³) | 20    | 184.3  | 24.0    | 197.6  | 24.4           | –13.3 (–28.9 to 2.2)  | 0.089 |
| Trabecular bone number (1/mm) | 20    | 2.21   | 0.30    | 2.18   | 0.39           | 0.04 (–0.13 to 0.20)  | 0.649 |
| Trabecular thickness (mm) | 20      | 0.070  | 0.009   | 0.075  | 0.009          | –0.005 (–0.010 to –0.001) | 0.029 |
| Trabecular separation (mm) | 20     | 0.391  | 0.062   | 0.386  | 0.060          | 0.005 (–0.025 to 0.035) | 0.732 |
| Trabecular inhomogeneity | 20      | 0.157  | 0.03    | 0.164  | 0.037          | –0.007 (–0.025 to 0.011) | 0.440 |
| Stiffness (kN/mm) | 20      | 195.3  | 27.9    | 207.5  | 37.1           | –12.2 (–31.2 to 6.8)  | 0.194 |
| Estimated failure load (kN) | 20     | 10.04  | 1.35    | 10.66  | 1.83           | –0.62 (–1.55 to 0.32) | 0.185 |
| (Tb.F/TF) distal (percentage of load carried by trabecular bone at distal surface) | 20     | 72.4   | 12.3    | 77.6   | 8.1            | –5.2 (–9.2 to –1.2)   | 0.013 |
| (Tb.F/TF) proximal (percentage of load carried by trabecular bone at proximal surface) | 20     | 54.7   | 14.1    | 59.7   | 9.6            | –5.0 (–9.8 to –0.1)   | 0.047 |
| Trabecular Von Mises stress (MPa) | 20    | 5.60   | 0.58    | 5.73   | 0.57           | –0.13 (–0.41 to 0.15) | 0.355 |
| Cortical Von Mises stress (MPa) | 20    | 8.09   | 0.68    | 8.02   | 0.55           | 0.07 (–0.17 to 0.31)  | 0.530 |

Significance is reached at p ≤ 0.05. BV/TV = bone volume fraction; N = number of matched pairs; mFEA = microfinite element analysis; T1DM = type 1 diabetes mellitus; Tb.F/TF = ratio of the load taken by the trabecular bone in relation to the total load.

At the tibia.(27) Despite this, no differences were observed in bone strength. Differences in the microarchitectural findings between adolescents and adults with T1DM, may in part relate to the impact of T1DM during skeletal development. Adolescence is a period of significant bone mass accrual and increased bone strength.(36) Thus, the impact of T1DM may differ during phases of skeletal development and maturity.

Multiple mechanisms by which T1DM may cause impaired bone turnover and mineralization have been proposed.(31) Our study showed that T1DM had a negative impact on the trabecular compartment at the radius and tibia, with others showing deterioration in the cortical bone compartment.(16,17,27) Insulin has an anabolic effect on bone by stimulating osteoblast differentiation in the bone marrow; thus, reduction in insulin may impair bone formation at a critical time of peak bone mass accrual.32,33 Adolescents with T1DM have lower osteocalcin and insulin-like growth factor 1 levels, factors that are important in skeletal development.(34) Production of advanced end glycosylation products secondary to chronic hyperglycemia have also been implicated in causing impaired bone formation.(35,36) T1DM also may also impair osteocyte function through its impact on sclerostin expression.(32,36,37)

Adolescents with T1DM were heavier and had a higher BMI compared with the healthy controls in our study. This corresponds with data from the National Pediatrics Diabetes Audit(38) showing a trend for higher BMI in children with T1DM. It could be postulated that the higher weight and BMI has led to skeletal microarchitectural deterioration rather than T1DM, as obesity has been associated with an increased risk of fractures and change in skeletal microarchitecture in children.(39,40) However, the mean BMI in our T1DM cohort was within the normal range for age. Although obesity has been recognized as a risk factor for fractures, increased fat mass that is not excessive could have a positive impact on skeletal development.(40) There was also no significant difference in fat and lean mass or percentage body fat between T1DM participants and paired controls in our group after adjustment for height and weight, and we further showed that the differences in trabecular parameters between our groups could not be explained by differences in fat or lean mass. Therefore, the deterioration in bone microarchitecture seen in our adolescents with T1DM cannot be explained by the higher BMI alone.

There were several limitations to our study. This was a small pilot study; thus, our ability to detect other differences in skeletal microarchitectural and integrity between the groups was limited. Studying a larger population of adolescents and children with T1DM using HRpQCT could further define the relationship between skeletal microarchitecture and duration of DM, age of onset, and glycemic control. Although we detected no significant differences in fat and lean mass between both groups and we also corrected for height and weight to remove these measures as confounding factors, matching for BMI in addition to age, gender, and pubertal stage would potentially preclude the impact of body composition skeletal microarchitecture. We recognize that the measures of bone strength using finite element analysis represent proxies of bone strength and cannot replace...
Table 7. Comparison of HRpQCT Cortical, Trabecular, and mFEA Tibial Parameters Between T1DM and Control Children (With Participants With T1DM of Duration <2 years and Their Pairs Controls Excluded) Matched for Age, Pubertal Stage, and Gender Calculated by Paired t Tests – Mean Difference (95% CI)

| Tibial HRpQCT parameters                          | T1DM Mean (SD) | Control Mean (SD) | Paired difference (T1DM – control) (Mean (95% CI)) | p Value |
|---------------------------------------------------|----------------|-------------------|----------------------------------------------------|---------|
| Total bone area (cm$^3$)                          | 13 803.3 (162.1) | 13 889.4 (155.1)  | -86.1 (–193.5 to 21.3)                              | 0.106   |
| Total bone density (mg/cm$^3$)                     | 13 242.9 (55.9)  | 13 235.2 (37.2)   | 7.7 (–28.8 to 44.2)                                | 0.655   |
| Cortical bone area (cm$^3$)                        | 13 67.8 (49.8)   | 13 52.8 (30.9)    | 15.0 (–10.3 to 40.4)                               | 0.221   |
| Cortical bone density (mg/cm$^3$)                  | 13 700.8 (128.3) | 13 667.7 (110.6)  | 33.1 (–29.9 to 96.1)                               | 0.275   |
| Cortical bone thickness (mm)                       | 13 0.648 (0.500) | 13 0.486 (0.312)  | 0.180 (–0.071 to 0.431)                            | 0.144   |
| Cortical bone perimeter (mm)                       | 13 111.9 (13.2)  | 13 117.8 (12.0)   | -5.8 (–14.0 to 2.3)                                | 0.145   |
| Cortical porosity                                  | 13 0.045 (0.025) | 13 0.048 (0.022)  | 0.004 (–0.019 to 0.012)                            | 0.635   |
| Trabecular bone area (cm$^3$)                      | 13 719.1 (185.9) | 13 816.6 (162.6)  | -97.5 (–213.7 to 18.64)                            | 0.092   |
| Trabecular bone density (mg/cm$^3$)                | 13 177.3 (30.0)  | 13 190.6 (23.5)   | -13.3 (–36.5 to 9.9)                               | 0.235   |
| Meta trabecular density (mg/cm$^3$)                | 13 222.2 (37.6)  | 13 235.5 (26.7)   | -13.3 (–43.0 to 16.4)                              | 0.348   |
| Inner trabecular density (mg/cm$^3$)               | 13 146.8 (22.5)  | 13 160.2 (25.9)   | -13.4 (–35.2 to 8.4)                               | 0.206   |
| Meta TB/inner TB                                   | 13 1.54 (0.33)   | 13 1.49 (0.18)    | 0.05 (–0.13 to 0.23)                               | 0.588   |
| Trabecular BV/TV                                   | 13 0.148 (0.019) | 13 0.159 (0.020)  | -0.011 (–0.030 to 0.008)                           | 0.234   |
| Trabecular bone number (1/mm)                      | 13 2.15 (0.23)   | 13 2.06 (0.37)    | 0.10 (–0.13 to 0.32)                               | 0.365   |
| Trabecular thickness (mm)                          | 13 0.069 (0.010) | 13 0.076 (0.009)  | -0.007 (–0.013 to 0.001)                           | 0.029   |
| Trabecular separation (mm)                         | 13 0.402 (0.046) | 13 0.405 (0.058)  | -0.003 (–0.041 to 0.034)                           | 0.861   |
| Trabecular inhomogeneity                           | 13 0.163 (0.028) | 13 0.177 (0.037)  | -0.014 (–0.038 to 0.010)                           | 0.237   |
| Stiffness (kN/mm)                                  | 13 194.3 (27.7)  | 13 205.3 (40.3)   | -10.9 (–40.6 to 18.7)                              | 0.437   |
| Estimated failure load (kN)                        | 13 9.95 (1.24)   | 13 10.47 (1.97)   | -0.52 (–1.96 to 0.93)                              | 0.542   |
| (Tb.F/TF) distal                                   | 13 70.2 (11.7)   | 13 75.4 (8.3)     | -5.2 (–10.7 to 0.3)                                | 0.062   |
| (Tb.F/TF) proximal                                 | 13 53.2 (14.0)   | 13 56.8 (9.5)     | -3.6 (–10.2 to 2.9)                                | 0.249   |
| Trabecular Von Mises stress (MPa)                   | 13 5.61 (0.62)   | 13 5.76 (0.54)    | -0.14 (–0.54 to 0.26)                              | 0.446   |
| Cortical Von Mises stress (MPa)                     | 13 8.20 (0.67)   | 13 8.15 (0.52)    | 0.05 (–0.30 to 0.40)                               | 0.766   |
| Periosteal perimeter (mm)                          | 13 116.5 (17.4)  | 13 122.8 (15.9)   | -6.3 (–16.0 to 3.3)                                | 0.179   |
| Endosteal perimeter (mm)                           | 13 106.0 (13.2)  | 13 112.5 (12.5)   | -6.5 (–14.5 to 1.6)                                | 0.104   |

Significance is reached at $p \leq 0.05$. BV/TV = bone volume fraction; $N$ = number of matched pairs; mFEA = microfinite element analysis; T1DM = type 1 diabetes mellitus; TB = Meta TB/inner TB = meta-to-inner trabecular density; Tb.F/TF = ratio of the load taken by the trabecular bone in relation to the total load.

ex-vivo bone strength analysis. However, FEA is a well-recognized process in engineering to assess material properties; our results thus provide insight into the potential impact of T1DM on skeletal strength. The rate of fractures in our population is higher than reported in previous studies; this may have resulted from an unconscious bias in families of participants who volunteered to be part of the study. Finally, as HRpQCT measures bone strength and microstructure of the ultradistal radius and tibia, we are unable to confirm whether the alterations observed in adolescents with T1DM reflect changes in other parts of the appendicular and axial skeleton. However, accounting for the limitations, we have found significant detrimental changes in the trabecular microarchitecture and bone strength proxies in adolescents with T1DM. Thus, we affirm our hypothesis that detrimental changes in bone microarchitecture and proxies in bone strength are seen in adolescents with T1DM, despite no significant changes in DXA-derived bone mass.

**Conclusion**

T1DM is associated with a reduction in the trabecular thickness in the tibia, and alterations in the loading properties at the ultradistal radius and tibia in adolescents with T1DM, despite there being no significant reduction in BMD. Alterations in radial trabecular microarchitecture were seen in participants who have had T1DM for at least 2 years, with no corresponding changes in BMD. Poor glycemic control was associated with a reduction in bone strength. Thus, in earlier life, bone microarchitecture and strength, rather than bone density, may better explain the increased risk of fracture observed in adults with T1DM.

**Disclosures**

None of the authors have a conflict of interest.

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Authors’ roles: Study Design: PD, JD. Study Conduct: JD, PD. Data Collection: CC, MP, JD. Data Analysis: RJ, MP, JD. Data Interpretation: RJ, JD. Manuscript Draft: JD. Manuscript Revision: PD, JD. Final Version Approved By: PD, JD. JD and PD take responsibility for the integrity of the data analysis.

**AUTHOR CONTRIBUTIONS**

Richard Jacques: Formal analysis; resources; software; validation. Margaret Paggiosi: Data curation; investigation; resources; software. Carolyn Clark: Formal analysis; funding acquisition; methodology; project administration. Paul Dimitri: Conceptualization; formal analysis; funding acquisition; project administration; resources;...
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