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Reduced Bone Mineral Density Is Associated with Celiac Disease Autoimmunity in Children with Type 1 Diabetes

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Abstract

Objective—To evaluate the association between bone mineral density (BMD), glycemic control (HbA1c) and celiac autoimmunity in children with type one diabetes (T1D) and in an appropriate control population.

Study design—BMD was assessed cross-sectionally in 252 children with T1D (123 positive for TG and 129 matched children who were negative for transglutaminase [TG]). Additionally, BMD was assessed in 141 children without diabetes who carried T1D-associated HLD-DR,DQ genotypes (71 positive for TG and 70 negative).

Results—Children with T1D who were positive for TG had significantly worse BMD L1-L4 z-score compared with children with T1D who were negative for TG (-0.45 ± 1.22 vs. 0.09 ± 1.10 , $p=0.0003$). No differences in growth measures, urine N-telopeptides, vitamin D 25OH, ferritin, TSH or HbA1c were found. However, both higher HbA1c ($\beta = -1.25 \pm 0.85$, $p=0.0016$) and TG ($\beta = -0.13 \pm 0.05$, $p = 0.0056$) were significant and independent predictors of lower BMD in multivariate analyses. No differences in BMD or other variables measured were found between children without diabetes who were positive versus negative for TG.

Conclusions—The results suggest a synergistic effect of hyperglycemia and celiac autoimmunity on low BMD.

Keywords

Celiac Disease; Transglutaminases; Diabetes Mellitus–Type 1; Bone Density; Child

Celiac disease (CD) is an autoimmune disease that results in gluten-triggered injury to the small bowel of genetically susceptible individuals (HLA haplotype DR3-DQ2 or DR4-

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DQ8), leading to malabsorption and a variety of extraintestinal manifestations.(1) Immunoglobulin A (IgA) anti-tissue transglutaminase (TG) antibody is a highly sensitive and specific serological marker for CD and is the preferred screening test for CD.(2) Large cohort studies suggest that up to 12% of individuals with type 1 diabetes mellitus (T1D) screen positive for TG.(3–5) A recent multinational study showed that children with genetic risk for T1D and CD followed from birth develop celiac disease autoimmunity at significant rates that are dependent on specific genotypes; up to 11% of DR3-DQ2 homozygous individuals are already positive by age 5.(6) More than half of screening-identified children found to have CD do not have symptoms,(7) even among those in high risk groups.(8–11) Even though pediatric guidelines recommend testing for TG antibody in symptomatic patients, (2, 12) screening in asymptomatic individuals is more controversial because the natural history of “asymptomatic” celiac disease is not known. Potential long-term effects of untreated celiac disease include iron deficiency anemia, osteoporosis and increased risk for certain malignancies, which may not be obvious during childhood.(12) For this reason, some groups recommend screening of asymptomatic individuals in high-risk groups, including those with T1D or first degree relatives of an individual with a confirmed diagnosis of CD, starting at 3 years of age provided they have had at least 1 year of an adequate gluten-containing diet.(2) Although there is no specific recommendation on how frequently to rescreen children with T1D, it is generally recognized that a previously negative screen does not preclude a later positive screen and development of confirmed CD.(13–15) The benefit of a gluten-free diet in children with screening-identified CD remains to be determined.

We have previously reported that children with T1D who were TG positive on routine screening (defined as persistently elevated TG antibodies, with or without a positive biopsy) had altered body composition and increased markers of bone turnover, but no significant change in bone mineral density (BMD).(16, 17) In addition, these children with T1D did not show increased adverse outcomes when followed over the subsequent two years on a regular diet.(17) As children with T1D are at risk for poor bone mineralization and poor growth, it is unclear whether the presence of T1D is a confounding factor, making detection of a CD effect on bone measures more difficult. (12, 18–22)

The aim of this observational study was to test whether TG positivity is associated with lower bone mineralization in children with and without T1D and T1D influences bone mineralization among patients who were positive for TG.

Methods

Since 1999, routine TG testing has been performed on patients with T1D who are followed at the Barbara Davis Center.(11) Subjects for this study were recruited from two cohorts: (1) patients followed at the Barbara Davis Center with a diagnosis of T1D and (2) subjects of The Diabetes Autoimmunity Study in the Young (DAISY). DAISY is a prospective study of about 2,500 children at increased risk for T1D who were recruited between 1993 and 2004. DAISY subjects were recruited in two groups. The first group is made up of first-degree relatives of patients with T1D, recruited between birth and 8 years of age (n = 850, 49.8%). The second group was recruited from infants born at St Joseph’s Hospital in Denver, Colorado. This group is representative of the general population of the Denver metropolitan

area. These infants were identified as having either moderate or high risk of developing T1D, based on HLA genotype of cord blood sample. Details of the newborn screening, sibling and offspring recruitment, and follow-up of both cohorts have been published previously.(23, 24) Cord blood or the first available blood sample (depending on enrollment group) was sent to Roche Molecular Systems, Inc. for PCR-based HLA class II typing. Subjects who were positive for TG either with T1D (n=123) or without T1D (n=71) were offered enrollment into this observational follow-up study, duodenal biopsy, and consultation with a dietician regarding gluten free diet (GFD). Of the 123 subjects with T1D who were positive for TG, 71 underwent duodenal biopsy; 57 of them were positive, 13 negative and 1 indeterminate. Of the 71 subjects without diabetes who were positive for TG, 36 had biopsy; 28 of these were positive and 8 were negative. The subjects who were positive for TG were frequency matched for sex and age with subjects who were negative for TG either with (n=130) or without (n=70) T1D. In those with T1D, the control group was also matched for duration of T1D. The Colorado Multiple Institutional Review Board approved all study protocols, and parents of all participating children gave informed consent. Assent was obtained from children age 7 years.

At the study visit, patients completed a questionnaire for self-report of adherence to gluten-free diet as well as presence, frequency and severity of celiac-associated symptoms. The questionnaire inquired about gastrointestinal symptoms including: diarrhea, abdominal pain, constipation, vomiting, gassiness, abdominal distension, and poor weight gain. Other celiac-associated symptoms queried included: irritability, decreased energy, itching or rash, edema, bleeding or bruising, anemia, pubertal delay, short stature, and bone fractures. Additionally, subjects with T1D self-reported the number of hypoglycemic episodes they encountered between visits and episode severity (loss of consciousness, seizure, glucagon administration, emergency room visit, hospitalization).

Anthropometric data including height, weight, and body mass index (BMI) was converted to age- and sex-specific z-scores.(25, 26) BMD of the lumbar spine (L2-L4) was calculated using Hologic Discovery W S/N 86437 bone densitometer with smart scan as previously described.(16) BMD was converted to age- and sex-specific z-scores. DXA results were defined as “low BMD” if z-score was 2 or more standard deviations below the mean for sex and age.(27)

Laboratory Tests

Screening for anti-tissue TG IgA antibody was performed by radioimmunoassay as previously described with a positive result defined as TG ≥ 0.05 .(11) Urinary cross-linked N-telopeptides of type 1 collagen (NTX) were measured in spot urine sample by EIA (Wampoles Osteomark, Princeton, NJ). Thyroid stimulating hormone (TSH), 25-hydroxyvitamin D, and ferritin were measured using standard laboratory methods.

Statistical analyses

Variables were checked for the distributional assumption of normality. BMD L1-L4, ferritin, urine N-telopeptides, creatinine and TG were treated with a natural log transformation and transformed variables were used in analyses. Independent samples t-test were used to test for

differences between study cohorts on continuous variables. Chi Square test of independence or Fisher Exact were used to test categorical variables. ANCOVA was used to test if BMD z-score was related to positive TG duration after adjustment for diabetes status and gluten consumption in the last 2 months. Regression analysis was used to test if BMD z-score was related to the natural log of HbA1c and TG levels, both individually and in a combined model. Data are presented as mean $\pm$ SD, geometric mean and 95% CI or frequency (%). BMI, height and weight z-scores were calculated by using the CDC macro using height, weight and sex norms. A p-value < 0.05 was considered significant. All analyses were performed using SAS 9.3.

Results

There were 252 children with T1D enrolled in the study, 123 who were positive for TG and 129 who were negative. Of the children who were positive for TG, 48% were males, compared with 41% of subjects who were negative for TG ($p=0.093$). The mean age of the subjects was not different between groups (13.5 ± 3.7 vs 13.9 ± 2.8 , $p=0.37$). The two groups were similar in height, weight and BMI z-scores (Table I). As expected, TG was higher in cases than in controls ($p<0.0001$). Children with T1D who were positive for TG had a significantly lower BMD z-score than did children with T1D who were negative for TG ($p=0.0003$). Of those with T1D, more children who were positive for TG had a low BMD on DXA scan than children who were negative for TG ($p=0.0076$). Thyroid stimulating hormone (TSH) levels were similar between the two groups. There were no differences between subjects with T1D positive versus negative for TG with respect to vitamin D 25OH, ferritin and urine N-telopeptides. TG positive status did not have a significant effect on HbA1c level at study visit (Table I). There was no significant difference in the report of celiac-related symptoms in the subjects with T1D who were positive versus negative for TG.

Effect of TG positive status on BMD in children without T1D

Of the 141 children without T1D enrolled in the study, 71 were positive for TG and 70 were negative. The two groups were similar in height, weight, and BMI z-score (Table IV; available at www.jpeds.com). The mean age for each group was 13.7 ± 3.3 for the children who were positive for TG and 14.1 ± 3.1 for the children who were negative for TG ($p=0.50$). There was no significant difference in sex distribution in subjects who were positive versus negative for TG ($p=0.21$). As expected, the children who were positive for TG had higher levels of TG autoantibodies than the children who were negative for TG ($p<0.0001$). There was no difference between individuals who were positive versus negative for TG in levels of vitamin D 25-OH, ferritin, urine n-telopeptides or BMD z-scores (Table IV). Although the differences in individual symptoms did not reach statistical significance (data not shown), the subjects who were positive for TG were more likely to report celiac-associated symptoms than controls (36% vs 20%, $p=0.038$). The most common symptoms reported in those children who were positive for TG were abdominal pain (13% vs 7%, $p=0.25$), diarrhea (10% vs 3%, $p=0.097$), constipation (10% vs 3%, $p=0.097$), and decreased energy (10% vs 1%, $p=0.097$).

Comparison of children with or without T1D who were positive for TG

In the study group as a whole, there were 123 children with T1D who were positive for TG and 71 children without T1D who were positive for TG. Children with and without T1D who were positive for TG had similar age, height, weight, and BMI z-scores (Table II). Children without T1D who were positive for TG had a similar BMD z-score to those with T1D ($p = 0.086$). In our study, children without T1D who were positive for TG had significantly lower TG levels than the children with T1D ($p=0.026$). TG positive duration was longer in the subjects without T1D than in the subjects with T1D ($p<0.0001$), but it should be noted that those without T1D were tested more frequently over a longer period of time. There was no significant difference in the proportion of subjects who were positive for TG who had eaten gluten over the previous two months between the groups with and without T1D (Table II).

Predictors of BMD in Children with T1D

In univariate regression analyses (Table III), higher HbA1c predicted lower BMD z-score ($p=0.021$). Similarly, higher TG level predicted lower BMD z-score ($p=0.015$). In a multivariate model, both HbA1c ($p=0.0016$) and TG ($p = 0.0056$) levels independently predicted lower BMD.

Adherence to Gluten-Free Diet

At the first visit, subjects were asked questions regarding adherence to a gluten-free diet. Of subjects with T1D who were positive for TG, 56% were on a regular diet, reporting having eaten gluten in the previous 2 months. This was significantly different than the subjects who were negative for TG, all of whom had eaten gluten in the previous month ($p<0.0001$). Among the subjects without T1D who were positive for TG, the majority (68%) also did not follow a gluten-free diet, with only 32% reporting no gluten-containing foods over the 2 months prior to study. This was significantly different than the subjects who were negative for TG, all of whom had eaten gluten in the previous month ($p<0.0001$).

Discussion

Both T1D and CD individually have known effects on lowering BMD and altering bone metabolism.(28–30) Previous studies have examined BMD in children with celiac autoimmunity and in T1D; however, none have studied controls without T1D who are not only similar in age, but also in HLA genotypes.(16, 17, 31) In our study, subjects with T1D who were positive for TG had significantly lower lumbar BMD, and a greater number of children had low BMD on DXA scan (BMD L1-L4 z-score -2) compared with subjects with T1D who were negative for TG. These findings are consistent with our previous study, which showed children with T1D with sustained and substantial ($TG>0.50$) elevation in TG over 2 year follow up had decreased lumbar BMD.(17) These findings raise the question of whether there is a role for higher TG index as a predictor of bone density in T1D, in contrast to a previous study in children with celiac disease alone which showed in that population the magnitude of TG index did not predict BMD.(32) As both T1D and celiac disease have known effects on bone health, our findings may also represent a synergistic negative effect of suboptimal glycemic control and celiac autoimmunity on bone density in children with

T1D.(28–30) This is supported by the different findings relative to BMD between the groups with and without T1D.

Unlike our previous findings in children with T1D, in the groups with and without T1D, there was no difference in weight or BMI when compared with controls who were negative for TG. It should be noted that the subjects with T1D who were positive for TG in this study had a wide variability in BMI z-score. This may reflect the older age of this group relative to our previously studied group.(16, 17) In addition, and our previous work showed changes in markers of turnover but no differences in BMD, in this older cohort, we now see differences in BMD. As puberty plays a major role in BMI changes as well as the accrual of BMD, the inclusion of a substantial portion of subjects of pubertal age may be a contributing factor to these differences.

Our previous findings showed delaying gluten-free diet over two years of follow up in patients with T1D and TG positive status did not result in worsening weight, height and HbA1c.(17) Other studies, however, have suggested that 12 to 48 months of gluten-free diet may improve height, weight, BMI and BMD in those with evidence of severe villous atrophy on intestinal biopsy.(33) Our current findings raise the question of whether TG and HbA1c levels may be used to identify those at risk for detrimental effects on bone density, thereby selecting children who may most benefit from a gluten-free diet and those in whom it may not be necessary.

This study had several limitations. A number of subjects did not undergo duodenal biopsy and of those who did, some biopsy results were negative. For this reason, these results apply to the broader group of children with positive TG antibody status, regardless of histologic signs of inflammation. Another limitation is the effect of gluten free diet on the ability to detect differences between the groups who were positive versus negative for TG. A substantial minority of children with and without T1D who were positive for TG were avoiding gluten for at least two months prior to enrollment; however, even among those who were avoiding gluten to some degree, there was significant variability in how frequently the individuals were adhering to recommended behaviors for a strict gluten-free diet. This makes the actual gluten exposure difficult to estimate and this was beyond the scope of this study. Another potential limitation of this study was the difference in duration of TG positivity between the subjects with and without T1D. This difference was likely due to ascertainment bias, as the subjects without T1D were recruited as part of the DAISY prospective study and were tested for TG more frequently and over a longer period of time than the subjects with T1D, who were typically first tested upon diagnosis with T1D. When comparing the effect of TG positive status in children with and without T1D, there was no difference in BMD in children with T1D relative to those without T1D, despite a longer duration of TG positivity in the subjects without T1D. Separate analysis showed that length of time with TG positive status was not significantly related to BMD (data not shown). Finally, the BMD z-scores were normalized to chronologic age; however, chronic inflammation could lead to delayed bone age. This could be a confounding factor making BMD appear lower for some individuals.

In conclusion, we found a significantly lower BMD in subjects who were positive for TG compared with subjects who were negative for TG only when there was concurrent T1D. This data supports screening patients with T1D for TG in order to identify those with higher risk of adverse effects, specifically on bone health. The utility of screening of children identified solely by genetic risk remains uncertain. Further longitudinal study is necessary to evaluate the role of GFD on long-term bone health, particularly in the population with T1D.

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Abbreviations

BMD	bone mineral density
CD	celiac disease
DXA	dual-energy x-ray absorptiometry
HbA1c	Hemoglobin A1c
IgA	Immunoglobulin A
T1D	type 1 diabetes
TG	transglutaminase
TSH	Thyroid stimulating hormone

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Table 1

Demographic and clinical data at enrollment for children with T1D. Comparison of those with (TG+) and without (TG–) serologic evidence of celiac disease.

	T1D, +TG (n=123)	T1D, –TG (n=129)	p-value
Sex (males)	59 (48%)	76 (59%)	0.082
Age (y)	13.5 ± 3.7	13.9 ± 2.8	0.37
Duration of Diabetes (y)	7.0 ± 4.4	6.0 ± 4.3	0.078
Height z-score	0.14 ± 1.28	0.24 ± 0.93	0.48
Weight z-score	0.29 ± 0.98	0.43 ± 0.94	0.24
BMI z-score	0.07 ± 2.28	0.36 ± 1.04	0.20
Vitamin D 25OH (ng/mL)	34 ± 9	33 ± 8	0.38
Ferritin (ng/mL)	37 (32–42)	40 (36–45)	0.25
Urine N-Telopeptides (nmol BCE/mmol creat)	223 (188–265)	239 (205–278)	0.55
TSH	2.1 (1.8–2.4)	2.0 (1.8–2.4)	0.78
HbA1c (%)	8.3 (8.1–8.6)	8.6 (8.3–8.9)	0.19
BMD L1-L4 z-score	–0.45 ± 1.22	0.09 ± 1.10	0.0003
Low BMD[¶]	15 (12%)	4 (3%)	0.0076[*]
Symptoms	57 (46%)	46 (36%)	0.085

Data are presented as mean ± SD, geometric mean and 95% CI or frequency (%).

^{*} Fisher Exact P-value due to cell sizes < 5

[¶] Low BMD defined by BMD L1-L4 z-score (for age and gender) of –2 SD.

Table 2

Demographic and clinical data at enrollment for children with and without T1D with positive TG.

	Non-T1D (n=71)	T1D (n=123)	p-value
Sex (males)	27 (38%)	59 (48%)	0.18
Age (y)	13.7 ± 3.3	13.5 ± 3.7	0.70
TG	0.09 (0.07–0.12)	0.14 (0.11–0.18)	0.026
TG+ duration (y)	8.3 ± 3.4	5.5 ± 3.1	<0.0001
Height z-score	0.41 ± 1.07	0.14 ± 1.28	0.13
Weight z-score	0.27 ± 1.05	0.29 ± 0.98	0.93
BMI z-score	0.08 ± 1.06	0.07 ± 2.3	0.98
Vitamin D 25OH (ng/mL)	34 ± 8	34 ± 9	0.83
Ferritin (ng/mL)	34 (29–40)	37 (32–42)	0.47
Urine N-Telopeptides (nmol BCE/mmol creat)	182 (147–224)	223 (188–265)	0.14
BMD L1-L4 z-score	−0.15 ± 1.08	−0.45 ± 1.22	0.086
Low BMD [¶]	3 (4%)	15 (12%)	0.075 [*]
Eaten gluten in past 2 months?	48 (68%)	70 (57%)	0.14

Data are presented as mean ± SD, geometric mean and 95% CI or frequency (%).

^{*} Fisher Exact P-value due to cell sizes < 5[¶] Low BMD defined by BMD L1-L4 z-score (for age and gender) of −2 SD.

Table 3

Predictors of BMD z-score in patients with T1D

	β -coefficient	p-value
Model 1		
TG	-0.81 ± 0.33	0.015
Model 2		
HbA1c	-0.89 ± 0.38	0.021
Model 3		
TG	-0.13 ± 0.05	0.0056
HbA1c	-1.25 ± 0.85	0.0016

Table 4

Demographic and clinical data at enrollment for children without T1D TG+ and TG– serologic evidence of celiac disease.

	No-T1D, TG+ (n=71)	No-T1D, TG– (n=70)	P-value
Sex (%males)	27 (38%)	34 (49%)	0.21
Age (y)	13.7 ± 3.3	14.1 ± 3.1	0.50
Height z-score	0.41 ± 1.07	0.22 ± 1.20	0.33
Weight z-score	0.27 ± 1.05	0.17 ± 1.37	0.61
BMI z-score	0.08 ± 1.06	0.08 ± 1.14	0.98
Vitamin D 25OH (ng/mL)	34 ± 8	33 ± 9	0.44
Ferritin (ng/mL)	34 (29–40)	35 (30–42)	0.79
Urine N-Telopeptides (nmol BCE/mmol creat)	182 (147–224)	174 (138–220)	0.79
BMD L1-L4 z-score	−0.15 ± 1.08	−0.04 ± 1.13	0.58
Low BMD [¶]	3 (4%)	2 (3%)	1.0000 *
Symptoms	25 (36%)	14 (20%)	0.038

Data are presented as mean ± SD, geometric mean and 95% CI or frequency (%).

* Fisher Exact P-value due to cell sizes < 5.

[¶]Low BMD defined by BMD L1-L4 z-score (for age and gender) of −2 SD.