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Celiac Autoimmunity in Children with Type 1 Diabetes: A two-year follow-up

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Abstract

Objective—To determine the benefits of screening for celiac autoimmunity via IgA transglutaminase autoantibodies (TG) in children with type 1 diabetes (T1D).

Study design—We followed 79 screening-identified TG+ and 56 matched TG– children with T1D for 2 years to evaluate growth, bone mineral density, nutritional status, and diabetes control. TG+ subjects self-selected to gluten-free or gluten-containing diet.

Results—Of the initial cohort, 80% were available for re-examination after 2 years. TG+ subjects had consistently lower weight z-scores and higher urine N-telopeptides than TG– subjects, but similar measures of bone density and diabetes outcomes. TG+ children who remained on a gluten-containing diet had lower IGF-BP3 z-scores compared with TG+ subjects who reported following a gluten-free diet. Children who continued with high TG index throughout the study had lower bone mineral density z-scores, ferritin, and vitamin D 25OH levels, compared with the TG– group.

Conclusions—No significant adverse outcomes were identified in children with T1D with screening-identified TG+ who delay GFD therapy for 2 years. Children with persistently high levels of TG may be at greater risk. The optimal timing of screening and treatment for CD in children with T1D requires further investigation.

Keywords

type 1 diabetes; pediatric; celiac disease; tissue transglutaminase autoantibodies; screening; gluten; diet

Up to 16% of children with type 1 diabetes mellitus (T1D) have celiac disease (CD)^{1,2,3,4,5}. Routine screening using IgA transglutaminase autoantibody (TG) has been recommended

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^{6,7}. However, important unanswered questions remain regarding benefit of gluten-free diet (GFD) in screening-identified TG+ children with T1D. Even though high TG levels are specific for biopsy-confirmed CD, low-positive TG may be associated with negative biopsy but may be a risk factor for future CD. The optimal timing of GFD initiation in screening-identified TG+ children, with or without T1D, remains unclear. The child with T1D and CD faces two life-long changes in diet, yet untreated CD has been associated with recurrent hypoglycemia and poor glycemic control.

We previously reported baseline data regarding children with T1D who were found to have celiac autoimmunity (persistently elevated TG, with or without positive biopsy) during routine screening ⁸. Anthropometric and metabolic characteristics of these children were compared with those of matched children with T1D negative for TG. The TG+ children had lower weight, BMI, and mid-arm circumference z-scores and increased bone turnover (increased urinary cross-linked N-telopeptides of type I collagen, a marker of bone resorption), compared with TG- controls. There were no differences in bone mineral density (BMD) or serum 25-OH-vitamin D levels.

To better define the natural history of celiac autoimmunity and to explore the benefit of early GFD, we have prospectively followed this cohort of subjects with T1D with and without celiac autoimmunity. The aim of this observational study was to determine the impact of screening-detected celiac autoimmunity and GFD on growth, bone mineralization, and diabetes control during a 2-year follow-up.

Methods

Since 1999, patients with T1D followed at the Barbara Davis Center for Childhood Diabetes have undergone routine TG testing ^{3,9}. TG+ subjects (TG index >0.05) were offered small bowel biopsy, dietary instruction on the GFD, and entry into this observational follow-up study. Subjects (their parents, in many instances) self-selected to continue a regular diet (RD) or GFD. Details of study methods have been previously reported ⁸. At baseline, 71 TG+ subjects were frequency matched for sex, age, and T1D duration with 63 TG- children. Included in this report are 8 additional TG+ subjects who were accrued after the baseline data were reported and who have completed the two year visit. Additionally, for the purposes of this analysis, we only included those subjects with at least two study visits; therefore only 56 of the original 63 TG- subjects were included in this analysis.

Anthropometrics and Bone densitometry

Height, weight, body mass index (BMI), and mid-arm circumference were converted to age- and sex-specific z- scores. Anthropometric measures were converted to age- and sex-specific z-scores ^{10,11}. Bone densitometry of the lumbar spine (L2-L4) was performed using a Lunar XRC1 version 4.7E bone densitometer with smart scan as previously described ⁸. Bone mineral density data were expressed as age- and sex-specific Z-scores for bone age. Bone age films were obtained annually and were determined in masked conditions by a single investigator (JS) using the method of Greulich and Pyle ^{12,12}.

Small bowel biopsy and sustained high TG index

TG+ subjects were offered small bowel biopsy to confirm the diagnosis of CD. Fifty-two of the 79 subjects had biopsies, and 67% (35/52) had a Marsh score of 3 (villous atrophy), consistent with a diagnosis of CD. An additional 3 subjects had Marsh score 2 (crypt hyperplasia), and 2 subjects had a Marsh score of 1 (lymphocytic infiltration). Parents of 27 TG+ children refused biopsy; however, some started GFD. Except for higher TG levels,

characteristics of TG+ children with biopsy-confirmed CD differed little from those of the TG+ children who did not undergo biopsy⁸.

Laboratory Tests

The immunoglobulin A (IgA) TG radioassay has been previously described^{9,13,14} and compared with commercially available ELISA TG assays¹⁵. 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 beta-counter (Packard Instrument Company, Meriden, CT). A TG index >0.05 is considered elevated¹⁶. A TG index of >0.05 has a positive predictive value for histologic confirmation of CD of 63%, and a TG index of >0.5 has a positive predictive value of 80% in asymptomatic screening-detected children¹. A TG index of 0.05 therefore has a similar sensitivity for positive confirmatory biopsy as 20 Units TG IgA measured by ELISA (Inova Diagnostics, Inc, San Diego, CA), though the values obtained by ELISA differ based on commercial assay (15). 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 (evaluated for bone age)¹⁷. As previously reported (8), IgA TG¹⁸, hemoglobin A1c (HbA1c), insulin-like growth factor binding protein 3 (IGF-BP3), intact parathyroid hormone (iPTH, normal range 13–54 pg/mL), 25-hydroxy-vitamin D (normal range 30–74 ng/mL), free T4 (FT4, normal range 0.8–1.7 ng/dL), thyroid stimulating hormone (TSH, normal range 0.36–5.4 mIU/L), vitamin B12 (normal range 211–911 pg/mL), and ferritin (normal range 15–119 ng/mL), urinary cross-linked N-telopeptides of type I collagen (NTX) as well as urine microalbumin/ creatinine were measured at study entry and annually thereafter.

Questionnaires

A symptom questionnaire was obtained via subject report at each study visit. This questionnaire inquired about the presence of abdominal symptoms such as diarrhea, abdominal pain, constipation, and abdominal distension as well as the presence of rashes or itching, easy bleeding or bruising, problems with pubertal delay or gaining weight, short stature, bone fractures, or anemia. Also obtained at each study visit was a diet recall questionnaire as well as self-reported episodes of severe hypoglycemia. Subjects were asked to report whether they had an episode of hypoglycemia requiring assistance from someone else (seizure, loss of consciousness, glucagon administration, emergency room visit, or hospitalization) in the interval between visits.

Statistics

Study subjects with at least two annual examinations were included in the analyses and all available data points were used in a mixed model repeated measures analysis with pre-planned contrasts between groups at baseline, one year, and two years. Such models are robust to missing data and allow the computation of least squares means $\pm$ SE for each time point. There were no adjustments made for multiple comparisons due to the sample size retained at each time point; therefore, $p < 0.05$ was considered significant. We compared TG– subjects with TG+ subjects, TG+ subjects who self-selected regular diet to those on self-selected GFD, and TG+ subjects with sustained TG > 0.5 at baseline, 12 months, and 2 years to TG– subjects. We also compared subjects with positive biopsies with those with negative biopsies and those with positive biopsies with those TG–.

Results

Of the baseline cohort of 135 subjects, 109 (80%) completed the 2-year study visits: 80% (63/79) of TG+ subjects and 82% (46/56) of TG− controls. These groups were matched for age (10.4 ± 0.4 vs. 10.2 ± 0.4 yr), duration of diabetes (3.8 ± 0.3 vs. 4.1 ± 0.4 yr) and sex (56% males vs. 46%) at baseline. The characteristics of subjects lost to follow-up did not differ from those remaining in the study. Among TG+ subjects, 86% (37/43) in the GFD group and 72% (26/36) in the RD group completed the 2-year follow-up.

Comparison of children with celiac autoimmunity to controls

Seventy-nine TG+ subjects and 56 TG− subjects had at least two study visits, and 61 TG+ and 54 TG− subjects had BMD measures available. Table I summarizes longitudinal changes in anthropometric and laboratory characteristics of these patients. At baseline, the two groups were similar in age, sex, and diabetes duration (data not shown). At baseline, TG+ subjects, compared with TG− subjects, had lower z-scores for weight and mid-arm circumference, free T4 and insulin/kg values, with higher urine NTX and intact PTH levels, and no differences in HbA1c and episodes of severe hypoglycemia, BMD, or other nutritional variables (ferritin and vitamin B12), data not shown.

At 1 year, there were no differences between TG+ patients and TG− subjects except in weight z-scores. At 2 years, TG+ patients continued to have higher urine NTX and lower weight and BMI z-scores than TG− subjects. The mean TG levels in TG+ group declined from 0.57 ± 0.04 at baseline to 0.37 ± 0.04 at 1 year and 0.33 ± 0.04 at 2 years, $p < 0.001$. The TG levels fully normalized (< 0.05) in only 14 (18.7%) TG+ subjects at 1 year and in 14 (22.2%) at 2 year follow-up. There were no other differences in any of the variables at either 12 or 24 months (data not shown).

Effect of GFD compared with RD

Of the 79 TG+ subjects, 43 chose a GFD and 36 chose RD. At baseline, the 2 groups were similar for age, diabetes duration, sex, and number of symptoms reported (data not shown). The TG index values, initially higher at baseline in the GFD than the RD group, were similar at 1 and 2 years follow-up (Table II). Between baseline and 2 years, the mean TG index decreased in both the GFD ($p < 0.0001$) and the RD ($p = 0.001$) groups. There were no differences between GFD and regular diet groups in one or more reported symptoms at 12 months (58% vs 71%, respectively) or at 2 years (66% vs 67%). Mean compliance rate with the gluten free diet (% reporting never/ almost never on a list of gluten-containing foods) was 91.6% for the GFD group during follow-up and 27.1% for the regular diet group. This did not change from 12 months to 24 months for either group. Those reporting a GFD had higher IGF-BP3 z-scores at 2 years than those on a RD. There were no other differences between groups in any of the variables studied.

Sustained high TG index (> 0.5) compared with TG−

There were 15 subjects (19% of TG+ group) who continued to have very high TG levels (> 0.5) at 1 year (10 in GFD group), and 9 subjects at 2 years. The characteristics of these subjects, presumably with persistent active celiac autoimmunity, were compared with those of TG− subjects (Table III). The persistently high TG+ group had lower BMD from baseline throughout the study follow-up, with lower volumetric lumbar spine z-scores at baseline and lower lumbar spine z-scores at 1- and 2-year follow up. The persistently high TG+ group also had elevated intact PTH and urinary NTX levels, and lower vitamin D 25-OH levels at various times during follow-up. Ferritin levels were lower at baseline and throughout the follow-up, pointing to more generalized malnutrition in children with persistently high TG+.

Biopsy findings

Outcomes in biopsy negative (n=17) and biopsy positive (defined as a Marsh score 3, n= 35) subjects are compared in Table IV (available at www.jpeds.com). Those with Marsh score of 0 (n=12) or 1 or 2 (n=5) were considered to be biopsy negative. At baseline, the biopsy positive group had higher TG index and lower ferritin levels. By 24 months, the biopsy positive group still had lower ferritin but higher prealbumin and z-scores for height, IGFI, and IGFBP3. There were no other differences between these groups.

Additionally, we compared the positive biopsy group with the TG– group (Table V; available at www.jpeds.com). At all times, urine NTX levels were higher in the positive biopsy group. At baseline, the positive biopsy group had lower ferritin and free T4 than those without celiac autoimmunity. At 24 months, BMI z-score was lower in the biopsy positive group compared with the TG– group.

Discussion

Guidelines from both pediatric diabetes¹⁹ and pediatric gastroenterology professional societies⁷ recommend screening children with T1D for CD. On the other hand, a 2004 NIH consensus statement stated that “current data do not indicate clear outcome benefit for early detection and treatment of asymptomatic individuals in higher risk groups such as T1D” and that studies are needed to determine the natural history and benefit of screening and treatment²⁰. The rationale for screening children with T1D for CD includes reducing hypoglycemia events, maximizing growth, bone health, and nutrition, and reducing long-term malignancy risks and mortality^{21,22}. In contrast, the argument against early GFD includes difficulty in handling the dietary, lifestyle, and medication management changes inherent in the care of children with both T1D and CD and lack of clear benefit in asymptomatic children²³. In children with T1D, those with evidence of symptomatic CD benefit from GFD^{4,24}; in asymptomatic cases the demonstrated benefit is limited to weight gain and BMD changes^{25,8,5,26}. In any case, adherence to GFD by children with T1D is only about 50%^{4,27,28,29,30}. The conflicting recommendations and diverse viewpoints highlight the need for better understanding of CD.

This 2-year prospective follow-up study has provided additional evidence that children with T1D who have few classical symptom of CD, but are screening-identified as TG+, present with a number of anthropometric and laboratory abnormalities, only some of which improve on GFD. We found that celiac autoimmunity was associated with lower weight and BMI and increased bone turnover, associated with increased fracture risk³¹ independent of bone mineral density in adults. Increased bone resorption may precede changes on DEXA and may contribute to osteoporosis in adults with T1D^{32,33}. Low vitamin D, found in 53% of our subjects, may be an additional risk factor for fractures³⁴. Of particular concern are children who continue with high TG levels, some despite reported GFD. Their bone mineral density, ferritin, and vitamin D 25OH levels were significantly lower, compared with the TG – group. School-children are less compliant to GFD than younger children and adults and less likely to recall dietary transgressions. This may explain persistence of TG+ despite reported GFD in some cases. The current study is the largest, carefully controlled, prospective study in children with T1D and celiac autoimmunity with 80% retention during the follow-up.

We did not see differences in HbA1c by TG status, consistent with many other studies^{35,5,27,36}, except for one report demonstrating a lower HbA1c with a gluten-free diet³⁷. There were also no differences in episodes of severe hypoglycemia.

This study has several important limitations. We did not randomize study participants to GFD or regular diet because families indicated they would not enroll or would not adhere to the diet they did not choose. Despite allowing self-selection to diet groups, adherence to the GFD was likely suboptimal since the TG levels did not normalize in most children reporting GFD. All families received identical initial dietary instruction; however, those diagnosed with CD by biopsy may have been more actively seeking additional resources, leading to possible improved adherence. Although there are no validated measures of gluten exposure, it has been suggested that antibodies to deamidated gliadin peptide decrease more promptly than TG in response to gluten elimination³⁸. Additionally there has been significant cross-over in the self-selected diet over the 2-year follow-up. Although this could decrease our ability to detect a benefit of GFD, by itself, a 27% cross-over from regular to gluten-free diet provides important information concerning changing attitudes to GFD among families with TG+ children. This study has limited power and could miss small differences in outcomes, however, a type II error is an unlikely explanation for the lack of major difference between outcomes in the GFD and regular diet groups because the mean TG levels were similar, suggesting similar gluten exposure in both diet groups^{30,39,40}. The duration of seropositivity prior to study enrollment was not possible to determine because many patients were positive for TG on first screening around the time of diagnosis of T1D. A few subjects reported starting GFD more than 6 months prior to enrollment. Finally, this 2 year follow-up cohort differs slightly from that used for baseline report⁸. Eight additional TG+ subjects were enrolled and followed for 2 years. Seven of the original 63 TG- subjects were excluded from analysis because they did not have any follow-up visits. Re-analyzing the group with 2 year follow-up for differences at baseline showed that there were no longer differences between groups at baseline for BMI z-scores ($p=0.07$) or IGF1 z-scores ($p=0.07$) but that the TG+ group required less insulin/kg/d compared with the TG- group ($p=0.03$).

In conclusion, this 2-year controlled prospective follow-up study of celiac autoimmunity in T1D children did not demonstrate significant adverse outcome in those children who delayed GFD. Differences in weight and bone turnover were found, but not in bone mineral density or glycemic control. Persistence of TG at high levels should be a reason for concern. The optimal timing of screening and treatment of celiac autoimmunity remains to be determined. Longer follow-up as well as cost-benefit and quality of life analyses will be helpful to further assess these issues.

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Abbreviations used in this paper

T1D	Type 1 diabetes
GFD	Gluten-free diet
PTH	Parathyroid hormone
IGF-1	insulin-like growth factor 1
TSH	Thyroid stimulating hormone
IGF-BP3	Insulin-like growth factor binding protein 3
TG	IgA tissue transglutaminase autoantibody
CD	Celiac Disease

HbA1c	Hemoglobin A1c
NTX	N-telopeptides
DXA	dual-energy x-ray absorptiometry

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Table 1

Characteristics (* z-score) of TG+ group compared with TG- group.

	Baseline			Year 1			Year 2		
	TG - n=56	TG + n=79	P > t	TG - n=55	TG + n=77	P > t	TG - n=46	TG + n=63	P > t
TG	-0.00 ± 0.04	0.57 ± 0.04	<.0001	0.00 ± 0.04	0.37 ± 0.04	<.0001	0.00 ± 0.05	0.33 ± 0.04	<.0001
Weight*	0.65 ± 0.14	0.25 ± 0.12	0.03	0.67 ± 0.14	0.27 ± 0.12	0.04	0.66 ± 0.15	0.18 ± 0.12	0.01
BMI*	0.74 ± 0.18	0.30 ± 0.15	0.07	0.68 ± 0.18	0.33 ± 0.16	0.15	1.07 ± 0.20	0.28 ± 0.17	0.003
Height*	0.29 ± 0.17	0.03 ± 0.14	0.24	0.28 ± 0.17	0.01 ± 0.14	0.23	0.33 ± 0.17	0.10 ± 0.14	0.29
Mid-arm circumference*	0.56 ± 0.14	0.19 ± 0.12	0.046	0.48 ± 0.14	0.22 ± 0.12	0.15	0.42 ± 0.14	0.22 ± 0.12	0.3
Intact PTH (pg/mL)	21.59 ± 1.46	25.69 ± 1.28	0.04	24.91 ± 1.46	25.36 ± 1.26	0.82	25.95 ± 1.60	29.25 ± 1.37	0.12
Urine N-telopeptides **	105.1 ± 11.63	157.9 ± 9.9	0.0007	108.1 ± 11.85	135.6 ± 9.9	0.08	102.8 ± 12.7	139.0 ± 11.1	0.03
Vitamin D 25OH (ng/mL)	31.5 ± 1.0	28.9 ± 0.9	0.05	27.7 ± 1.0	29.1 ± 0.86	0.29	30.1 ± 1.1	28.4 ± 0.9	0.24
Free T4 (ng/dL)	1.33 ± 0.03	1.20 ± 0.03	0.006	1.32 ± 0.03	1.28 ± 0.03	0.32	1.33 ± 0.04	1.28 ± 0.03	0.29
TSH (mIU/L)	2.75 ± 0.55	2.42 ± 0.47	0.65	1.83 ± 0.55	2.42 ± 0.47	0.42	3.37 ± 0.60	2.52 ± 0.51	0.28
HbA1c (%)	8.3 ± 0.2	8.1 ± 0.1	0.29	8.3 ± 0.2	8.1 ± 0.1	0.31	8.4 ± 0.2	8.1 ± 0.1	0.32
Insulin dose U/kg/d	1.2 ± 0.2	0.8 ± 0.1	0.03	0.9 ± 0.2	0.8 ± 0.2	0.70	0.9 ± 0.2	0.9 ± 0.2	0.96
Episodes of Severe Hypoglycemia	4 (7.55%)	8 (10.26%)	0.32	4 (7.41%)	12 (15.8%)	0.22	7 (15.6%)	8 (12.9%)	0.78

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

Data presented as mean ± SE.

Table 2

Characteristics (* z-score) of TG+ subjects consuming a regular diet compared with TG+ subjects consuming a gluten-free diet.

	Baseline			12 Months			24 Months		
	Regular n=36	GFD n=43	P > t	Regular n=34	GFD n=43	P > t	Regular n=26	GFD n=37	P > t
TG	0.45 ± 0.07	0.66 ± 0.07	0.03	0.37 ± 0.07	0.38 ± 0.07	0.89	0.31 ± 0.08	0.35 ± 0.07	0.71
Weight*	0.43 ± 0.19	0.11 ± 0.18	0.22	0.41 ± 0.20	0.16 ± 0.18	0.37	0.38 ± 0.21	0.03 ± 0.18	0.21
BMI*	0.42 ± 0.15	0.20 ± 0.14	0.29	0.40 ± 0.15	0.29 ± 0.14	0.60	0.50 ± 0.16	0.16 ± 0.14	0.11
Height*	0.26 ± 0.23	-0.1 ± 0.21	0.19	0.23 ± 0.24	-0.16 ± 0.21	0.21	0.02 ± 0.24	0.11 ± 0.22	0.8
IGF-BP3*	-0.91 ± 0.20	-0.68 ± 0.18	0.38	-0.76 ± 0.20	-0.65 ± 0.18	0.68	-1.16 ± 0.23	-0.23 ± 0.18	0.002
HbA1c (%)	8.3 ± 0.2%	7.9 ± 0.2%	0.16	8.4 ± 0.2%	7.9 ± 0.2%	0.07	8.2 ± 0.2%	8.1 ± 0.2%	0.60
Episodes of Severe Hypoglycemia	5 (14.3%)	3 (6.98%)	0.59	4 (11.76%)	8 (19.1%)	0.35	2 (8.0%)	6 (16.2%)	0.46

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

Data presented as mean ± SE.

Table 3

Characteristics (*z-scores) of TG- subjects compared with those of subjects with sustained TG > 0.50 and all bone measurements.

	Baseline			12 Months			24 Months		
	TG - N=54	TG + > 0.5 n=17	P > t	TG - N=53	TG + > 0.5 n=15	P > t	TG - N=32	TG + > 0.5 n=9	P > t
TG	0 ± 0.02	1.08 ± 0.04	<.0001	0 ± 0.02	0.93 ± 0.04	<.0001	0 ± 0.02	0.83 ± 0.04	<.0001
Weight*	0.65 ± 0.13	0.23 ± 0.23	0.11	0.67 ± 0.13	0.4 ± 0.23	0.3	0.67 ± 0.13	0.48 ± 0.23	0.48
BMI*	0.74 ± 0.22	0.3 ± 0.37	0.32	0.68 ± 0.22	0.45 ± 0.38	0.60	1.06 ± 0.24	0.15 ± 0.42	0.06
Height*	0.29 ± 0.15	0.13 ± 0.25	0.59	0.28 ± 0.15	0.13 ± 0.25	0.61	0.33 ± 0.15	0.53 ± 0.26	0.49
Lumbar spine*	-0.44 ± 0.19	-1.19 ± 0.34	0.06	-0.48 ± 0.19	-1.41 ± 0.35	0.02	-0.44 ± 0.21	-1.45 ± 0.40	0.03
Volumetric lumbar spine*	0.09 ± 0.17	-0.65 ± 0.31	0.04	-0.10 ± 0.17	-0.78 ± 0.31	0.06	-0.23 ± 0.19	-0.82 ± 0.34	0.13
Intact PTH (13-54 pg/ml)	21.6 ± 1.4	27.8 ± 2.5	0.04	24.9 ± 1.4	32.2 ± 2.5	0.01	26 ± 1.6	31.4 ± 2.7	0.08
Urine N-telopeptides **	104.1 ± 9.1	156.6 ± 15.8	0.005	109.1 ± 9.3	122.0 ± 16.3	0.49	103.9 ± 10	123.5 ± 16.8	0.32
VitD25OH (15-45 ng/mL)	31.5 ± 1	27.3 ± 1.7	0.03	27.7 ± 1	27.3 ± 1.7	0.81	30.1 ± 1	26.1 ± 1.8	0.05
FreeT4 (0.8-1.7 ng/dl)	1.33 ± 0.04	1.16 ± 0.07	0.03	1.32 ± 0.04	1.31 ± 0.07	0.89	1.33 ± 0.04	1.24 ± 0.07	0.28
TSH (0.36-5.4 ng/dl)	2.75 ± 0.71	2.38 ± 1.21	0.79	1.83 ± 0.71	2.44 ± 1.21	0.66	3.37 ± 0.77	3.33 ± 1.31	0.98
Ln Ferritin (ng/ml)	3.52 ± 0.10	2.96 ± 0.17	0.006	3.52 ± 0.10	3.11 ± 0.17	0.04	3.66 ± 0.11	3.24 ± 0.18	0.05
HbA1c (%)	8.3 ± 0.2%	8.4 ± 0.3%	0.76	8.3 ± 0.2%	8.3 ± 0.3%	0.97	8.4 ± 0.2%	8.5 ± 0.3%	0.70
Episodes of Severe Hypoglycemia	4 (7.55%)	2 (11.11%)	0.72	4 (7.41%)	4 (26.67%)	0.0714	5 (16.1%)	2 (22.2%)	0.64

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

Data presented as mean ± SE.

Table 4

Characteristics (*z-scores) of TG+ subjects with negative biopsy findings compared with those of subjects with positive biopsy findings.

	Baseline			12 Months			24 Months		
	Negative biopsy (Marsh 0,1, or 2) n=17	Positive biopsy (Marsh 3) n=35	P > t	Negative biopsy (Marsh 0,1, or 2) n=17	Positive biopsy (Marsh 3) n=35	P > t	Negative biopsy (Marsh 0,1, or 2) n=11	Positive biopsy (Marsh 3) n=31	P > t
Outcome									
TG	0.28 ± 0.11	0.76 ± 0.07	0.0003	0.21 ± 0.11	0.43 ± 0.07	0.09	0.22 ± 0.12	0.43 ± 0.07	0.13
Weight*	0.08 ± 0.27	0.28 ± 0.19	0.54	0.07 ± 0.27	0.33 ± 0.19	0.42	-0.15 ± 0.28	0.46 ± 0.19	0.08
BMI*	0.25 ± 0.24	0.30 ± 0.17	0.87	0.22 ± 0.24	0.37 ± 0.17	0.61	0.23 ± 0.26	0.31 ± 0.17	0.81
Height*	-0.12 ± 0.29	0.19 ± 0.20	0.36	-0.15 ± 0.29	0.21 ± 0.20	0.30	-0.63 ± 0.31	0.48 ± 0.20	0.003
IGFI*	-2.35 ± 0.28	-1.90 ± 0.18	0.18	-2.17 ± 0.28	-1.68 ± 0.18	0.14	-2.50 ± 0.30	-1.68 ± 0.19	0.02
IGFBP3*	-1.01 ± 0.29	-0.53 ± 0.19	0.17	-0.71 ± 0.29	-0.70 ± 0.19	1.0	-1.58 ± 0.32	-0.16 ± 0.20	0.0004
Intact PTH (pg/mL)	27.37 ± 3.24	25.33 ± 2.22	0.60	21.65 ± 3.06	25.71 ± 2.14	0.28	26.77 ± 3.72	29.99 ± 2.28	0.46
Urine N-telopeptides *#	122.4 ± 24.80	159.2 ± 17.02	0.22	119.8 ± 24.10	155.3 ± 17.02	0.23	112.6 ± 29.51	169.8 ± 18.61	0.10
VitD25OH (ng/ mL)	28.99 ± 1.82	31.79 ± 1.25	0.21	30.76 ± 1.74	30.17 ± 1.21	0.78	30.81 ± 2.03	30.71 ± 1.28	0.97
FreeT4 (ng/dL)	1.24 ± 0.05	1.19 ± 0.03	0.36	1.31 ± 0.05	1.23 ± 0.03	0.18	1.33 ± 0.06	1.21 ± 0.04	0.09
TSH (mIU/L)	2.42 ± 0.50	2.36 ± 0.35	0.93	3.13 ± 0.50	2.13 ± 0.35	0.11	1.83 ± 0.59	2.15 ± 0.37	0.65
Prealbumin (mg/dl)	18.63 ± 0.83	20.43 ± 0.58	0.08	18.89 ± 0.83	20.82 ± 0.58	0.06	18.41 ± 0.98	21.85 ± 0.60	0.004
Ln Ferritin (ng/ml)	3.65 ± 0.15	3.22 ± 0.11	0.02	3.76 ± 0.15	3.30 ± 0.11	0.01	3.83 ± 0.17	3.41 ± 0.11	0.04
HbA1c (%)	7.90 ± 0.26	8.03 ± 0.18	0.67	8.08 ± 0.26	8.01 ± 0.18	0.82	8.11 ± 0.29	8.20 ± 0.18	0.80

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

Data presented as mean ± SE.

Table 5
 Characteristics (*z-scores) of TG- subjects compared with those of TG+ subjects with positive biopsy findings.

	Baseline			Year 1			Year 2		
	TG- n=56	Positive biopsy (Marsh =3) n=35	P > t	TG- n=55	Positive biopsy (Marsh =3) n=35	P > t	TG- n=46	Positive biopsy (Marsh =3) n=31	P > t
TG	-0.00 ± 0.04	0.76 ± 0.05	<0001	0.00 ± 0.04	0.43 ± 0.05	<0001	0.00 ± 0.04	0.43 ± 0.05	<0001
Weight*	0.65 ± 0.13	0.28 ± 0.17	0.08	0.67 ± 0.13	0.33 ± 0.17	0.12	0.67 ± 0.13	0.46 ± 0.17	0.33
BMI*	0.74 ± 0.20	0.30 ± 0.26	0.192	0.68 ± 0.20	0.37 ± 0.26	0.35	1.07 ± 0.22	0.29 ± 0.28	0.03
Height *	0.29 ± 0.15	0.19 ± 0.18	0.68	0.28 ± 0.15	0.21 ± 0.18	0.79	0.33 ± 0.15	0.48 ± 0.19	0.52
IGF1*	-1.77 ± 0.14	-1.89 ± 0.18	0.59	-1.85 ± 0.14	-1.68 ± 0.18	0.45	-1.80 ± 0.15	-1.68 ± 0.19	0.63
IGFBP3*	-0.70 ± 0.14	-0.55 ± 0.18	0.52	-0.65 ± 0.14	-0.70 ± 0.18	0.83	-0.56 ± 0.15	-0.15 ± 0.19	0.09
Intact PTH (pg/mL)	21.59 ± 1.39	25.31 ± 1.83	0.11	24.91 ± 1.39	25.71 ± 1.76	0.72	25.93 ± 1.51	29.97 ± 1.88	0.10
Urine N- telopeptides **	105.0 ± 11.58	159.3 ± 14.60	0.004	108.2 ± 11.80	155.6 ± 14.60	0.01	102.9 ± 12.65	170.0 ± 16.03	0.001
VitD25OH (ng/mL)	31.54 ± 1.00	31.78 ± 1.29	0.88	27.73 ± 0.99	30.17 ± 1.25	0.13	30.05 ± 1.06	30.70 ± 1.31	0.70
FreeT4 (ng/dL)	1.33 ± 0.04	1.19 ± 0.04	0.02	1.32 ± 0.04	1.23 ± 0.04	0.10	1.33 ± 0.04	1.21 ± 0.05	0.06
TSH (mIU/L)	2.75 ± 0.63	2.36 ± 0.80	0.71	1.83 ± 0.63	2.13 ± 0.80	0.77	3.37 ± 0.68	2.15 ± 0.84	0.26
Prealbumin (mg/ dl)	21.06 ± 0.51	20.43 ± 0.65	0.45	22.23 ± 0.51	20.82 ± 0.65	0.09	21.75 ± 0.55	21.85 ± 0.68	0.91
Ln Ferritin (ng/ml)	3.52 ± 0.09	3.22 ± 0.12	0.048	3.52 ± 0.09	3.30 ± 0.12	0.15	3.66 ± 0.10	3.41 ± 0.12	0.12
HbA1c (%)	8.31 ± 0.15	8.03 ± 0.19	0.27	8.30 ± 0.15	8.01 ± 0.19	0.24	8.35 ± 0.16	8.20 ± 0.20	0.57

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

Data presented as mean ± SE.