

Impact of Celiac Autoimmunity on Children with Type 1 Diabetes

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Objective Children with type 1 diabetes (T1DM) are at increased risk for celiac disease (CD); however, the benefits of screening for IgA tissue transglutaminase autoantibodies (TG), a marker for CD, are unclear.

Study design We compared 71 screening-identified TG+ with 63 matched TG- children with T1DM. Growth, bone density, and diabetes control measures were obtained.

Results The group was 10 ± 3 years of age, 46% male, with T1DM for 4 ± 3 years. Z scores for weight (0.3 ± 1 vs 0.7 ± 0.8 , $P = .024$), body mass index (BMI) (0.3 ± 0.9 vs 0.8 ± -0.8 , $P = .005$), and midarm circumference (0.3 ± 1.1 vs 0.6 ± 0.9 , $P = .031$) were lower in the TG+ group. Bone mineral density and diabetes control measures were similar. When limiting the analysis to the 35 TG+ subjects with biopsy changes of CD, the BMI Z score was lower than the control group (0.4 ± 0.9 vs 0.7 ± 0.7 , $P = .05$).

Conclusions In children with T1DM, screening-identified evidence of CD is associated with altered body composition, but not bone mineral density or diabetes control. Further study is needed to determine the benefit of early diagnosis and treatment of CD in T1DM children. (*J Pediatr* 2007;150:461-6)

Up to 16% of children with type 1 diabetes (T1DM) express the highly specific serological markers of celiac disease (CD)—autoantibodies to endomysium or tissue transglutaminase.¹⁻⁵ The majority of these children are asymptomatic or do not have symptoms severe enough to seek medical attention.⁶⁻¹⁰ These patients are identifiable only through screening. However, they have the same genetic background (HLA DQ2, DQ8) and characteristic changes on small bowel biopsy as those who present with clinical signs or symptoms. The long-term consequences of untreated subclinical CD remain unclear.¹¹

Manifestations of CD include diarrhea, abdominal pain, iron deficiency anemia, pubertal delay, growth failure, decreased bone mineralization, and villous atrophy on small bowel biopsy.^{3,12-16} A diet free of gluten leads to complete clinical resolution and mucosal healing¹²⁻¹⁶ in the majority of children. If a gluten-free diet (GFD) is initiated late in childhood or adolescence, bone mineralization may not normalize.¹⁶ Although a GFD is effective, only a minority of patients achieve long-term compliance; patients diagnosed because of clinical manifestations have higher compliance rates¹³ than those identified through screening.^{17,18}

In poorly controlled T1DM, poor growth,^{19,20} delayed sexual development,²¹⁻²³ and diminished bone mineralization²⁴⁻²⁷ have been reported. Thus, CD places the child with T1DM at increased risk for these complications.^{3,28} In addition, variable nutrient absorption because of CD-associated intestinal injury may destabilize diabetic control, leading to recurrent hypoglycemia.²⁹

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BMI	Body mass index	LBMDV	Volumetric lumbar bone mineral density
CD	Celiac disease	NTX	Crosslinked N-telopeptides of type I collagen
GFD	Gluten-free diet	PTH	Parathyroid hormone
HbA1c	Hemoglobin A1c	T1DM	Type 1 diabetes mellitus
IGF-I	Insulin-like growth factor I	TG	IgA tissue transglutaminase autoantibodies
IGF-BP3	Insulin-like growth factor binding protein 3	TSH	Thyroid stimulating hormone
LBMDA	Areal lumbar bone mineral density		

Table I. Demographic and clinical data at enrollment of children with diabetes with (TG+) and without (TG-) serologic evidence of celiac disease

	TG+ n = 71	TG- n = 63	P value
Age (y)	10.1 ± 2.9	10.2 ± 3.3	.738
T1DM duration (y)	4.3 ± 3.3	4.4 ± 3.2	.0614
Sex (males)	33 (46.4%)	29 (46.0%)	.959
TG index	0.56 ± 0.50	-0.004 ± 0.02	<.0001
HbA1c (4.2-6.3%)	8.3 ± 1.3%	8.3 ± 1.0%	.680
Insulin dose/kg/day	0.78 ± 0.32	1.18 ± 2.90	.322
% subjects with severe hypoglycemic event*	14.9%	7.9%	.412
Wt Z score	0.29 ± 1.0	0.68 ± 0.84	.024
BMI Z score	0.34 ± 0.9	0.75 ± 0.76	.005
Height Z score	0.02 ± 1.45	0.34 ± 1.02	.369
Triceps skinfold Z score	1.0 ± 0.85	0.93 ± 0.77	.612
Midarm circumference Z score	0.31 ± 1.15	0.60 ± 0.91	.031
L-spine Z score for bone age	-0.69 ± 1.46	-0.41 ± 1.49	.073
Volumetric L-spine Z score for bone age	-0.21 ± 1.22	0.07 ± 1.3	.237
Bone age delay (y)	0.05 ± 1.7	0.006 ± 0.92	.304
PTH (13-54 pg/mL)	24.8 ± 8.5	21.5 ± 7	.022
Vitamin D 25OH (15-45 ng/mL)	29.0 ± 7.9	31.2 ± 7.8	.099
Urine n-telopeptides†	105.3 ± 60.2%	69.0 ± 33.2%	<.0001
Vitamin B12 (211-911 pg/mL)	714.7 ± 297.6	759.7 ± 311.9	.299
Prealbumin (18-35.7 mg/dL)	20.2 ± 2.8	21.0 ± 4.0	.064
Ferritin (15-119 ng/ mL)	36.6 ± 22.2	39.8 ± 18.4	.164
Urine microalbumin/creatinine ratio (0-30 ug/mg creat)	12.5 ± 16.8	17.7 ± 34.4	.882
Free T4 (0.8-1.7 ng/dL)	1.18 ± 0.21	1.31 ± 0.25	.001
TSH (0.36-5.4 ng/dL)	2.45 ± 1.93	2.55 ± 6.79	.002
IGF-I Z score	-2.12 ± 0.99	-1.82 ± 1.02	.037
IGF-BP3 Z score	-0.78 ± 1.0	-0.68 ± 1.23	.999

*% of subjects with severe hypoglycemic event in the 2 years prior to enrollment

†Urine N-telopeptides: % of age- and sex-specific reference mean (evaluated for bone age)

The primary aim of this study was to determine the impact of screening-identified CD on growth, bone mineralization, and diabetes control.

METHODS

Research Design/Methods

Since 1998, patients with T1DM followed at the Barbara Davis Center have undergone routine screening for CD with testing for IgA anti-tissue transglutaminase autoantibodies (TG).^{4,10} Those with elevated TG levels were offered small bowel biopsy, enrollment into this study, and dietitian instruction in the GFD. Patients or their parents self-selected to a regular diet or GFD. Subjects 2 to 18 years of age and TG+ were frequency matched with TG- subjects for sex, age ± 1 year, and T1DM duration ± 1 year (Table I). Patients were excluded if they had chronic glucocorticoid use, had another systemic illness, or required medications known to adversely affect linear growth or bone mineralization (patients with well-controlled thyroid disease were not excluded).

Anthropometrics/Bone Densitometry

Height, weight, body mass index (BMI), triceps skinfold measurements, and midarm circumference were con-

verted to age- and sex-specific Z scores ([value-mean value for sex and age]/standard deviation).^{30,31} Bone densitometry was performed in the anteroposterior direction at the lumbar spine (L2-L4) using a Lunar XRC1 version 4.7E bone densitometer with smart scan (Granite Microsystems, Mequon, Wis). Data were expressed as age- and sex-specific Z scores for both bone age and chronologic age. Areal lumbar bone mineral density (LBMDA, grams per square centimeter) was obtained and volumetric lumbar bone mineral density (LBMDV, grams per cubic centimeter) was calculated based on the LBMDA and the width of the lumbar vertebrae using the formula $LBMDA \times (4/[\pi \times \text{width}]) = LBMDV$.³²

Small Bowel Biopsy

Small bowel biopsy was performed on TG+ subjects consuming a normal gluten-containing diet. At upper intestinal endoscopy, two biopsies from the distal duodenum and two biopsies from the proximal duodenum were obtained. A pediatric pathologist, unaware of the clinical and laboratory results, interpreted the sample according to the criteria defined by Marsh,³³ as previously described.¹⁰ A normal biopsy is Marsh 0, increased intraepithelial lymphocytes is Marsh 1, crypt hyperplasia is Marsh 2, and villous atrophy is Marsh 3. A Marsh score ≥2 is considered to be evidence for CD.

Laboratory Tests and Bone Age

The IgA TG radioassay has been previously described^{10,34} and compared with commercially available enzyme-linked immunosorbent TG assays.¹ Briefly, *in vitro* transcribed and translated full-length human recombinant transglutaminase was used. Radiolabeled samples were measured in the fluid phase with duplicates in 96-well plates using a Top Count β -counter (Packard Instrument Company, Meriden, Conn). A TG index >0.05 is considered elevated.³⁴ A TG index of >0.05 has a positive predictive value for histologic confirmation of CD of 76%, and a TG index of >0.5 has a positive predictive value of 96%.³⁵

Hemoglobin A1c (HbA1c) was measured by the DCA 2000TM (Bayer Diagnostics, Elkhart, Ind) by latex agglutination procedure. Insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein 3 (IGF-BP3) were determined by enzyme-immunoassay (R&D Systems, Minneapolis, Minn) and evaluated as Z scores adjusted for bone age (SD from the mean for age- and sex- matched lab controls). Urinary cross-linked N-telopeptides of type I collagen (NTX) were determined by EIA (Wampoles Osteomark, Princeton, NJ) using a spot urine collection. Results for urinary NTX/creatinine ratios were expressed as a percentage of age- and sex-specific mean values using published reference data.³⁶ Serum intact parathyroid hormone (PTH), 25-hydroxyvitamin D, free T4, thyroid stimulating hormone (TSH), pre-albumin, ferritin, urine microalbumin/creatinine, and Vitamin B12 measurements were performed using standard laboratory methods. Bone age was determined in masked conditions by a single investigator (JS) using the method of Greulich and Pyle.³⁷

Hypoglycemia/Other Assessments

Episodes of severe hypoglycemia, defined as seizures, altered consciousness, emergency department visits, or hospitalizations as a result of hypoglycemia within 2 years prior to study enrollment were obtained from the Barbara Davis Center clinical electronic database. Additionally, the percentage of blood glucose levels <70 mg/dL from home glucose meter downloads at the visit before enrollment were obtained. These downloads provide information regarding the month before the download. A questionnaire ascertaining each subject's daily insulin regimen was administered and daily dose of insulin per kilogram was then calculated. A symptom questionnaire regarding the presence of diarrhea, abdominal pain, constipation, vomiting, irritability, decreased energy, gas, itch/rash, edema, bleeding disorder, pubertal delay, failure to gain weight, short stature, or bone fracture was administered by a study dietitian.²⁸

Statistics

Log transformations were applied to highly skewed variables. Chi-square test of independence or Fisher's exact test was used to test the distribution of discrete variables. The Wilcoxon's rank sum test was used to test the difference

among groups in continuous variables at baseline. There were no *P* value adjustments for multiple tests. A subanalysis was performed with pair-matched TG- and TG+ subjects with Marsh scores ≥ 2 . These subjects were matched for age, sex, and diabetes duration. A matched group analysis was performed using the rank sum test. Symptoms were analyzed using a χ^2 test; Fisher's exact test was used when the frequency of a symptom was <5 .

RESULTS

There were 71 TG+ and 63 TG- children enrolled, all with T1DM. The TG+ group was 10 ± 3 years of age, 46% male, 94% self-described non-Hispanic white, and had a T1DM duration of 4 ± 3 years. Because of frequency matching, age, sex, and diabetes duration were similar in the TG+ and TG- groups (Table I). The median duration of GFD was 0 months in the TG+ group (mean 5.4 ± 11.2 months). Twenty percent of TG+ subjects stated that they had been following a GFD for ≥ 6 months; the mean TG index of this group was similar to the mean of the remainder of the TG+ group (0.50 ± 0.47 vs 0.58 ± 0.51 , *P* = .768). The TG+ group reported increased frequency of decreased energy, flatulence, itching/rash, failure to gain weight, and short stature (data not shown, results obtained after TG results were known).

The TG+ group had lower weight, BMI, and midarm circumference Z scores than the TG- group, but the groups were similar for bone mineral density. There were no differences between the TG+ and TG- groups in HbA1c at the baseline visit (Table I) or in the average HbA1c during the 2 years before enrollment between the TG+ ($8.4 \pm 1.5\%$) and TG- groups ($8.6 \pm 1.0\%$), *P* = .245. There were also no differences in episodes of severe hypoglycemia, as 14.9% of subjects in the TG+ group and 7.9% in the TG- group had a single episode of severe hypoglycemia during the 2 years before enrollment (*P* = .412). No subject had more than one episode of severe hypoglycemia during the 2 years before enrollment. The TG+ group had $9.7 \pm 6.0\%$ of blood glucose values <70 mg/dL (obtained from glucose meter downloads at the visit before enrollment), compared with $9.0 \pm 5.8\%$ in the TG- group (*P* = .470). There were no differences between groups in insulin dose/kg.

The TG+ group had lower IGF-I Z scores than the TG- group, but both were decreased compared with control values. The TG+ group had higher PTH and urine NTX levels and lower free T4 and TSH levels. (Table I). Five subjects in the TG+ group (7%) and four subjects in the TG- group (6%) had hypothyroidism and were receiving replacement therapy. There were no other differences between groups in any other variables. A subanalysis of TG+ subjects on GFD <6 months (*n* = 57, mean 1 ± 1.6 months and median 0 months) at enrollment compared with TG- controls demonstrated the same differences in weight, BMI, midarm circumference Z scores, PTH, urine NTX, free T4, and TSH levels; there was no longer a statistically significant

Table II. Demographic and clinical data at enrollment of children with diabetes with histologic (Biopsy+) and without serologic (TG-) evidence of celiac disease

	Biopsy + n = 35	TG- matched controls n = 35	P value
Age (y)	10.52 ± 2.70	10.13 ± 3.07	.488
Diabetes mellitus duration (y)	4.00 ± 3.22	4.12 ± 3.25	.660
Sex (males)	17 (48.6%)	17 (48.6%)	1.000
TG index	0.67 ± 0.55	-0.001 ± 0.02	<.001
HbA1c (4.2-6.3%)	8.1 ± 1.3%	8.2 ± 1.2%	.919
Insulin dose/ kg/ day	0.80 ± 0.40	1.39 ± 3.89	.835
Wt Z score	0.35 ± 1.09	0.53 ± 0.75	.431
BMI Z score	0.36 ± 0.87	0.68 ± 0.67	.050
Height Z score	0.25 ± 1.17	0.12 ± 0.92	.445
Triceps skinfold Z score	1.08 ± 0.85	0.86 ± 0.79	.594
Midarm circumference Z score	0.41 ± 1.29	0.51 ± 0.82	.208
L-spine Z score for bone age	-0.41 ± 1.57	-0.54 ± 1.71	.831
Volumetric L-spine Z score for bone age	0.04 ± 1.24	-0.0001 ± 1.37	.960
Bone age delay (y)	0.22 ± 2.24	-0.04 ± 0.90	.648
PTH (13-54 pg/mL)	25.7 ± 7.5	21.4 ± 6.2	.021
Vitamin D 25OH (15-45 ng/mL)	31.3 ± 7.7	31.9 ± 6.2	.689
Urine n-telopeptides*	107.6 ± 58.2%	70.7 ± 36.3%	.0004
Vitamin B12 (211-911 pg/mL)	769.5 ± 301.2	839.1 ± 330.9	.065
Prealbumin (18-35.7 mg/dL)	20.4 ± 2.2	21.0 ± 2.9	.384
Ferritin (15-119 ng/ mL)	30.9 ± 16.3	39.1 ± 18.0	.065
Urine microalbumin/creatinine ratio (0-30 ug/mg creat)	9.0 ± 9.6	19.9 ± 40.9	.572
Free T4 (0.8-1.7 ng/dL)	1.16 ± 0.23	1.33 ± 0.31	.015
TSH (0.36-5.4 ng/dL)	2.42 ± 1.58	3.33 ± 9.06	.029
IGF-I Z score	-1.84 ± 1.10	-1.99 ± 0.96	.834
IGF-BP3 Z score	-0.50 ± 0.99	-0.86 ± 1.20	.091

*Urine N-telopeptides: % of age- and sex-specific reference mean (evaluated for bone age)

difference between groups in IGF-I Z scores (data not shown).

Small bowel biopsy was performed in 48 of the 71 TG+ subjects (68%). Villous atrophy (Marsh score 3) was found in 33 and crypt hyperplasia (Marsh score 2) in an additional 2 subjects. Thus 73% of those with a biopsy and 50% of all screening-identified TG+ subjects had confirmation of CD on small bowel biopsy. None of the TG- group had a small bowel biopsy. A subanalysis was performed comparing these 35 TG+ subjects with biopsy evidence of CD with TG- subjects matched for age, sex, and diabetes duration (Table II). The group with biopsy evidence of CD, as the entire TG+ group, had lower BMI Z scores and similar HbA1c and bone mineral density compared with the TG- group, but no difference in weight or midarm circumference Z scores. As in the total TG+ group, the biopsy positive group had higher PTH and urine NTX and lower free T4 and TSH than the group without TG. The biopsy positive group had increased frequency of flatulence (28.6% vs 5.7%), *P* = .023, but there were no other differences in reported symptoms (data not shown).

DISCUSSION

This study evaluated a large number of children with T1DM and celiac autoimmunity. In children with T1DM,

celiac autoimmunity is associated with decreased weight and BMI Z scores. These findings are important for several reasons.

First, whether to screen children with T1DM for CD is controversial. The 2004 National Institutes of Health consensus statement on CD¹¹ reported that for those with T1DM “current data do not indicate a clear outcome benefit for early detection and treatment of asymptomatic individuals.” Routine screening was not recommended. However, areas for future research included “a cohort study to determine the natural history of untreated celiac disease, especially silent celiac disease” and to “analyze the benefit of screening high-risk groups relevant to clinically important outcomes.” This study from a large single-center group of subjects provides much-needed information to guide clinical practice.

Second, there is uncertainty regarding the optimal timing of therapy for CD in children with T1DM.³⁸ In children with recently diagnosed T1DM, the psychological burden of a second chronic illness requiring significant life-long diet change was emphasized.³⁹ Third, the clinical impact of CD in children seems to vary from person to person, probably because of the variable severity of the disease process. The multiple terminologies used in the literature (latent, subclinical, mild, screening-identified) exemplify the limited understanding of the natural history, pathogenesis, and modifying factors in CD. Continued follow-up of this cohort will eval-

uate the effect of early initiation of GFD on screening-identified patients as well as the effect of GFD over time.

Although the results of our study are not decisive enough to assert that universal screening is justified, the evidence is also not conclusive enough to renounce the position statements by the American Diabetes Association⁴⁰ and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition³ that the T1DM population should undergo screening for CD. This study extends to children with T1DM our previous finding of mild differences in BMI,²⁸ and is in agreement with one other study.⁴¹ However, others found no differences in anthropometrics.^{18,42,43} Of note, we and others^{18,42,43} did not find an impact of CD on height in patients with T1DM, although one other study found improvement in height with GFD.⁴⁴ Some studies have suggested that CD has an impact on glycemic control,^{41,44} but we and others^{42,43} have not confirmed this. IGF-I values were low in both TG+ and TG- patients with T1DM. Circulating IGF-I levels are reduced in T1DM and levels are dependent on the degree of metabolic control.^{45,46} However, our study demonstrated lower values in those T1DM patients who also have CD; this may have adverse implications for both final height and bone mineralization.

We did not find any differences in bone density in these relatively young patients, although decreased bone mineral density has been associated with childhood CD.^{12,13,16} However, we did find increased urine NTX, a marker of bone resorption, in patients with T1DM and evidence of CD. Our patient population may be too young to have abnormalities demonstrated by dual-energy x-ray absorptiometry, and bone turnover markers may precede these abnormalities. Importantly, Vitamin D 25-OH levels were normal; therefore, Vitamin D deficiency is not the cause of increased bone turnover.

Through screening, we identified 35 patients (49.3% of the TG+ patients) who had small bowel biopsy-confirmed CD. These patients had abnormalities in anthropometric measures and in bone turnover markers, as did the entire TG+ group. Importantly, it does not appear that having histologic evidence of CD has a more profound clinical effect than having TG.

An important limitation of this study is that 20% of the subjects in the TG+ group claimed to be following a GFD for at least 6 months before enrollment. This could result in a type II error, of finding no difference when one does exist. However, the mean TG index in the TG+ group at enrollment was >0.5 and not different from those recently begun on a GFD, suggesting that the GFD was not strictly followed.^{13,17,18} Additionally, analysis excluding those reporting a GFD for >6 months before enrollment revealed results similar to the analysis of the entire cohort.

Another limitation is that not all patients underwent biopsies, and they did not therefore all have biopsy-proven CD. However, our primary aim was to investigate the significance of having evidence of CD as measured by TG+, as not all patients in clinical practice agree to a small bowel biopsy. We demonstrated that those with histologic evidence of CD

had similar clinical and laboratory differences from the TG- group as did the entire TG+ group.

In conclusion, we demonstrated differences in weight and BMI Z scores between TG+ and TG- T1DM patients. There were no differences in bone density or in diabetes control between these groups. Differences in urine NTX between these groups is of uncertain significance. There continues to be evidence for screening patients with T1DM for TG at regular intervals, as it aids in identifying patients for small bowel biopsy. Further longitudinal studies are needed to describe the natural history of untreated CD, to assess the mechanisms of decreased bone mineral density, and to determine the optimal timing of dietary therapy.

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