Cortical Bone Size Deficit in Adult Patients With Type 1 Diabetes Mellitus

Charlotte Verroken,[1,2] Wout Pieters,[1,2] Loïc Beddeleem,[1,2] Stefan Goemaere,[1] Hans-Georg Zmierczak,[1] Samyah Shadid,[2] Jean-Marc Kaufman,[1,2] and Bruno Lapauw[1,2]

[1]Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital, 9000 Ghent, Belgium; and [2]Department of Endocrinology, Ghent University Hospital, 9000 Ghent, Belgium

Context: The increased fracture risk associated with type 1 diabetes mellitus (T1DM) remains unexplained by traditional risk factors such as low areal bone mineral density (aBMD). Nonetheless, few data exist on other determinants of bone strength in T1DM, including volumetric bone mineral density (vBMD) and bone geometry.

Objective: We compared areal and volumetric bone parameters and cortical bone geometry in adult T1DM patients and sex- and age-matched controls.

Design: Cross-sectional study including 64 adult T1DM patients (38 men; mean age, 41.1 ± 8.1 years) and 63 sex- and age-matched controls.

Main Outcome Measures: Areal bone parameters using dual-energy X-ray absorptiometry; volumetric bone parameters and cortical bone geometry using peripheral quantitative computed tomography.

Results: T1DM was associated with lower aBMD at the total body, femoral neck, and total hip; lower trabecular vBMD at the distal radius; and higher cortical but lower total vBMD at the radial shaft. In addition, subjects with T1DM had a similar periosteal but larger endosteal circumference, smaller cortical thickness, and lower cortical over total bone area ratio. Differences in bone parameters could not be explained by differences in bone turnover markers or body composition, but cortical area was inversely associated with glycemic variability and long-term glycemic control.

Conclusions: Besides decreased aBMD and trabecular vBMD, adult T1DM patients present with a cortical bone size deficit, which may contribute to their increased fracture risk. This deficit is mainly situated at the endosteal envelope, suggesting imbalanced remodeling rather than compromised modeling processes as the underlying mechanism. (***J Clin Endocrinol Metab*** **102: 2887–2895, 2017)**

Osteoporosis and its related fractures remain a major health problem, leading to increased morbidity and mortality in both men and women. Besides conditions such as rheumatoid arthritis and hypogonadism, type 1 diabetes mellitus (T1DM) is now recognized as another risk factor for developing osteoporosis. Indeed, the overall fracture risk in subjects with T1DM has been estimated to be about threefold higher than in a general population (1), whereas their risk of hip fractures is about sevenfold increased compared with nondiabetic subjects (2, 3). Moreover, the observed fracture incidence in patients with T1DM is much higher than expected based

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; aBMD, areal bone mineral density; BMD, bone mineral density; BMC, bone mineral content; CGM, continuous glucose monitoring; CSA, cross-sectional area; CTX, C-terminal telopeptide of type 1 collagen; CV, coefficient of variation; DXA, dual-energy X-ray absorptiometry; HbA1c, glycated hemoglobin; HR-pQCT, high-resolution peripheral quantitative computed tomography; IGF-1, insulinlike growth factor 1; MRI, magnetic resonance imaging; MVD, microvascular disease; P1NP, procollagen type 1 *N*-terminal propeptide; pQCT, peripheral quantitative computed tomography; PTH, parathyroid hormone; SD, standard deviation; T1DM, type 1 diabetes mellitus; vBMD, volumetric bone mineral density.

on their moderately reduced areal bone mineral density (aBMD) (3), suggesting that other factors might be responsible for the increased fracture risk in T1DM. On the one hand, certain indirect factors may play a role, including an increased fall risk because of diabetic complications and treatment-induced hypoglycemia. On the other hand, T1DM may be associated with an increased bone fragility which is not entirely captured by traditional dual-energy X-ray absorptiometry (DXA) measurements.

Besides by bone mass, the strength of a bone is importantly determined by its material and structural properties. However, data on these parameters in subjects with T1DM are scarce and inconclusive. Deficits in trabecular microarchitecture were reported in adult women with childhood-onset T1DM using magnetic resonance imaging (MRI) at the proximal tibia (4), and in T1DM patients with microvascular disease (MVD) using high-resolution peripheral quantitative computed tomography (HR-pQCT) at the ultradistal radius and tibia (5), whereas another study found no differences in histomorphometric and microcomputed tomography analyses of transiliac biopsies (6). Studies investigating bone geometry using peripheral quantitative computed tomography (pQCT) have mainly been performed in pediatric and adolescent populations. These studies generally showed a smaller cortical area in children or adolescents with T1DM vs controls (7–9), whereas the smaller trabecular area reported by some studies could not be confirmed in others (7, 9, 10). Although one longitudinal study suggested that trabecular and cortical bone size deficits in adolescent T1DM patients persist over time (11), data on cortical bone geometry in adult patients with T1DM are lacking.

This study aimed to compare areal and volumetric bone parameters, bone geometry, and possible mediators thereof in adult individuals with T1DM and sex- and age-matched controls. In addition, because T1DM is considered a condition of impaired bone turnover, bone turnover markers were measured and related to bone density and geometry.

Methods

Study population

Sixty-four adult patients with T1DM were recruited from the outpatient clinic of the Endocrinology Department at the Ghent University Hospital. Patients were eligible for inclusion if they had a diagnosis of T1DM with a disease duration of at least 7 years, and no known macrovascular disease. Data on medication use, the presence of MVD, and glycated hemoglobin (HbA1c) levels were extracted from the patient's electronic health record. Patients were classified as having MVD if diabetic retinopathy (diagnosed by an ophthalmologist based on retinal examination) and/or diabetic nephropathy (urinary albumin/creatinine ratio >30 mg/g in two out of three random voided urine samples) and/or diabetic neuropathy (based on electromyography) were present. Mean HbA1c over the last 5 years was calculated if at least three measurements were available (n = 63; mean number of available measurements, 9.7 $\pm$ 3.0), with HbA1c variability defined as the standard deviation (SD) of these measurements. Immediately after the study visit, patients started wearing a continuous glucose monitoring (CGM) device (DexCom G4 Platinum; DexCom, San Diego, CA) from which short-term glycemic variability (defined as the SD of glucose levels over a 7-day period) was evaluated. During this 7-day period, patients were asked to maintain their normal activity pattern and were blinded to the results of the CGM. Patients were matched based on age and sex with 63 nondiabetic control subjects. Male controls were selected from a previously studied male sibling-pair cohort, recruited from semirural communities around Ghent, Belgium (12). Female controls were selected from a previously studied female control cohort, recruited by poster campaign at the Ghent University Hospital, on its Web site, and in schools (13). Exclusion criteria for the control subjects were defined as illnesses or medication use known to affect body composition, hormone levels, or bone metabolism. In women, a history of menstrual irregularities, hirsutism, or polycystic ovarian syndrome were additional exclusion criteria. The study protocol was approved by the ethical committee of the Ghent University Hospital, and written informed consent was obtained from all participants.

Anthropometry, areal bone parameters, and whole-body soft tissue composition

Body weight was measured to the nearest 0.1 kg in light indoor clothing without shoes. Standing height was measured to the nearest 0.1 cm using a wall-mounted Harpenden stadiometer (Holtain Ltd., Crymuch, UK). Areal bone parameters [including bone mineral content (BMC), bone area, and aBMD at the whole body minus head, lumbar spine, femoral neck, and total hip region] and whole-body soft tissue composition (including total body lean and fat mass) were measured using DXA with a Hologic QDR-4500A device (software version 11.2.1; Hologic, Bedford, MA). The coefficients of variation (CVs) for both spine and whole-body calibration phantoms were $<1\%$ for aBMD and $<3\%$ for BMC as calculated from daily and weekly phantom measurements, respectively.

Volumetric bone parameters, bone geometry, and regional soft tissue composition

Volumetric bone parameters, bone geometry, and regional soft tissue composition were determined at the radius using a pQCT device (XCT-2000; Stratec Medizintechnik, Pforzheim, Germany). Trabecular bone area, BMC, and volumetric bone mineral density (vBMD) were measured at the distal radius (4% of bone length from the distal end); cortical bone area, BMC, and vBMD as well as bone geometry and regional soft tissue composition were measured at the radial shaft (66% of bone length from the distal end). Imaging and the calculation of numerical values were performed using the manufacturer's software package (version 5.4). The cross-sectional area (CSA) of the radius was determined after detecting the outer bone

contour at a threshold of 280 mg/cm^3. By default, 55% of this bone CSA was peeled off to separate trabecular bone from the cortical shell at the distal radius. For determining cortical vBMD, the threshold was set at 710 mg/cm^3; for trabecular bone, the threshold was set at 180 mg/cm^3. Periosteal and endosteal circumference and cortical thickness were estimated using a circular ring model, with cortical thickness as the difference between the outer and inner radius. The cortical over total bone area ratio (%) was calculated as cortical bone area divided by total bone area. Polar strength-strain index was calculated as previously described (14). Muscle and fat CSA surrounding the bone were estimated using a threshold below water equivalent linear attenuation set at 0.22/cm. The cortical bone over muscle area ratio (%) was calculated as cortical bone area divided by muscle CSA. Bone marrow density was estimated using a threshold set at 100 mg/cm^3, with lower values indicating a higher marrow fat content. The CV for the calibration phantom was <1% as calculated from daily phantom measurements.

Biochemical measurements

Venous blood samples were obtained after an overnight fast. Serum samples were stored at −80° until batch analysis. C-terminal telopeptide of type 1 collagen (CTX), procollagen type 1 *N*-terminal propeptide (P1NP), intact parathyroid hormone (PTH), and 25-hydroxyvitamin D [25(OH)D] were measured using electrochemiluminescence immunoassays (Roche Diagnostics, Mannheim, Germany). Intra- and inter-assay CVs were 0.7% and 8.5% at 183 μg/L for P1NP, and 1.1% and 3.8% at 1.15 μg/L for CTX.

Statistics

Descriptive statistics are expressed as mean ± SD or median (first to third quartile) if criteria for normality were not fulfilled. Visual inspection of histograms and quantile-quantile plots and Shapiro-Wilk tests were performed to assess normality. Nonnormally distributed variables were log-transformed to meet required model assumptions. Differences in general characteristics between subjects with T1DM and their matched controls were evaluated using paired *t* tests (for age, height, weight, and BMI), Wilcoxon matched-pairs signed-rank test (for alcohol intake), or McNemar test (for smoking behavior; categorized as current smoker vs nonsmoker). Unless stated otherwise, between-group differences in bone variables were assessed using multivariate linear regression analysis with adjustment for age, height, weight, and sex. To investigate whether between-group differences in bone variables differed according to sex, an interaction term between sex and health status (T1DM or control) was added to the models. In case of a statistically significant interaction, age-, height-, and weight-adjusted between-group differences were evaluated separately for men and women. Women taking oral contraceptives (n = 7) were excluded from analyses involving bone turnover markers. In subjects with T1DM, associations between disease characteristics and bone variables were assessed using multivariate linear regression analysis with adjustment for age, height, weight, and sex. All analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY). *P* values were considered significant at values <0.05; all tests were two-tailed.

Results

Characteristics of the study population

General characteristics of the study population and disease-related parameters of the subjects with T1DM are summarized in Table 1. Both the T1DM and control groups included 38 men, accounting for 59.8% of the study population. Participants were between 22 and 60 years old, and no differences in height, weight, or BMI were observed between subjects with T1DM and their respective controls. Alcohol intake was lower [2 (1 to 6) vs 5 (2 to 14) units per week, $P = 0.002$], whereas the number of current smokers was nonsignificantly higher (25.0% vs 12.7%, $P = 0.078$) in the T1DM group. Seven premenopausal women with T1DM used oral contraceptives compared with none of the control women. In the T1DM group, six participants used a vitamin D and two used a calcium supplement. Age at diagnosis of T1DM ranged from 1 to 41 years; 39 subjects (61.9%) were ≤20 years at diagnosis. Current metabolic control ranged from good to poor with HbA1c values between 6.4% and 9.9%. Thirty-seven patients (57.8%) were classified as having MVD, including 27 (42.2%) with diabetic retinopathy, 22 (34.4%) with nephropathy, and 14 (21.1%) with neuropathy. None of the participants had an estimated glomerular filtration rate <60 mL/min/1.73 m^2.

Areal and volumetric bone parameters and bone geometry

As shown in Table 2, subjects with T1DM presented with lower BMC and aBMD at the total body (Δ = −9.9% and −9.3%, respectively), the femoral neck (Δ = −8.7% and −8.5%), and the total hip (Δ = −5.0% and −5.3%). In addition, T1DM was associated with a 0.9% smaller bone area at the total body, whereas no differences in DXA measurements were observed at the spine. For BMC and aBMD at the total body, a significant interaction existed between health status and sex ($P = 0.002$ and $P < 0.001$, respectively), with greater bone deficits in men (Δ = −12.5% for BMC and −13.2% for aBMD, both $P < 0.001$) than in women (Δ = −8.2%, $P = 0.001$ for BMC; Δ = −4.6%, $P = 0.006$ for aBMD) with T1DM compared with controls. No interactions between health status and sex were observed at the femoral neck, total hip, or spine.

Differences in pQCT-derived volumetric and geometric bone parameters in subjects with vs without T1DM are summarized in Table 3 and Fig. 1. At the distal radius, subjects with T1DM presented with a 10.4% larger trabecular area but 8.8% lower trabecular vBMD compared with controls. A significant interaction between health status and sex was observed for trabecular

Table 1. General Characteristics of the Study Population, Bone Turnover Markers, and Disease-Related Parameters in Subjects With T1DM

	All			Men		Women	
	T1DM (n = 64)	Control (n = 63)	*P*	T1DM (n = 38)	Control (n = 38)	T1DM (n = 26)	Control (n = 25)
Age, y	41.1 ± 8.1	41.4 ± 8.4	0.005	41.4 ± 8.5	42.2 ± 9.3	40.6 ± 7.6	40.3 ± 6.8
Height, cm	173.5 ± 9.8	172.5 ± 8.3	0.304	179.2 ± 7.1	177.0 ± 6.1	165.3 ± 7.0	165.7 ± 6.4
Weight, kg	76.2 ± 13.4	75.9 ± 10.7	0.946	81.1 ± 12.3	79.5 ± 9.5	68.9 ± 11.8	70.4 ± 10.2
BMI, kg/m^2	25.20 ± 3.34	25.49 ± 3.11	0.421	25.22 ± 3.08	25.42 ± 3.18	25.19 ± 3.75	25.61 ± 3.07
Age at disease onset, y	18.6 ± 9.7	—	n/a	18.9 ± 9.1	—	18.2 ± 10.6	—
Disease duration, y	22.1 ± 8.7	—	n/a	21.9 ± 8.4	—	22.4 ± 9.3	—
HbA1c, %	7.71 ± 0.71	—	n/a	7.82 ± 0.76	—	7.54 ± 0.60	—
Mean glucose level during CGM, mg/dL	160 ± 31	—	n/a	163 ± 33	—	155 ± 28	—
Glycemic variability during CGM, mg/dL	71.4 ± 12.2	—	n/a	69.9 ± 11.5	—	73.5 ± 12.9	—
Mean HbA1c over last 5 y, %	7.9 ± 0.7	—	n/a	8.0 ± 0.7	—	7.7 ± 0.5	—
HbA1c variability over last 5 y, %	0.43 ± 0.27	—	n/a	0.41 ± 0.27	—	0.46 ± 0.28	—
P1NP, μg/L	38.7 (28.9–48.1)	42.6 (35.5–49.5)	0.218	36.3 (29.3–47.7)	42.6 (34.6–47.9)	42.3 (29.0–47.9)	42.8 (36.2–51.2)
CTX, μg/L	0.20 (0.16–0.25)	0.23 (0.12–0.31)	0.940	0.21 (0.16–0.26)	0.29 (0.23–0.34)[a]	0.19 (0.16–0.24)	0.12 (0.10–0.16)[a]
25(OH)D, ng/mL	27.1 (21.2–39.4)	29.8 (21.5–35.9)	0.213	23.8 (19.9–32.7)	31.3 (24.9–36.0)[b]	34.0 (24.6–42.8)	25.3 (19.3–35.9)
PTH, ng/L	34.1 (27.4–42.8)	30.3 (24.7–39.2)	0.187	34.4 (27.6–39.9)	26.9 (20.9–34.1)[a]	34.9 (22.7–46.8)	35.7 (29.0–44.9)

Data are expressed as mean ± SD or median (first to third quartile). *P* values are derived from paired *t* tests (for age, height, weight, and BMI) or from multivariate regression analysis with adjustment for age, height, weight, and sex (for log-transformed bone turnover markers).

Abbreviations: BMI, body mass index; n/a, not applicable.

[a] $P < 0.050$ for sex-specific age-, height-, and weight-adjusted differences in subjects with vs without T1DM (only evaluated in case of statistically significant interaction between sex and health status).

[b] $P < 0.010$ for sex-specific age-, height-, and weight-adjusted differences in subjects with vs without T1DM (only evaluated in case of statistically significant interaction between sex and health status).

area ($P = 0.039$), with a larger area in men ($\Delta = 13.9\%$, $P < 0.001$) but not women ($\Delta = 3.3\%$, $P = 0.482$) with vs without T1DM. At the radial shaft, cortical vBMD was 2.1% higher, whereas total vBMD was 5.0% lower in subjects with T1DM. Furthermore, T1DM was associated with a similar periosteal but 6.1% larger endosteal circumference, a 5.6% smaller cortical thickness, and a 6.0% lower cortical over total bone area ratio, with no significant interactions between health status and sex.

All between-group differences in DXA- and pQCT-derived bone parameters remained significant after additional adjustment for alcohol intake and smoking status, as well as after the exclusion of six postmenopausal women (data not shown).

Bone turnover markers

P1NP, CTX, PTH, and 25(OH)D levels were not different in subjects with T1DM vs controls when the whole study population was considered (Table 1); however, significant interactions between health status and sex were observed for CTX, PTH, and 25(OH)D ($P = 0.001$, $P = 0.018$, and $P = 0.019$, respectively). Further analysis showed that CTX and 25(OH)D levels were lower and PTH levels were higher in male T1DM patients compared with controls ($\Delta = -27.6\%$, $P = 0.023$ for CTX; $\Delta = -24.0\%$, $P = 0.009$ for 25(OH)D; $\Delta = 27.9\%$, $P = 0.017$ for PTH), whereas female T1DM patients presented with higher CTX ($\Delta = 58.3\%$, $P = 0.028$), but no differences in 25(OH)D or PTH ($P = 0.126$ and $P = 0.341$, respectively). After additional adjustment for alcohol intake and smoking status, the difference in PTH levels in men remained significant ($P = 0.003$), whereas other results were somewhat attenuated (CTX: $P = 0.056$ in men and $P = 0.061$ in women; 25(OH)D in men: $P = 0.077$). Additional adjustment for bone turnover, PTH, and 25(OH)D levels did not affect the previously described differences in areal and volumetric bone parameters and bone geometry between subjects with T1DM and controls (data not shown).

Soft tissue composition and bone marrow density

Neither total body lean mass (56.1 ± 11.5 vs 53.7 ± 9.6 kg, $P = 0.707$), fat mass (17.2 ± 6.6 vs 18.0 ± 6.4 kg, $P = 0.733$), or percentage of fat mass (24.0% ± 8.2% vs 25.8% ± 8.3%, $P = 0.198$), nor muscle CSA (3705.9 ± 959 vs 3741 ± 916 mm^2, $P = 0.529$) or fat CSA (1158 ± 564

Table 2. Differences in DXA-Derived Areal Bone Parameters Between Subjects With T1DM and Controls

	All			Men		Women	
	T1DM	Control	*P*	T1DM	Control	T1DM	Control
Whole body							
Area, cm^2	1961.1 ± 228.0	1969.9 ± 177.3	0.002	2081.9 ± 171.1	2070.8 ± 125.8	1766.9 ± 165.9	1848.8 ± 153.6
BMC, g	1819.8 ± 360.6	2005.7 ± 387.8	<0.001	1994.0 ± 322.5	2279.3 ± 275.1[a]	1539.4 ± 212.9	1677.3 ± 202.6[b]
aBMD, g/cm^2	0.919 ± 0.088	1.012 ± 0.119	<0.001	0.953 ± 0.090	1.098 ± 0.087[a]	0.867 ± 0.056	0.909 ± 0.052[b]
Total hip							
Area, cm^2	41.1 ± 7.2	40.9 ± 6.5	0.775	45.5 ± 5.2	45.0 ± 4.5	34.8 ± 4.4	34.7 ± 3.4
BMC, g	39.6 ± 10.4	41.7 ± 10.0	0.022	44.8 ± 9.6	47.2 ± 8.7	32.1 ± 5.8	33.2 ± 4.3
aBMD, g/cm^2	0.956 ± 0.140	1.010 ± 0.128	0.006	0.980 ± 0.151	1.044 ± 0.135	0.922 ± 0.114	0.957 ± 0.099
Femoral neck							
Area, cm^2	5.50 ± 0.54	5.57 ± 0.62	0.143	5.84 ± 0.32	5.95 ± 0.45	5.01 ± 0.39	4.99 ± 0.30
BMC, g	4.31 ± 0.72	4.72 ± 0.83	<0.001	4.56 ± 0.73	5.04 ± 0.83	3.95 ± 0.52	4.22 ± 0.54
aBMD, g/cm^2	0.776 ± 0.143	0.848 ± 0.123	0.001	0.782 ± 0.124	0.848 ± 0.138	0.767 ± 0.169	0.847 ± 0.099
Spine							
Area, cm^2	66.1 ± 8.4	65.0 ± 9.3	0.755	71.0 ± 5.8	69.3 ± 7.3	58.4 ± 5.5	58.5 ± 8.1
BMC, g	67.8 ± 11.6	68.9 ± 11.1	0.200	72.8 ± 11.4	71.5 ± 11.6	59.8 ± 6.5	65.0 ± 9.2
aBMD, g/cm^2	1.025 ± 0.106	1.054 ± 0.117	0.094	1.024 ± 0.118	1.032 ± 0.126	1.026 ± 0.087	1.087 ± 0.095

Data are expressed as mean ± SD. *P* values are derived from multivariate regression analysis with adjustment for age, height, weight, and sex.

[a] $P < 0.001$ for sex-specific age-, height-, and weight-adjusted differences in subjects with vs without T1DM (only evaluated in case of statistically significant interaction between sex and health status).

[b] $P < 0.010$ for sex-specific age-, height-, and weight-adjusted differences in subjects with vs without T1DM (only evaluated in case of statistically significant interaction between sex and health status).

vs 1123 ± 465 mm^2, $P = 0.601$) were different in subjects with vs without T1DM. No interactions were observed between health status and sex. Furthermore, we observed no difference in cortical bone over muscle area ratio (2.45% ± 0.44% vs 2.47% ± 0.40%, $P = 0.793$).

Subjects with T1DM presented with 33.3% lower bone marrow density compared with controls (19.8 ± 7.8 vs 29.7 ± 9.6 mg/cm^3, $P < 0.001$). In all participants, marrow density was positively associated with cortical thickness and cortical over total bone area ratio ($\beta = 0.20$, $P = 0.017$ and $\beta = 0.27$, $P = 0.021$, respectively), and inversely with endosteal circumference ($\beta = -0.19$, $P = 0.021$). Moreover, after additional adjustment for bone marrow density, the differences in endosteal circumference, cortical thickness, and cortical over total bone area ratio between subjects with T1DM and controls lost

Table 3. Differences in pQCT-Derived Volumetric Bone Parameters and Cortical Bone Geometry Between Subjects With T1DM and Controls

	All			Men		Women	
	T1DM	Control	*P*	T1DM	Control	T1DM	Control
Distal radius							
Trabecular vBMD, mg/cm^3	192 ± 37	210 ± 45	0.010	201 ± 35	219 ± 42	178 ± 36	198 ± 48
Trabecular BMC, mg/mm	35.6 ± 10.9	35.2 ± 8.7	0.844	42.1 ± 10.1	39.5 ± 7.5	27.0 ± 7.3	28.6 ± 5.9
Trabecular bone area, mm^2	185.5 ± 40.0	168.1 ± 28.1	<0.001	207.4 ± 30.3	182.1 ± 23.6[a]	151.8 ± 28.0	146.9 ± 20.2
Radial shaft							
Total vBMD, mg/cm^3	683 ± 91	719 ± 83	0.018	675 ± 96	711 ± 77	693.7 ± 85	730 ± 91
Cortical vBMD, mg/cm^3	1136 ± 49	1113 ± 36	0.004	1128 ± 54	1110 ± 33	1148 ± 39	1118 ± 41
Cortical BMC, mg/mm	99.8 ± 19.9	99.8 ± 18.1	0.877	109.6 ± 18.2	108.6 ± 16.7	84.8 ± 11.5	86.5 ± 10.7
Cortical bone area, mm^2	87.8 ± 16.9	89.7 ± 16.2	0.284	96.8 ± 14.4	97.8 ± 14.9	73.8 ± 9.5	77.3 ± 8.5
Cortical/total bone area ratio, %	50.3 ± 8.0	53.5 ± 6.9	0.014	50.2 ± 8.7	53.6 ± 6.7	50.5 ± 6.9	53.5 ± 7.5
Periosteal circumference, mm	47.1 ± 5.5	46.0 ± 4.6	0.115	49.7 ± 4.9	48.0 ± 4.2	43.1 ± 3.9	42.8 ± 3.2
Endosteal circumference, mm	33.3 ± 6.1	31.4 ± 4.8	0.030	35.2 ± 6.3	32.8 ± 4.7	30.3 ± 4.6	29.2 ± 4.3
Cortical thickness, mm	2.20 ± 0.36	2.33 ± 0.32	0.012	2.31 ± 0.38	2.43 ± 0.31	2.02 ± 0.24	2.19 ± 0.28
SSIp, mm^3	357 ± 100	338 ± 101	0.165	412 ± 81	394 ± 88	273 ± 60	255 ± 47

Data are expressed as mean ± SD. *P* values are derived from multivariate regression analysis with adjustment for age, height, weight, and sex.

Abbreviation: SSIp, polar strength-strain index.

[a] $P < 0.001$ for sex-specific age-, height-, and weight-adjusted differences in subjects with vs without T1DM (only evaluated in case of statistically significant interaction between sex and health status).

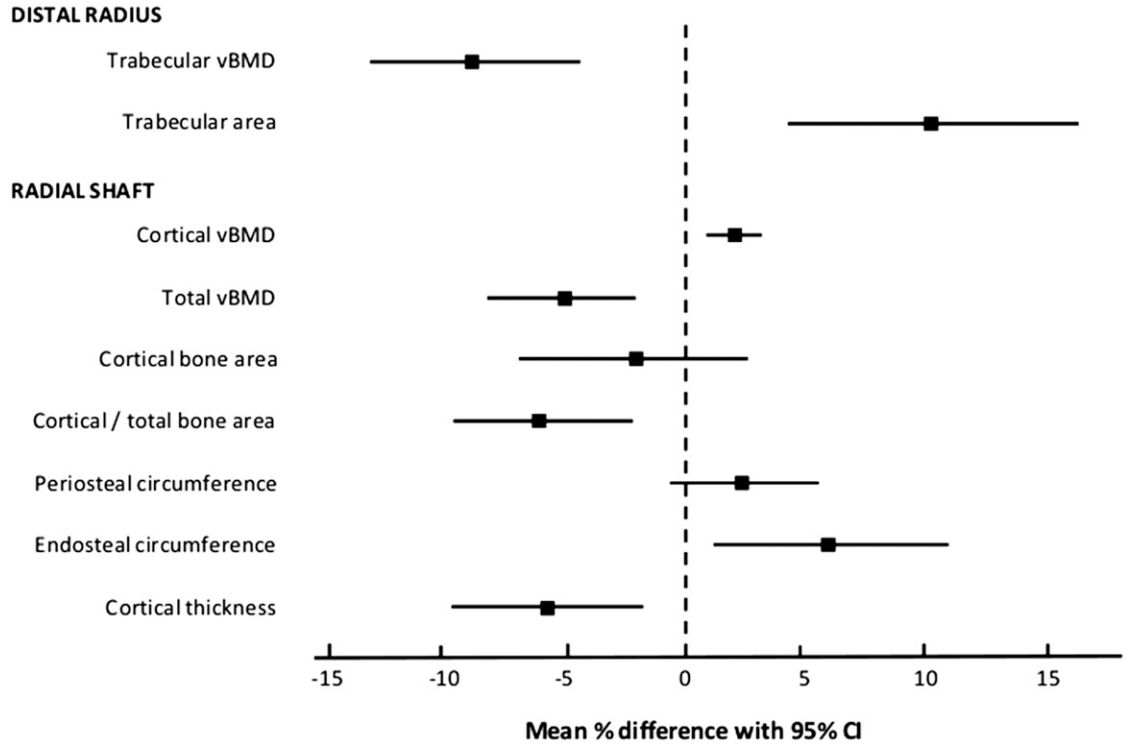

Figure 1. Relative differences in pQCT-derived volumetric and geometric bone parameters in subjects with T1DM vs controls (reference line). CI, confidence interval.

significance (P = 0.251, P = 0.136, and P = 0.258, respectively).

Associations of bone parameters with disease characteristics

Areal or volumetric bone parameters were not associated with disease duration, age of disease onset, current HbA1c, or the presence of MVD (data not shown). Short-term glycemic variability, mean HbA1c over the last 5 years, and HbA1c variability were inversely associated with cortical area (β = −0.24, P = 0.008 for glycemic variability; β = −0.20, P = 0.030 for HbA1c; β = −0.18, P = 0.048 for HbA1c variability) and cortical BMC (β = −0.23, P = 0.021 for glycemic variability; β = −0.19, P = 0.053 for HbA1c; β = −0.19, P = 0.055 for HbA1c variability). In addition, HbA1c variability was inversely associated with total body BMC and aBMD (β = −0.15, P = 0.039 and β = −0.23, P = 0.029, respectively).

Discussion

This study investigated cortical bone geometry using pQCT in adult patients with T1DM. Our results indicate that T1DM is associated with a cortical bone size deficit at the radial shaft, characterized by a similar periosteal but larger endosteal circumference, a smaller cortical thickness, and a lower cortical over total bone area ratio compared with a nondiabetic age- and sex-matched population. In addition, we showed that individuals with T1DM present with a larger trabecular area, a lower trabecular but higher cortical vBMD at the radius, and a lower aBMD at the total body, femoral neck, and total hip. Whereas these differences could not be explained by differences in body composition or current bone turnover or mineral metabolism, patients with T1DM presented with a higher bone marrow fat content. Furthermore, although bone parameters in subjects with T1DM were not associated with current metabolic control, disease duration, age of disease onset, or MVD, a higher mean HbA1c over the last 5 years as well as higher glycemic variability were associated with a smaller cortical bone area.

Few studies have investigated cortical bone geometry in adult T1DM patients, with previous work mainly focusing on pediatric and adolescent populations. In line with our findings, these studies generally reported a smaller cortical area in subjects with T1DM compared with a reference population (7–9). Whereas this cortical bone size deficit persisted over a 1-year period in a longitudinal extension of one study (11), it normalized over a 5-year period in another report (15). Only two other studies have investigated bone geometry in adults with T1DM, showing a cortical bone size deficit both at the hip using central quantitative computed tomography (16), and at the ultradistal radius using HR-pQCT (5). The results of our study corroborate these findings, and

suggest that rather than reduced periosteal apposition (*i.e.*, modeling), increased endosteal resorption (*i.e.*, remodeling) might be the main cause of this cortical bone size deficit. Data on trabecular bone geometry in subjects with T1DM have been more conflicting, with studies in children showing a similar (7) or smaller trabecular area (9–11), whereas we and others observed a larger trabecular area in adults with T1DM compared with controls (5). The mechanisms behind these discrepancies are unclear; however, it has been hypothesized that the increase in trabecular area might serve as a mechanism to offset microstructural changes in the trabecular bone tissue (4, 5).

Our findings concerning DXA-measured aBMD largely corroborate the results of two meta-analyses (3, 17); however, we did not find a difference in aBMD at the spine. This may at least in part be explained by the fact that a substantial number of subjects in our study had diabetic nephropathy, which is often associated with falsely elevated aBMD measurements at the spine because of aortic calcifications. Measuring trabecular bone mineral density (BMD) at peripheral sites might be more appropriate in patients with T1DM, and in agreement with previous studies, we indeed observed a lower trabecular vBMD in subjects with T1DM vs controls (5, 7, 9, 18, 19). In line with our findings, cortical vBMD has generally been shown to be preserved in children with T1DM (7–9, 11, 15); however, lower values were reported in one other study in adults (5). Nonetheless, the latter study was performed using HR-pQCT at the ultradistal radius, which is mainly a trabecular bone site and therefore less suitable to assess cortical bone parameters.

One possible explanation for the bone size and/or density deficits associated with T1DM is that these patients have an altered bone turnover and/or mineral metabolism. Several studies have shown that T1DM is associated with a state of low bone turnover, with decreased levels of bone resorption as well as formation markers (4, 5, 20–24). In our study population, however, we only observed somewhat lower CTX levels in men, whereas P1NP levels were not different in subjects with vs without T1DM. Furthermore, our finding of increased endosteal circumference rather contrasts with a putative decrease in local bone turnover, suggesting that other factors may underlie the observed cortical bone size deficit in T1DM.

T1DM is also characterized by alterations in the growth hormone/insulinlike growth factor 1 (IGF-1) axis, which may be another contributing factor to the bone phenotype observed in these patients. First, IGF-1 is an important regulator of bone mass acquisition and maintenance (25). Although the current study did not investigate IGF-1 levels, other authors have indeed reported lower levels of IGF-1 in patients with T1DM, as well as positive associations of IGF-1 and its binding proteins with BMD, cortical bone area, and trabecular microstructure (4, 8, 16, 19). Second, growth hormone and IGF-1 are involved in the regulation of body composition (26–28), which in turn importantly determines bone health (29–32). Nonetheless, in agreement with previous reports, we observed no differences in body composition in subjects with vs without T1DM in the current study (7, 15). Furthermore, we found no differences in the bone over muscle area ratio, indicating an adequate adaptation of bone size to muscle size and therefore a preserved muscle-bone relationship in patients with T1DM.

A third putative explanation for the bone size deficit associated with T1DM involves the differentiation of mesenchymal stem cells, which are the common progenitors of adipocytes, osteoblasts, and chondroblasts residing in the bone marrow. A reciprocal relationship exists between adipogenesis and osteoblastogenesis, and studies in nondiabetic populations have shown inverse associations between bone marrow adiposity on the one hand and bone size or density on the other (33–37). Moreover, increased bone marrow adiposity has been shown to be associated with a smaller cortical but not total bone area, suggesting that the inverse association between marrow adiposity and cortical bone size might preferentially occur through increased endosteal expansion (34–36). In line with experimental data demonstrating increased bone marrow adiposity in T1DM mice (38, 39), our T1DM population had lower pQCT-derived bone marrow density values compared with controls. Lower bone marrow density was moreover associated with a larger endosteal circumference and a smaller cortical thickness, and adjustment for marrow density attenuated the differences in cortical bone geometry between subjects with T1DM and controls. Thus, our findings support a possible role of increased bone marrow fat content in the development of the cortical bone size differences associated with T1DM. Only two other clinical studies have investigated bone marrow adiposity in T1DM, with one study showing no difference in MRI-derived vertebral, femoral, or tibial marrow adiposity (40), and another study showing a nonsignificant trend toward higher vertebral marrow adiposity in young T1DM women (4). Nonetheless, these studies were hampered by small sample sizes, and the possibility of increased marrow adiposity as a contributor to the alterations in bone geometry in T1DM merits further research.

To date, little consensus exists on the clinical determinants of bone health in patients with T1DM.

Meta-analyses have suggested an association of bone turnover but not BMD with metabolic control, but no associations with disease duration (3, 24). In line with other studies, we observed no association between bone geometry and disease duration, age of disease onset, or current metabolic control (5, 8, 10, 11, 16). However, we did observe inverse associations of cortical bone area with short- and long-term glycemic variability, as reflected by CGM-derived glucose SD over a 7-day period and HbA1c variability over the last 5 years. Although no previous studies have included glycemic variability as a possible clinical determinant of bone fragility in T1DM, long-term fluctuations in metabolic control have been shown to contribute to the development and/or progression of other micro- or macrovascular complications (41, 42). Our findings suggest that in parallel herewith, fluctuations in long-term metabolic control may also adversely affect cortical bone size. Whereas recent studies have been pointing toward the presence of MVD as a predictor of deficits in trabecular microarchitecture (4, 5), we could not confirm any association with cortical bone geometry.

Strengths of our study include the homogeneous population of adult patients with relatively long-standing T1DM, well-characterized in terms of metabolic control and the presence of MVD, as well as the use of an age- and sex-matched control group. Bone geometry was assessed using state-of-the-art methods, with pQCT measurements performed by an experienced study team to minimize measurement variation. Besides the cross-sectional design of our study, which obviously does not allow for drawing conclusions about causality, an important limitation includes the lack of information on physical activity. Nonetheless, the fact that we observed no differences between subjects with T1DM and controls in terms of body composition and muscle size suggests that if any differences in physical activity were present, they might not have been large enough to affect bone size through effects on muscle mass. The lack of information on sex steroid levels in all, and on age of menarche, parity, and history of lactation in female participants represents another limitation. Further, although a high level of agreement between marrow fat quantification by microcomputed tomography and histology analysis has been shown in rats (43), the use of pQCT to examine bone marrow density in humans has not been validated against histomorphometry or MRI measurements, and our findings regarding bone marrow density should therefore be interpreted with caution. Although our sample size was comparable with previous studies investigating bone geometry in T1DM, it was not sufficient to evaluate differences in men and women separately. Moreover, we only performed bone geometry measurements at the radius, and further studies are needed to investigate whether bone geometry in T1DM is similarly affected in both sexes as well as at other skeletal sites.

In conclusion, this study showed that in addition to the known deficits in aBMD and trabecular vBMD, adult patients with T1DM present with a cortical bone size deficit, specifically characterized by a similar periosteal but larger endosteal circumference compared with nondiabetic subjects. These differences in bone geometry cannot be explained by differences in body composition or bone turnover, but may be associated with glycemic variability as well as with a higher bone marrow fat content in subjects with T1DM. Given the important contribution of bone geometry to overall fracture risk, we hypothesize that the cortical bone size deficit may contribute to the increased fracture risk associated with T1DM.

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Address all correspondence and requests for reprints to: Charlotte Verroken, MD, Unit for Osteoporosis and Metabolic Bone Diseases, Department of Endocrinology, Ghent University Hospital, De Pintelaan 185, 9K12IE, B-9000 Ghent, Belgium. E-mail: Charlotte.Verroken@UGent.be.

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