Abnormal Cortical and Trabecular Bone in Youth With Type 1 Diabetes and Celiac Disease

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OBJECTIVE

This study compared bone health in youth with type 1 diabetes and celiac disease (CD) versus type 1 diabetes alone.

RESEARCH DESIGN AND METHODS

This was a case-control study of 42 youth with coexisting type 1 diabetes and CD and 40 with type 1 diabetes matched for age, sex, diabetes duration, and HbA_{1c}. Bone mineral density (BMD), bone mineral content (BMC), and BMC-to-lean tissue mass (LTM) ratio were measured using DXA and reported as *z*-scores for height. Total, trabecular, and cortical bone and muscle parameters were measured using peripheral quantitative computed tomography (pQCT) and reported as *z*-scores for age.

RESULTS

Mean age at assessment was 14.3 ± 3.1 years; diabetes duration, 8.0 ± 3.5 years; HbA_{1c}, 8.2 ± 1.5% (66 ± 5 mmol/mol); and 25-hydroxy vitamin D, 71 ± 21 nmol/L. Comparing youth with coexisting CD versus type 1 diabetes alone, DXA showed lower BMC-to-LTM ratio (0.37 ± 1.12 vs. 0.73 ± 2.23, $P = 0.007$) but no difference in total BMD. Youth with coexisting CD also had lower BMC-to-LTM ratio versus the general population ($P = 0.04$). Radial pQCT showed lower total BMC (−0.92 ± 1.40 vs. −0.26 ± 1.23, $P = 0.03$) despite similar bone and muscle cross-sectional area. In multivariable linear regression, lower BMC was associated with higher insulin dose ($P = 0.03$) but not HbA_{1c}.

CONCLUSIONS

Youth with both type 1 diabetes and CD have lower BMC relative to LTM and lower BMC, indicating abnormal trabecular and cortical bone development despite similar bone and muscle size. These findings suggest that the two conditions confer a lower bone turnover state. We recommend further examination of bone health in this population; future research should examine early interventions to improve bone health.

There is substantial evidence that adults with type 1 diabetes have abnormal bone mineral density (BMD) and are at increased risk of fractures (1). There is also limited evidence that children and adolescents with type 1 diabetes have lower bone density (2) and smaller bone mass (3,4). Although the mechanisms for adverse bone health are multifactorial, in type 1 diabetes they include inadequate accrual of peak bone mass due to impaired bone formation and osteoblast function (5), elevated HbA_{1c} (6), and increased production of advanced glycation end products (7).

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Adults with celiac disease (CD) also have an increased fracture risk (8), whereas children and adults with CD both have lower BMD compared with the general population. Proposed mechanisms include dietary malabsorption of calcium and vitamin D, which are important for bone growth and development (9), or chronic intestinal inflammation, which interferes with bone formation and increases bone resorption (10).

Collectively, these data suggest that individuals with coexisting type 1 diabetes and CD have an additive risk for adverse measures of bone health, but the evidence for this is limited. Low BMD at the lumbar spine, defined as a *z*-score of <-2 SD, was more prevalent in a cross-sectional study of children and adolescents with type 1 diabetes and celiac autoimmunity (but not biopsy-confirmed CD) versus type 1 diabetes alone (12% vs. 3%); however, actual BMD *z*-scores were not reported (11). In contrast, coexisting type 1 diabetes and CD was not associated with an increased fracture risk in a population-based Swedish cohort study of individuals aged <30 years; however, BMD was not examined (12).

Observed rates of hip fractures in adults with type 1 diabetes exceed calculated theoretical increases, suggesting factors beyond BMD, such as bone quality, contribute to increase fracture risk (6). Traditional measures of bone, using DXA in children and adolescents, include BMD for age, height, and weight, bone mineral content (BMC), and the ratio of BMC to lean tissue mass (LTM), which takes into account the influence of muscle on BMC (13). In contrast, peripheral quantitative computed tomography (pQCT) characterizes bone architecture, including volumetric BMD (vBMD), bone geometry (dimension, area, and cortical thickness), and mineral distribution within the bone cross-section (14). These parameters allow for calculation of bone strength. pQCT also enables the separate measurement of trabecular and cortical bone compartments, which may allow for earlier detection of changes in bone in response to disease (14). Trabecular bone is metabolically active; thus, any changes in bone structure would usually be first observed here (3,4). Although pQCT has demonstrated that children with type 1 diabetes have smaller bones compared with control subjects without diabetes (3,4), this tool has not been used to examine bone in youth with coexisting type 1 diabetes and CD.

Using both DXA and pQCT, we performed a case-control study of young people with coexisting type 1 diabetes and CD versus type 1 diabetes alone to address our hypothesis that coexisting CD confers a greater risk of abnormal BMD, BMC, and bone structure.

RESEARCH DESIGN AND METHODS

Study Design and Population

This was a matched cross-sectional case-control study conducted at The Children's Hospital at Westmead, Australia. Inclusion criteria were age 8–18 years, type 1 diabetes duration $\geq$1 year, and biopsy-proven CD for at least 6 months. Patients with type 1 diabetes and CD were recruited at routine clinic appointments, and the first 42 who consented to participate were included in the study. For each individual case patient, a control patient with type 1 diabetes alone, matched for age ($\pm$1 year), sex, diabetes duration ($\pm$1 year), and HbA_{1c} ($\pm$0.5%) was invited to participate (15).

CD screening was performed based on international guidelines (16). All patients with diabetes had serological testing for CD at the time of diabetes diagnosis and at 1–2 yearly assessments thereafter (17). Screening was performed by measurement of serum IgA and anti-tissue transglutaminase IgA antibodies by ELISA. Deamidated IgG antibodies were also measured to account for false-negative results in IgA-deficient patients. Those with a positive screen were referred to a pediatric gastroenterologist and underwent small bowel biopsy. Only patients with specimen-proven CD were included in this study.

The control population was drawn from patients with type 1 diabetes who were matched by age, diabetes duration ($\pm$1 year), most recent HbA_{1c} ($\pm$0.5%), and mode of diabetes management—either multiple daily injections (MDI) or insulin pump therapy (continuous subcutaneous insulin infusion [CSII]). The control population had a negative screening test result for CD at least once within the previous 12 months. The first 40 to consent to participate were included in the study. Exclusion criteria were unknown CD status or treatment regimens other than MDI or CSII.

The Sydney Children's Hospital Network Research Ethics Committee approved the study. Consent was obtained from all patients and parents before participation.

Study Visits and Data Collection/ Clinical Assessment

Demographic and clinical characteristics documented were age at diabetes diagnosis, type 1 diabetes duration, mode of diabetes management (MDI or CSII), insulin dose (units/kg/day), age at CD diagnosis, CD duration, CD-related symptoms (documented at the time of CD diagnosis), and anthropometric measurements (height, weight, and BMI), with *z*-scores computed using U.S. Centers for Disease Control and Prevention 2000 reference data. The most recent HbA_{1c} was documented, and lifetime mean HbA_{1c} was computed from all available data. Blood tests were performed at the study visit for 25-hydroxy vitamin D (25-OHD), albumin, thyroid function, and liver function. Deficiency of 25-OHD was defined as <50 nmol/L. Pubertal development was assessed and documented by the clinician and quantified by hormone levels (luteinizing hormone, follicle stimulating hormone, and testosterone or estradiol).

Gluten-Free Diet Adherence

Gluten-free diet (GFD) adherence was assessed clinically and serologically, as previously described (18). An accredited practicing dietitian documented families' usual dietary intake, precautions taken when eating out, and their perceived GFD adherence. Tissue transglutaminase IgA and deamidated IgG serology was measured to document adherence. Patients with tissue transglutaminase titers in the normal range (or declining titers if recently diagnosed) and GFD adherent (GFD^+), as assessed by the dietitian, were classified as GFD^+. Patients with elevated titers and GFD nonadherent (GFD^-), as assessed by the dietitian, were classified as GFD^-. There was complete concordance between dietetic assessment of GFD^+ or GFD^- and celiac titers. Assessment of GFD adherence by a dietitian is recognized as the best available measure (19).

Bone Densitometry

Total body, posteroanterior lumbar spine (LS), and femoral neck BMD and body composition were determined by DXA

using a GE-Lunar Prodigy (enCORE 8.6 software; GE Lunar Radiation Corp., Madison, WI), with positioning, scanning, and standard analysis according to the manufacturer's recommendations. These provided total body, LS, and femoral neck BMD and BMC adjusted for age and height, as previously described (20). Total BMC-to-LTM ratio and BMC adjusted for bone area (BA) (BMC-to-BA ratio) were also calculated. Volumetric LS BMD was calculated as per Carter et al. (21) to reduce the influence of height. Reduced bone mass and density for age and height was defined as *z*-score values of <-2.0, according to the International Society for Clinical Densitometry guidelines (22). Height *z*-scores for DXA measures were used to adjust for any variance in stature within and between groups, whereas age *z*-scores were used for pQCT because it is a true volumetric density measure.

Cross-sectional measurements of the nondominant lower leg and forearm were performed by pQCT using a Stratec XCT-2000 (Stratec Medizintechnik GmbH, Pforzheim, Germany). Measurements were made and analyzed using software version 6.0B. Epiphyseal scans were performed at the 4% site of the nondominant tibia and radius. Diaphyseal scans were undertaken at the 66% site of the radius and 66% of the tibia. Both the tibia and radius were acquired with a voxel size of 0.4 mm. A scan speed of 15 and 20 mm/s was used for the radius and tibia, respectively. The slice thickness of the machine was 2.4 mm, as previously described (23). Bone measurements included vBMD (mg/cm^3), vBMD trabecular bone, total and cortical cross-sectional area (CSA, mm^2), muscle CSA (mm^2), total and cortical BMC (mg/mm), and polar strength-strain indices (pSSI, mm^3). pSSI provides a good estimate of mechanical strength (24). Conversion from pQCT raw data to sex- and age-matched *z*-scores was based on published pediatric reference data (25).

Assessment of Glycemic Variability

Glycemic control was measured by HbA_{1c} using high-performance liquid chromatography (nondiabetic range 4–6%) (Diamat BioRad, Hercules, CA). Fluctuations in HbA_{1c} over the duration of diabetes was calculated as previously described (26). For each patient, the intrapersonal mean and SD of all recorded glycemic control measurements was calculated, and the SD-HbA_{1c} was considered a measure of glycemic variability (26). Because the number of individual visits (*n*) could influence the SD-HbA_{1c} (with fewer visits likely to artificially inflate SD), values for SD-HbA_{1c} were divided by *n* to adjust for this possibility. We also calculated coefficient of variation (CV), a normalized measure of glycemic variability. CV was computed as the division of SD-HbA_{1c} by a factor of mean HbA_{1c} (i.e., CV = SD-HbA_{1c}/[mean HbA_{1c}/10]).

Sample Size

In our previous study of BMD in patients with cystic fibrosis–related diabetes (27), we found a difference in the total BMD (TBMD) *z*-score of 0.99 ± 1.11 compared with cystic fibrosis alone and a difference in the LS vBMD *z*-score of 0.62 ± 0.76. We anticipated smaller but clinically significant differences may be observed for bone parameters measured in this study population and therefore aimed to recruit 40 patients per group (*z*-score difference, 0.5 ± 0.8, $\alpha = 5\%$, power = 90%).

Data Analysis

Descriptive statistics are reported as mean $\pm$ SD for continuous variables, which were normally distributed. Categorical variables were compared between groups using χ^2 tests. Continuous variables were compared between groups using Student *t* tests, because all data were normally distributed. Multivariable linear regression analysis was used to examine the association between bone health indices and explanatory variables, including presence of CD, diabetes duration, lifetime HbA_{1c}, and insulin dose/kg/day. Statistical analyses were performed using SPSS 25.0 (IBM, Armonk, NY) and Stata 13.0 (StataCorp, College Station, TX) software.

RESULTS

Study Population and Characteristics

We recruited 82 youth with type 1 diabetes (42 with coexisting CD, 40 with type 1 diabetes alone). The total study population had a mean age of 14.3 ± 3.1 years, age at diabetes diagnosis of 6.7 ± 3.6 years, HbA_{1c} of $8.2 \pm 1.5\%$ (66 ± 5 mmol/mol), 25-OHD of 68 ± 10.5 mmol/mol, and mean height *z*-score of 0.2 ± 1.2. Characteristics of participants stratified by presence or absence of CD are reported in Table 1. Youth with coexisting CD had significantly higher prescribed insulin doses (0.95 ± 0.30 vs. 0.78 ± 0.21 units/kg/day, $P = 0.005$), but all other characteristics such as glycemic control and anthropometric measures were comparable. 25-OHD levels were significantly different between youth with type 1 diabetes and youth with coexisting CD; however, both values were clinically in the normal range, and the proportion of patients with 25-OHD deficiency did not differ. None of the participants had abnormal results on thyroid or liver function tests or evidence of active inflammation (based on full blood count, erythrocyte sedimentation rate, and C-reactive protein levels), and all patients with 25-OHD deficiency had normal alkaline phosphatase levels. None of the participants demonstrated delayed puberty.

DXA Scan Results

Youth with coexisting CD versus type 1 diabetes alone had a significantly lower BMC-to-LTM ratio ($P = 0.007$), suggesting an abnormal muscle and bone relationship. Both groups had similar-sized BA, height (Table 2), and TBMD. When youth with coexisting CD were stratified by GFD adherence (27 GFD$^+$ vs. 15 GFD$^-$), there were no statistically or clinically significant differences in any of the DXA measures (e.g., BMC-to-LTM ratio *z*-score -0.34 ± 0.85 vs. -0.42 ± 1.54, $P = 0.86$). Youth with coexisting type 1 diabetes and CD had lower TBMD for height (*z*-score -0.42, $P = 0.02$), BMC-to-LTM ratio (*z*-score -0.37, $P = 0.04$), and BMC-to-BA ratio (*z*-score -0.69, $P = 0.001$) compared with the general population (results not shown). In multivariable linear regression, these associations remained significant after adjustment for total daily insulin dose and HbA_{1c}.

pQCT Results

Radial pQCT showed that youth with coexisting CD had lower cortical total BMC and lower trabecular bone vBMD ($P = 0.03$) than youth with type 1 diabetes (Table 3), despite similar muscle CSA ($P = 0.45$) and cortical CSA *z*-scores, $P = 0.12$). Lower pSSI *z*-scores in those with type 1 diabetes and CD ($P = 0.01$) indicate reduced bone strength. Youth with coexisting type 1 diabetes and CD had higher vBMD compared with the general population (*z*-score 0.42, $P < 0.001$),

Table 1—Clinical characteristics of patients stratified by presence or absence of CD

	Type 1 diabetes + CD (n = 42)	Type 1 diabetes (n = 40)	P value
Females	26 (62)	23 (58)	0.17
Age (years)	14.0 ± 3.3	14.7 ± 2.8	0.33
Age at diabetes diagnosis (years)	6.3 ± 3.9	6.5 ± 3.5	0.83
Diabetes duration (years)	7.8 ± 3.8	8.1 + 3.0	0.73
CD duration (years)	5.0 ± 3.6	—	
GFD adherent	27 (64)	—	
Median HbA_{1c} year before visit (% [mmol/mol])	8.5 ± 1.5 [69 ± 17]	8.0 ± 1.0 [64 ± 11]	0.10
HbA_{1c} at visit (% [mmol/mol])	8.4 ± 1.4 [68 ± 16]	8.1 ± 1.5 [65 ± 17]	0.26
Lifetime HbA_{1c} to visit (% [mmol/mol])	8.1 ± 0.9 [65 ± 10]	7.8 ± 0.8 [62 ± 9]	0.07
HbA_{1c} variability (SD-HbA_{1c}) (%)	0.86 ± 0.31	0.94 ± 0.30	0.21
Insulin (units/kg/day)	**0.95 ± 0.30**	**0.78 ± 0.21**	**0.005**
Height SDS	0.07 ± 1.26	0.34 ± 1.15	0.31
Weight SDS	0.60 ± 0.81	0.62 ± 0.97	0.93
BMI SDS	0.67 ± 0.71	0.51 ± 0.96	0.40
Overweight/obese	13 (31)	11 (28)	0.73
25-OHD at visit (nmol/L)	76 ± 22	65 ± 18	0.02
25-OHD deficient†	6 (14)	6 (15)	0.93
Alkaline phosphatase (units/L; ref: 50–350 units/L)	201 ± 119	195 ± 104	0.79

Data are mean ± SD or n (%). Values in boldface type are statistically significant. †25-OHD deficiency defined as <50 nmol/L.

whereas trabecular bone vBMD measures were lower in those with coexisting type 1 diabetes and CD versus the general population (z-score −1.00, $P < 0001$) and total BMC (z-score −1.02, $P < 0.001$). When youth with coexisting CD were stratified by GFD adherence, there were no statistically significant differences in any of the pQCT measures, although there was a trend to a lower 66% BMC cortical z-score in those GFD^- versus GFD^+ (−0.06 ± 0.78 vs. 0.64 ± 0.98, P = 0.08). In multivariable linear regression, lower total BMC remained significantly associated with coexisting CD and type 1 diabetes and was also associated with higher insulin dose (β = 0.28; 95% CI 0.12, 2.49; P = 0.03). Neither diabetes duration nor lifetime HbA_{1c} was significant in the model. Lower pSSI was associated with higher insulin dose (β = 0.32; 95% CI 0.37, 2.80; P = 0.01) and diabetes duration (β = −0.25; 95% CI −0.19, −0.007; P = 0.04) but not lifetime HbA_{1c}. Duration of CD was not associated with any bone health parameter. Tibial pQCT results are provided in Supplementary Table 1.

CONCLUSIONS

This is the first study to examine the impact of biopsy-proven CD on bone in youth with coexisting type 1 diabetes. We found abnormal bone structure in those with type 1 diabetes and CD, characterized by lower radial BMC, lower trabecular bone vBMD, and lower cortical BMC, despite similar-sized bone compared with youth with type 1 diabetes alone. Those with coexisting CD also had a lower BMC-to-LTM ratio with higher material density (vBMD), suggesting an impairment of bone development compared with those with type 1 diabetes alone. Compared with the general population, youth with coexisting type 1 diabetes and CD had abnormal bone structure, as demonstrated by lower TBMD, lower BMC-to-BA ratio, and lower BMC-to-LTM ratio. Moreover, a lower BMC-to-LTM ratio coupled with higher total vBMD indicates a state of lower bone turnover, resulting in older and stiffer bones (28).

The BMC-to-LTM ratio was significantly lower in those with coexisting type 1 diabetes and CD, even though neither LTM adjusted for height nor muscle size were significantly different between the two groups. Muscle is essential for bone development and maintenance, modeling, and remodeling: changes in bone follow changes in muscle mass (29) as bones adapt to muscle force (30). The low BMC-to-LTM in the setting of normal LTM for height suggests the skeleton is unable to adequately respond to the force applied to it through muscle pull and implies a primary bone abnormality (31). Alternatively, it

Table 2—DXA results comparing youth with type 1 diabetes and CD versus type 1 diabetes alone

	Type 1 diabetes + CD (n = 42)	Type 1 diabetes (n = 40)	P value
Age (years)	14.0 ± 3.3	14.7 ± 2.7	0.52
Height SDS	0.07 ± 1.26	0.34 ± 1.15	0.36
Weight SDS	0.60 ± 0.81	0.62 ± 0.97	0.97
BMI SDS	0.67 ± 0.71	0.51 ± 0.96	0.57
TBMD height z-score	−0.42 ± 1.15	−0.19 ± 1.20	0.37
TBMC height z-score	−0.13 ± 1.29	0.24 ± 1.77	0.29
BMC-to-LTM ratio z-score	**−0.37 ± 1.12**	**0.73 ± 2.23**	**0.007**
BMC-to-BA ratio z-score	−0.69 ± 1.22	−0.99 ± 1.65	0.36
BA height z-score	0.13 ± 1.30	0.69 ± 2.19	0.16
LTM height z-score	0.04 ± 1.22	−0.29 ± 1.19	0.21
LS 1–4 vBMD z-score	−0.59 ± 1.20	−0.30 ± 0.88	0.21

Data are presented as the mean ± SD. Values in boldface type are statistically significant.

Table 3—Radial pQCT results stratified by absence or presence of CD

	Type 1 diabetes + CD (n = 39)	Type 1 diabetes (n = 39)	P value
CSA cortical	−0.25 ± 1.21	0.13 ± 0.91	0.12
CSA muscle	−0.89 ± 1.56	−0.64 ± 1.23	0.45
4% BMC total	**−0.92 ± 1.40**	**−0.26 ± 1.23**	**0.03**
4% CSA total bone	−0.63 ± 1.40	−0.39 ± 1.40	0.45
4% vBMD trabecular	**−1.00 ± 1.49**	**−0.36 ± 1.09**	**0.03**
66% BMC cortical	**−0.26 ± 0.88**	**0.21 ± 0.92**	**0.02**
66% BMC total	**−1.02 ± 1.20**	**−0.44 ± 1.12**	**0.03**
66% cortical thickness	−0.03 ± 0.73	0.02 ± 0.81	0.78
66% CSA cortical	−0.26 ± 1.21	0.12 ± 0.91	0.13
66% CSA relative cortical	0.20 ± 0.81	0.00 ± 0.92	0.34
66% CSA total bone	−0.40 ± 1.48	0.13 ± 1.20	0.08
66% pSSI	**−0.39 ± 1.31**	**0.32 ± 1.18**	**0.01**
66% vBMD cortical	0.42 ± 2.03	1.04 ± 1.00	0.09
66% vBMD total	0.47 ± 1.24	0.49 ± 1.29	0.93

Data are presented as the z-score ± SD. Values in boldface type are statistically significant.

may be that muscle force and power are additionally reduced in those with coexisting type 1 diabetes and CD, because adolescents with type 1 diabetes alone have decreased muscle power and force as evaluated by jumping mechanography (32). Exercise, particularly resistance training, increases muscle strength (33) and BMD (34) in children. However, we did not document activity levels in this population or undertake measures of muscle force, so it is unknown whether there are differences in these factors between the two groups.

Total body BMC as assessed by DXA reflects cortical BMC. The lower total BMC in youth with coexisting CD therefore indicates lower cortical bone content, despite similar muscle and cortical bone size. The similar total and cortical bone size in our study supports the finding of bone size normalization in youth with type 1 diabetes of similar age (35). Two studies of youth with type 1 diabetes, from Finland (36) and France (37), demonstrated lower BMC compared with healthy control subjects despite similar anthropometrical measurements, suggesting that diabetes impairs bone mass accrual during skeletal growth. Youth with coexisting CD had higher insulin requirements, and similarly, those with lower BMC had higher insulin requirements in the French study (37). In type 1 diabetes, adolescence is associated with an exaggerated dysregulation of the growth hormone IGF-I/IGF-binding protein axis, contributing to a puberty-associated deterioration in glycemic control and worsening of insulin resistance (2) and resulting in higher insulin requirements. Although HbA_{1c} was not different between groups in our study and was not correlated with BMC in the French study (37), we speculate that functional insulopenia at the bone level (2) may impair bone formation.

Glycemic control and overall glycemic variability were similar between those with type 1 diabetes alone and coexisting CD in our study, despite higher total daily insulin doses. The limited existing data on youth with diabetes and celiac autoimmunity are conflicting: one study found no association between glycemic control and BMD (38), while two studies demonstrated a relationship between higher HbA_{1c} and lower BMD (11,39). However, in contrast to our population, none of the patients in these studies had biopsy-confirmed CD, which limits the generalizability of the data. We previously showed that glycemic control was also not associated with early evidence of renal disease in adolescents with coexisting type 1 diabetes and CD (40). Together, this suggests the mechanism for low BMD in CD is multifactorial and not dependent on glycemic control alone. Although the higher insulin requirements in those with CD may also reflect dietary differences, in our previous study of the same population, we did not find differences in total daily carbohydrate intake in those with coexisting type 1 diabetes and CD versus type 1 diabetes alone (41).

The risk of fractures is higher in patients with type 1 diabetes and microvascular complications (42). Adults with type 1 diabetes and microvascular complications have deficits in cortical and trabecular bone vBMD as examined by pQCT, which may partly explain the excess skeletal fragility (43). In contrast, the bone microarchitecture in adults with type 1 diabetes without microvascular complications was not different from control subjects. The increased risk of microvascular complications in those with coexisting CD (44,45) identifies a subgroup of patients with type 1 diabetes who require ongoing monitoring, particularly as life expectancy increases (46).

We have shown for the first time, using pQCT, that youth with CD and diabetes had lower radial trabecular bone and lower pSSI, indicating both abnormal bone structure and reduced bone strength. Diabetes-induced changes in BMD are expected to be first noted in the metabolically active trabecular bone (2), which is best visualized by pQCT. However, only two studies have used pQCT in patients with type 1 diabetes (3,4), and none have used this tool in those with coexisting CD. In the only study using pQCT in children and adolescents with type 1 diabetes alone, trabecular bone density was lower than in age- and sex-matched control subjects (3). Hence, our data suggest that the coexistence of CD confers an additional burden on trabecular bone.

Nutritional, metabolic, and demographic factors may influence BMD, size, and content. There were no clinically significant differences in 25-OHD levels between those with coexisting CD and type 1 diabetes alone, and in our analysis of micro- and macronutrients in this study population, we found no differences in intake of calcium, carbohydrate, protein, or dietary fat (18). The standardized BMI score (SDS) was also not different between groups. Although none of the patients had evidence of inflammation at the time of assessment (based on full blood count, erythrocyte sedimentation rate, and C-reactive protein), we cannot exclude the possibility that patients with coexisting CD may have a heightened inflammatory state that influences bone metabolism (10). Notably, however, BMD and other bone measures did not differ between GFD^+ and GFD^- youth.

The strengths of our study include the use of pQCT, which enables assessment of bone structure, in addition to DXA, and the confirmation of CD based on a biopsy specimen.

Limitations include lack of data on exercise, which influences muscle and bone formation. A lower BMC-to-LTM ratio coupled with higher total vBMD

indicates a state of lower bone turnover, but this is best evaluated by bone histomorphometry. Although most were in late puberty, follow-up of the study population later in adolescence will be important to examine whether differences are sustained. Owing to the small sample size of GFD^- individuals (n = 15), the study was underpowered. Given the observed association between GFD^+ and diabetes complications, the association between GFD^+ and bone outcomes should be explored in future studies.

We cannot exclude the possibility that genetics plays a role in bone development; however, this has yet to be examined in youth with type 1 diabetes. In a community cohort study of adults, osteoporosis was associated with positive tissue transglutaminase antibodies but not HLA DQ2 or DQ8 (47).

Longitudinal analysis from before puberty would enable examination of the impact of puberty on differences in bone structure development throughout childhood and adolescence. We did not have fracture data in this cohort of patients; however, this is currently being investigated in a larger study from our center. Recruitment of a larger sample size may have enabled adjustment for potential confounding variables; however, the study groups were matched for age, diabetes duration, HbA_{1c}, and sex (48).

In conclusion, we have shown youth with type 1 diabetes and CD appear to have abnormal bone structure, with deficits in cortical and trabecular bone, and a low bone turnover state, resulting in high BMD compared with those with diabetes alone. Youth with coexisting type 1 diabetes and CD also demonstrated lower radial trabecular bone and BMC compared with those with diabetes alone. These structural differences are independent of LTM, glycemic control, and dietary calcium intake, but insulin doses were higher in those with CD. We recommend regular monitoring of bone health to monitor changes and implementing early interventions, such as regular weight-bearing exercise, to optimize bone health, particularly as longer diabetes duration is associated with increased fracture risk (49).

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