Raising the Cut-Off Level of Anti-Tissue Transglutaminase Antibodies to Detect Celiac Disease Reduces the Number of Small Bowel Biopsies in Children with Type 1 Diabetes: A Retrospective Study

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Objective To study the optimal cut-off value for anti-tissue transglutaminase type 2 IgA antibodies (TG2A) in serum to select for diagnostic small bowel biopsies for celiac disease in children with type 1 diabetes mellitus.

Study design Children with type 1 diabetes mellitus with elevated TG2A titers and duodenal biopsies performed during the course of their diabetes treatment were included. Anti-endomysial antibodies were recorded if present. The optimal TG2A cut-off value, expressed as the ratio between obtained value and upper limit of normal (ULN), was determined using receiver operating characteristic curve analysis and compared with the cut-off value used in the European Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines in terms of sensitivity, specificity, positive and negative predictive value.

Results We included 63 children. The optimal cut-off value for performing biopsies is demonstrated to be 11 times the ULN. Raising the cut-off value from 3 times the ULN to 11 times the ULN changed sensitivity from 96% to 87% and increased specificity from 36% to 73%, increased the positive predictive value from 88% to 94% and lowered negative predictive value from 67% to 53%. The percentage of normal histology was decreased from 12% to 6%.

Conclusions Increasing the TG2A cut-off value for performing duodenal biopsies in children with type 1 diabetes mellitus and suspected celiac disease leads to a substantial reduction of unnecessary biopsies. We advocate to adapt the European Society for Pediatric Gastroenterology, Hepatology and Nutrition 2012 guidelines for this group of children, including monitoring patients with TG2A levels of less than 11 times the ULN over time. *(J Pediatr 2020;223:87-92)*.

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Children with type 1 diabetes mellitus (T1DM) are at risk of developing celiac disease (CD). Both conditions are autoimmune diseases showing strong linkage to the HLA-system.[1] The prevalence of CD among patients with T1DM is estimated to be between 3% and 10%.[2] Most children with both T1DM and CD are asymptomatic or present with nonspecific symptoms for CD.[3] Duodenal biopsies are the gold standard for diagnosis of CD in children with T1DM.[3] CD may result in complications, including decreased bone density and gastrointestinal malignancies.[1,4] Owing to the risks, children with diabetes are regularly screened for CD; at diagnosis of T1DM and subsequently every 1-2 years thereafter. Anti-tissue transglutaminase type 2 IgA antibodies (TG2A) are commonly used for screening and have a sensitivity and specificity of greater than 90%.[5,6] Despite this high accuracy, the interpretation of the TG2A titers in children with T1DM has proven difficult. Significant quantitative differences exist among different TG2A assays

CD	Celiac disease
CoN	Cut-off values for normality
EMA	Endomysial antibodies
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology and Nutrition
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operating characteristic
T1DM	Type 1 diabetes mellitus
TG2A	Anti-tissue transglutaminase type 2 IgA antibodies
ULN	Upper limit of normal

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and elevated TG2A titers often show spontaneous normalization in children with T1DM.[7,8] Additionally, people at genetic risk for CD (like children with T1DM) often have more false-positive TG2A results.[9] In 2012, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) introduced new guidelines for diagnosing CD, with conditions for a no-biopsy approach in symptomatic children and an algorithm for asymptomatic children belonging to a high-risk group, like children with T1DM.[10] In this algorithm, the cut-off value of serum TG2A titers for performing biopsies in these children is three times the upper limit of normal (ULN). In January 2020, these guidelines were updated and expanded based on interim evidence.[11] The authors specifically stated that the new recommendations with regard to the no-biopsy approach were not applicable to children with T1DM because they were not included in the literature search undertaken. This current study was prompted by our observation that biopsies performed in children with T1DM and TG2A titers of greater than three times the ULN are often not consistent with a confirmed CD diagnosis. We hypothesize that the chosen cut-off value of three times the ULN was too low. The aim of our study was to investigate the optimal cut-off value for the TG2A titers to decrease the number of negative biopsies in children with T1DM, but without losing sensitivity.

Methods

This retrospective observational study covers the time period from 2002 to 2015. Data were collected both at university hospitals and middle to large secondary care clinics: Leiden University Medical Center, University Medical Center Groningen, Rijnstate Hospital Arnhem, Haga Hospital The Hague, Children's Diabetes Centre Nijmegen, Maas Hospital Pantein Beugen, Spaarne Hospital Hoofddorp, St. Antonius Hospital Nieuwegein, Zuwe Hofpoort Hospital Woerden, MC Zuiderzee Lelystad, Isala Hospital Zwolle, Deventer Hospital, and University Medical Center Utrecht. Owing to the retrospective nature of this study, informed consent was not required. The procedures followed were in accordance with the ethical standards of the Medical Research Involving Human Subjects Act and the principles of the declaration of Helsinki (59th General assembly, Seoul, October 2008) of the World Medical Association. Formal approval from the local feasibility committee of Rijnstate Hospital Arnhem was obtained.

The study population consisted of all consecutive children and adolescents (<19 years of age) with T1DM who underwent esophagogastroduodenoscopy with duodenal biopsies because of elevated TG2A titers (>3 × ULN).[10] Screening with CD specific serology in these children was done at diagnosis of T1DM and every 1-2 years thereafter according to the International Society for Pediatric and Adolescent Diabetes international guideline for the management of pediatric T1DM, regardless of symptoms.[5] Exclusion criteria were IgA deficiency, a gluten-free diet at the time of duodenal biopsies, CD diagnosed before T1DM, and an interval more than 180 days between measurement of the TG2A titer and duodenal biopsies.

Data were retrieved from either patient charts or electronic data systems and entered into standard forms using Research Manager version 5.2.0.5 (Cloud9 Health Solutions, Deventer, the Netherlands). Clinical, anthropometric, and laboratory data were collected, including baseline characteristics such as age at first duodenal biopsies, sex, other autoimmune disease(s), family history of CD and other autoimmune diseases, and gluten-free diet adherence. The presence of symptoms suggestive for CD was also registered: chronic or intermittent diarrhea, failure to thrive, weight loss, delayed puberty, amenorrhea, iron-deficiency anemia, chronic abdominal pain, chronic constipation, chronic fatigue, dermatitis herpetiformis-like rash, and spontaneous fracture/osteopenia.[10,12]

Because 13 different hospitals participated in this study, TG2A titers were collected using different types of assays, different arbitrary units of measurement, and different cut-off values. To compare the TG2A titers, results were expressed as the ratio between the value obtained and the ULN and this ratio was rounded to whole numbers. For example a TG2A result of 55 with an ULN of 7 was analyzed as eight times the ULN. When a TG2A level was written in the file as greater than 50, it was regarded as 50 and greater than 128 was regarded as 128, and so on. Because some patients were analyzed twice (accompanied by a second biopsy), without starting a gluten-free diet in between, the total number of measurements exceeds the total number of patients included in our study. TG2A IgA enzyme-linked immunosorbent assays used were obtained from six different manufacturers: Aesku (Wendelsheim, Germany), n = 4; Euroimmun (Lübeck, Germany), n = 2; Inova (San Diego, California), n = 4; Orgentec (Mainz, Germany), n = 3; Phadia (Freiburg, Germany) n = 50; and Sanquin (Amsterdam, the Netherlands), n = 2. Anti-endomysial antibodies (EMA) as determined by indirect immunofluorescence were recorded in all patients.

All children included in this study underwent esophagogastroduodenoscopy to obtain duodenal biopsies, four from the duodenum and one or two from the duodenal bulb. Histologic findings were revised and classified according to the Marsh criteria by a single pathologist, specialized in Marsh typing.[13] This pathologist was blinded to all previous interpretations, and clinical and laboratory findings. Definite CD was confirmed by Marsh 2 or 3 histology in combination with the already known positive celiac serology. CD autoimmunity without histology alterations in the small bowel biopsies was considered potential CD.[10]

Continuous data are presented as mean ± SD. Differences in mean between groups were tested using the Student *t* test. Categorical data are presented as frequencies and percentages. Differences in percentages between groups were tested using the Pearson χ^2 test or the Fisher exact test. Receiver operating characteristic (ROC) analyses were performed to determine the optimal TG2A cut-off value. Sensitivity,

specificity, and positive predictive values (PPV) and negative predictive values (NPV) were calculated. Sensitivity and specificity were tested by the McNemar test and the predictive value by the weighted generalized score statistic.[14] Statistical analysis was performed using IBM SPSS Statistics (version 22.0, IBM, Herndon, VA). A *P* value of less than .05 was considered to indicate statistical significance.

Results

A total of 63 children fulfilled the inclusion criteria; 14 children were excluded (Figure 1). The median interval between TG2A measurement and duodenal biopsies was 59 days (range 0-178 days). The total number of analyzed TG2A titers was 65, because 2 patients underwent a second paired antibody determination and gastroduodenoscopy for retrieving duodenal biopsies.

The baseline characteristics of all patients are presented in Table I. In our study population, there was a female prevalence (62%). Symptoms suggestive off CD were present in 37% of the patients. When comparing asymptomatic with symptomatic children, no statistically significant differences were observed in baseline characteristics, neither in associated autoimmune disease, family history of associated autoimmune disease, family history of CD, nor in Marsh histology. Three children suffered from autoimmune hypothyroidism. The prevalence of CD in the total group was 83%, with a higher prevalence in the asymptomatic patients when compared with the symptomatic children, 88% and 74%, respectively ($P > .05$). The prevalence of CD was highest in the 21 patients who were biopsied owing to elevated TG2A found at diagnosis of T1DM (90%).

ROC curve analysis showed that the optimal TG2A cut-off value for performing a biopsy in children with T1DM is 11 times the ULN. This cut-off value provides a sensitivity of 87% and a specificity of 73%. The cut-off value of three times the ULN, described and advised in the latest ESPGHAN guideline, results in our study in a sensitivity of 96% and a specificity of 36%. Figure 2 shows the ROC curve. Figure 3 demonstrates the relationship between different levels of TG2A cut-off values and Marsh classification in asymptomatic and symptomatic children.

Table I. The baseline characteristics and differences between the asymptomatic and symptomatic children with T1DM and elevated tissue transglutaminase antibodies

Characteristics	Study population (n = 63)	Asymptomatic children (n = 40)	Symptomatic children (n = 23)	*P* value
Age, at time of first biopsy, years	9.7 ± 4.7	10.5 ± 4.2	8.2 ± 5.1	.06
Female	39 (62)	27 (68)	12 (52)	.23
Other autoimmune disease	4 (7)	4 (10)	0 (0)	.31
Family history of other autoimmune disease	21 (34)	13 (33)	8 (36)	.76
Family history of coeliac disease	4 (6)	2 (5)	2 (9)	.62
CD (Marsh 2-3)	52 (83)	35 (88)	17 (74)	.19

Values are mean ± SD or number (%).

Changing the Cut-Off Value of TG2A: Consequences for Clinical Practice

Table II (available at www.jpeds.com) illustrates the different PPVs for small bowel mucosal atrophy, depending on different cut-off values for normality (CoN), from 3 times the ULN to 11 times the ULN. The PPV for CoN increases from a minimum of 88% at 3 times the ULN to a

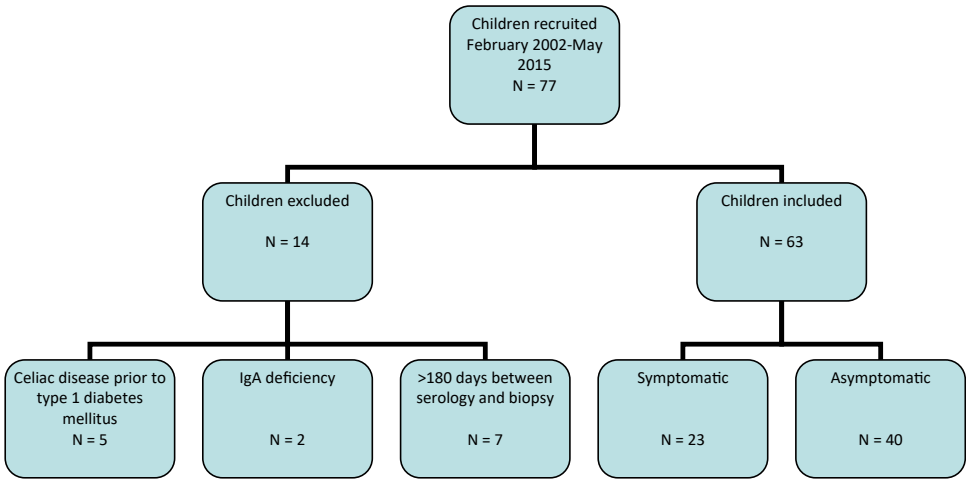

Figure 1. Flowchart of participants (children with T1DM).

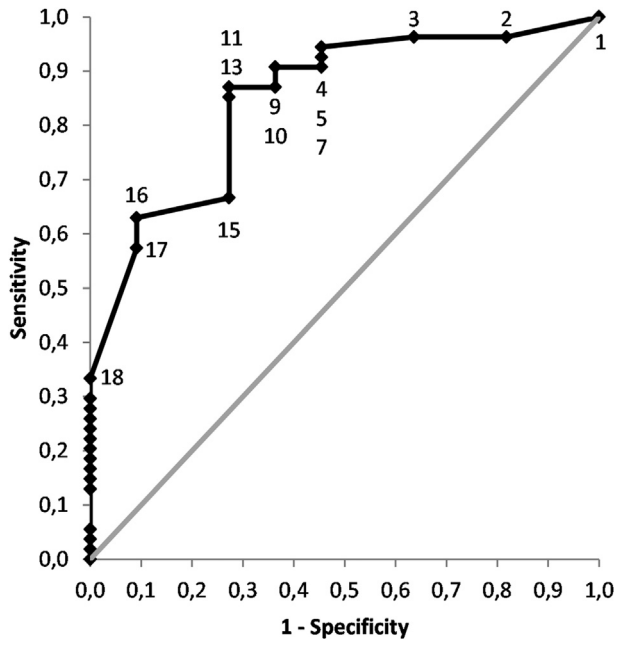

Figure 2. ROC curve to determine the optimal tissue transglutaminase antibodies cut-off value for performing diagnostic biopsies for celiac disease in T1DM.

maximum of 94% at 11 times the ULN with NPV of 67% and 53%, respectively. Increasing the CoN from 3 times the ULN to 11 times the ULN results in a decrease in sensitivity from 96% to 87% ($P = .06$) while providing a substantial increase in specificity from 36% to 73% ($P = .13$). Overall, a CoN of 3 times the ULN and 11 times the ULN resulted, respectively, in 12% (7/59) and 6% (3/50) normal (false-positive) duodenal biopsies ($P = .081$).

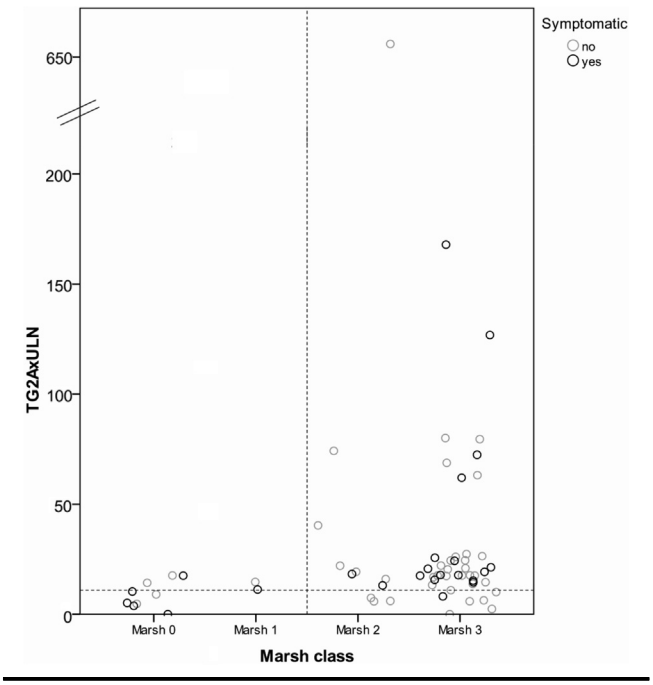

Figure 3. Scatterplot demonstrating the relationship between tissue transglutaminase antibodies cut-off value and Marsh classification in asymptomatic and symptomatic children with T1DM.

EMA as an Additional Test

EMA was negative in only three cases, all of which had Marsh 0 or 1 histology. Adding EMA-positive results did not improve the PPV of increased TG2A levels for villous atrophy, because 50% of EMA-positive patients had a normal duodenal histology.

Discussion

With this study in children with T1DM, we have shown that it is justified to increase the specificity and PPV by increasing the current TG2A cut-off value for performing diagnostic biopsies for CD. To have the highest NPV, we believe it is best increased to 11 times the ULN and not to 10 times the ULN, even though the latter is commonplace for pediatricians when determining not to perform duodenal biopsies in symptomatic children. Our data underline the fact that the choice of the cut-off of more than three times the ULN for performing diagnostic biopsies in children with T1DM, as part of the diagnostic algorithm for asymptomatic risk groups in the 2012 ESPGHAN guidelines for CD, was not based on evidence, but on consensus aiming to avoid unnecessary biopsies.[10] We decided not to exclude the symptomatic children, who were also found in our study population, because the TG2A screening was done during regular, planned visits rather than owing to symptoms. In our cohort, 55% of the children with Marsh 0 or 1 histology were also symptomatic, which may reflect the fact that the symptoms are nonspecific for CD. Our results are in line with those of several recent studies in children with T1DM showing that TG2A levels varying from 5 to 8 to 10 times the ULN were stronger predictors of villous atrophy than values of more than three times the ULN.[7,8,15,16] Although screening tests usually optimize sensitivity to find new patients, specificity is the measure that needs optimization to avoid false-positive results.[17] The latter is in our opinion crucial in children with T1DM suspected of CD. First because endoscopy is a significant burden for children who already have a chronic disease, and omitting biopsies means avoiding the risks of anesthesia in these children. Second, unnecessary biopsies should be prevented from a cost-effective point of view.[17]

In our opinion, the decrease in sensitivity by increasing the CoN of TTGA to more than 11 times the ULN is acceptable, because normalization of elevated TG2A can occur in up to one-third of patients with asymptomatic T1DM on a gluten-containing diet.[18] This factor allows clinicians to wait and further assess patients before subjecting them to biopsy. In a recent retrospective study in Israel of newly diagnosed children with T1DM, high TG2A levels (>10 × ULN) at diagnosis and 3 months thereafter, were

predictive of CD.[18] Furthermore, if normalization does not occur and CD diagnosis is established with duodenal biopsies after all, this state does not seem to have short-term adverse effects either on diabetes regulation or on bone mineral density.[19,20] In our cohort, EMA did not contribute to answering the question on whether or not to perform diagnostic biopsies. EMA negativity seemed to point to normal histology, but we were not able to draw definite conclusion owing to the small number of EMA negative patients, so future (prospective) studies are needed to evaluate this further.

Because children with T1DM with positive CD serology but normal duodenal histology can be considered patients with potential CD, regular monitoring of CD serology is warranted. Recommendations on treatment and frequency of follow-up for potential CD are lacking, but because the development of active CD is described in one-third of the patients on a gluten-containing diet, follow-up is important particularly in this group.[21] In patients with T1DM and potential CD, young age and persistent positive TG2A over time seem to increase the risk of transfer into active CD.[18] In our cohort, we also found a tendency toward a younger age in the group that was diagnosed with CD ($P = .06$). Our results indicate that withholding biopsies is acceptable in children with T1DM and low TG2A titers if serology is being followed over time. Other studies, that show spontaneous normalization or fluctuation of CD specific antibodies support our finding that low TG2A titers should be followed over time without performing immediate duodenal biopsies.[8,15,19,22] Because children with T1DM need medical checks on a regular basis, assessment of TG2A every 6-12 months is in our opinion feasible. Performing CD specific serology only in symptomatic children is not advised, because we have found an even higher prevalence of CD in asymptomatic patients when compared with symptomatic children (88% and 74%, respectively). Other studies report varying results. In 1 study, 71% of children with both T1DM and CD reported no gastrointestinal symptoms, and in another study, 76% of children with both conditions had at least 1 gastrointestinal symptom.[23,24] Based on our results, we recommend duodenal biopsies be performed in case of an increase over time of a TG2A of more than 11 times the ULN. Whenever elevated TG2A (<11 × ULN) persists, we advise shared decision making between the physician and the patient and parents. As suggested also by the 2020 ESPGHAN guidelines for diagnosing CD, future larger and prospective studies are mandatory to elucidate the exact algorithm in T1DM patients.[11]

One of the strengths of our study is that we performed a ROC curve analysis to determine the TG2A cut-off value for performing biopsies in children with T1DM. Furthermore, biopsies were reviewed by a single pathologist specialized in Marsh typing. For this reason, histologic examination was not affected by interobserver variability.[25] In addition, this study of children with type 1 diabetes assessed the performance of the revised ESPGHAN diagnostic criteria for CD.[10]

The limitations of our study relate to its retrospective nature and the sample size. Furthermore, we have compared TG2A measured with different types of assays. In the absence of an international standard, expressing the outcome in multiples of the ULN is currently the best option and has been used in several other studies. Hopefully, in the near future an international standard will be introduced. It has been stated that comparison based on multiples of the ULN are valid[26], because studies have shown acceptable agreement between most second-generation kits.[27,28] Several other studies have used multiples of ULN to compare data from different manufacturers.[28,29] A ROC curve analysis in which only data from Phadia, Aesku, and Euroimmun (chosen because they showed good agreement in times of the ULN in Table A from the ESPGHAN guidelines) were included, and resulted in the same ROC curve (data not shown).[10]

In conclusion, we have shown that raising the current cut-off level of TG2A to 11 times the ULN in children with T1DM to perform duodenal biopsies results in a 50% decrease of false positives and thus decreases the rate of unnecessary biopsies. In children with diabetes with TG2A levels lower than 11 times the ULN, one could choose to do serological follow-up while on a gluten containing diet instead of performing immediate diagnostic duodenal biopsies. ■

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Table II. Diagnostic performance for different cut-off values of normality of tissue transglutaminase antibodies

TG2A × ULN	No. of children biopsied	Diagnosed with CD	Sensitivity (%)	Specificity (%)	PPV for CD (95% CI interval)	NPV for CD (95% CI interval)
>1.0	65	54	100	0	83.1 (72-91)	100
>3.0	59	52	96	36	88.1 (77-95)	66.7 (29.0-91.0)
>5.0	55	50	93	55	90.9 (80-97)	60 (34-82)
>10.0	51	47	87	64	92.2 (81-98)	50 (31-70)
>11.0	50	47	87	73	94.0 (83-99)	53.3 (34.0-71.0)
>13.0	49	46	85	73	93.9 (85-98)	50 (32-68)
>15.0	38	35	67	73	92.1 (81-97)	29.6 (20.0-41.0)