Digestive Diseases

Endoscopy and Imaging

Dig Dis 2025;43:225–234
DOI: 10.1159/000543168

Received: June 30, 2024
Accepted: December 12, 2024
Published online: January 8, 2025

The Overlap between Type 1 Diabetes and Celiac Disease in Children and the Role of Tissue Transglutaminase-IgA Positivity in Endoscopy Decision

Elif Eviz[a] Sinan Sari[b] Nuray Uslu Kizilkan[c] Esra Doger[d]
Gul Yesiltepe Mutlu[a] Ödül Eğritaş[b] Cigdem Arikan[c] Aysun Bideci[d]
Buket Dalgic[b] Sukru Hatun[a]

[a]Department of Pediatric Endocrinology and Diabetes, Faculty of Medicine, Koc University, Istanbul, Turkey; [b]Department of Pediatric Gastroenterology, Faculty of Medicine, Gazi University, Ankara, Turkey; [c]Department of Pediatric Gastroenterology, Faculty of Medicine, Koc University, Istanbul, Turkey; [d]Department of Pediatric Endocrinology and Diabetes, Faculty of Medicine, Gazi University, Ankara, Turkey

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026

Keywords
Celiac disease · Decision of endoscopy · Transient tissue transglutaminase IgA positivity · Type 1 diabetes

Abstract

Introduction: Celiac disease (CD)-related antibody positivity in children with type 1 diabetes (T1D) may fluctuate and become negative spontaneously. There are uncertainties about the optimal tissue transglutaminase IgA (tTG-IgA) titre and timing of endoscopy in the diagnosis of CD, and this study aimed to contribute to the debate on the tTG-IgA threshold titre for endoscopy decisions in children with T1D. ***Methods:*** The data of 991 children with T1D who had undergone serologic evaluation for CD were analysed retrospectively. The tTG-IgA positivity rate and the upper limit of normal (ULN) tTG-IgA positivity were assessed. Participants were grouped according to the frequency, course, and test results of tTG-IgA tests. Those with and without histopathologic diagnosis of CD by endoscopic biopsy were compared in terms of tTG-IgA screening time and tTG-IgA predictive values. ***Results:*** In 10.2% (*n*:101) of all cases, tTG-IgA antibody was positive and endoscopic biopsy was performed in 68.3% (*n*:69) of these cases. Of all cases, 4.3% (*n*:43) were diagnosed with CD by endoscopic biopsy. A tTG-IgA titre of 7×ULN and above was found to be the best predictive value for the diagnosis of CD with 79.1% sensitivity, 80.8% specificity 87.2% positive predictive value, and 70% negative predictive value. ***Conclusions:*** Approximately 10% of antibody positive cases showed fluctuating and low-titre positivity, and no CD was detected by endoscopic biopsy in the group with fluctuating antibody course. The results of our study suggest that endoscopy in children with tTG-IgA levels 7×ULN or above may prevent both false-positive results and missed cases.

© 2025 S. Karger AG, Basel

Elif Eviz and Sinan Sari contributed equally to this work and share first authorship, and Buket Dalgic and Sukru Hatun contributed equally to this work.

karger@karger.com
www.karger.com/ddi

© 2025 S. Karger AG, Basel

Correspondence to:
Elif Eviz, evzelf@gmail.com

Karger

Introduction

Celiac disease (CD), characterized by autoimmune enteropathy triggered by gluten, exhibits notable similarities with type 1 diabetes (T1D). These similarities include a strong association with human leucocyte antigen (HLA) class II genotypes, the fact that a significant proportion of affected individuals are children, and the early emergence of disease-related autoantibodies [1]. The presence of HLA-DQ2 and HLA-DQ8 represents a common genetic factor shared between the two diseases. The prevalence of CD in children with T1D has been reported with a frequency ranging between 1 and 16.4% [2–5]. In an international comparative study on 53,000 children and adolescents with T1D, the prevalence of biopsy-proven CD was reported to be 3.5%, with rates varying from 1.9% in the USA to 7.7% in Australia [2, 6]. In a meta-analysis, it was reported that the frequency of CD was higher in children who had been diagnosed with T1D before the age of 5 years, and it was observed that the diagnosis of CD preceded the diagnosis of T1D in only 7% of the cases [4]. In Turkey, the frequency of biopsy-proven CD in children with T1D was reported to be 6, 6.9, and 6.3%, according to single-centre data, and 4.3% in a multicentre study [7–10].

Since the association between the two diseases is well defined and CD is highly asymptomatic in children with T1D, screening with tissue transglutaminase IgA (tTG-IgA) is recommended by international organizations at the time of diagnosis of T1D and in subsequent follow-up, regardless of symptoms. The classical approach is to perform an endoscopic biopsy in patients with antibody positivity and initiate gluten-free diet treatment in those with histopathological evidence of CD [6, 11]. It has been reported that CD-associated antibody positivity in T1D people is 2–3 times higher than the rate of diagnosis of CD by biopsy; antibody positivity exhibits a fluctuating course with a rate of 10.7–41% and becomes negative spontaneously with a rate of 30–40% [8, 12]. In a study, antibody negativity with a rate of 23.3% was reported in children with T1D within 5 years in the absence of a gluten-free diet [8]. Contemplating these factors, the debate continues to revolve around determining the optimal tTG-IgA titre (in terms of multiples of the upper limit of normal [ULN]) and the timing of endoscopy, i.e., whether it should occur immediately post-diagnosis of T1D or after the resolution of the "antibody storm" [13]. Alongside this, there are also suggestions that histological confirmation of CD may be postponed in children with newly diagnosed T1D who have no symptoms in terms of CD [14]. When the guidelines of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the International Society for Paediatric and Adolescent Diabetes (ISPAD) are reviewed, it should be noted that, thus far, there are no specific recommendations on these issues [6, 11]. This uncertainty may lead to unnecessary endoscopy procedures and/or high threshold values for endoscopies in children with T1D [15]. This study aimed to evaluate the features of CD in children with T1D within the framework of new approaches and especially to contribute to the discussion of tTG-IgA cut-off titre for endoscopy decisions.

Methods

The data of 994 children who were followed up with a diagnosis of T1D and screened with tTG-IgA for CD and tTG-IgG in those with selective IgA deficiency between 2016 and 2022 in the Division of Paediatric Endocrinology and Diabetes in Koç University School of Medicine and between 2012 and 2022 in the Division of Paediatric Endocrinology and Diabetes in Gazi University School of Medicine were analysed retrospectively. The screening protocols in both centres were as follows: patients were screened for CD immediately after diagnosis of T1D and those who tested positive for tTG-IGA underwent intestinal biopsy. Patients who were antibody-negative, as well as those who were antibody-positive but had a normal biopsy at initial screening, were rescreened for tTG-IgA under the following conditions: (a) immediately if symptoms or signs suggestive of CD were present and (b) routinely every 1–2 years if asymptomatic. Testing for anti-endomysial antibodies (EMA) was not available at either centre.

The participants were evaluated in terms of the time which had elapsed between the diagnosis of T1D and the first tTG-IgA screening, when antibody positivity was first detected, how many times it was screened, the rate of tTG-IgA positivity and how many times the ULN tTG-IgA positivity was. The participants were grouped according to the frequency of tTG-IgA tests and test results: group 1 was defined as those who had more than one antibody test and were consistently negative; group 2 was defined as those who had one antibody test; group 3 was defined as those with a fluctuating course (antibody positivity was detected in one period of follow-up and became negative spontaneously); group 4 was defined as those who became positive when the antibody test was negative. Histopathological evaluation was performed

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026

using MARSH classification where MARSH 2 and 3 were accepted as CD [16].

Among the participants who had undergone endoscopic biopsy, those with and without a histopathological diagnosis of CD were compared by the age at diagnosis of T1D, gender, presence of concomitant autoimmune thyroiditis (AIT), time of tTG-IgA screening and tTG-IgA predictive values. Cases diagnosed with CD were also evaluated in terms of age at diagnosis of T1D and CD, clinical findings of CD, time of tTG-IgA measurement and tTG-IgA predictive values.

The protocols were conducted according to the Declaration of Helsinki principles and were approved by the Koç University Institutional Research Ethics Committee (2023. 298.IRB1.094). Written informed consent was obtained from the parent/legal guardian of participants prior to the study.

Data were analysed using SPSS 26 IBM software. For continuously distributed variables, mean ± standard deviation was used to describe normally distributed variables, median, and interquartile ranges were used to describe non-normally distributed variables, and frequency and percentage were used to describe categorical variables. The Mann-Whitney U test was used in independent groups, the Wilcoxon test in dependent groups and the Friedman test in more than two dependent groups to determine statistically significant difference in pairwise group comparisons in continuous variables that were non-normally distributed. Pairwise group comparisons were performed using the Wilcoxon test to determine which of the groups the difference was between. The Chi-Square test was used to determine the statistical difference between categorical variables and Fisher's exact test was used when the expected value was below 5. The diagnostic decision-making properties of tissue transglutaminase IgA in predicting CD were analysed with receiver operating characteristics (ROC) curve analysis to find the most appropriate predictive value. Sensitivity, specificity, and positive and negative predictive values were calculated for different predictive values, and $p < 0.05$ was considered as statistically significant.

Results

A total of 994 children, comprising 445 from Koç University and 549 from Gazi University, were included in the study. Three cases were excluded from the analyses because they had been diagnosed with CD before the diagnosis of T1D, and so 991 cases were analysed. The mean age at the time of diagnosis of T1D was 7.9 ± 4 years and 51.1% (*n*:528) of them were male. At the time of diagnosis of T1D, 33.3% (*n*:344) of the children were younger than 5 years of age. A total of 58 cases (5.6%) had concomitant AIT. The median time for the first screening for CD was 2.1 months after the diagnosis of T1D, and it was repeated at a median of 13.4 months (IQR: 10.5–23.5 months) after the initial test. The rate of the first antibody screening was 66% (*n*:654) in the first year after the diagnosis of T1D, 27% (*n*:268) in the 1–5 years period, and 7% (*n*:69) after 5 years.

In 10.2% (*n*:101) of the children who underwent serological evaluation, tTG-IgA antibody positivity was detected with a median onset of 7.8 months following the diagnosis of T1D. The first screening time of these children was median 1.6 months (1 day - 13.5 months) after diagnosis of T1D. The distribution of the time of antibody positivity following the diagnosis of T1D was as follows: 59.4% (*n*:60) in the first year, 30.7% (*n*:31) between 1 and 5 years, and 9.9% (*n*:10) 5 years after diagnosis. An endoscopic biopsy was performed in 68.3% (*n*:69) of the antibody-positive cases. The interval between tTG-IgA positivity and endoscopic evaluation was median 35 days (4 days-6.5 months). Of these cases, 62.3% (*n*:43) were compatible with stage 2–3 and 37.7% (*n*:26) with stage 0–1 according to MARSH classification.

CD was diagnosed by endoscopic biopsy in 4.3% (*n*: 43) of all cases. The tTG-IgA titres were 8.1×ULN in participants who had undergone endoscopic biopsy and 2.7×ULN in those who had not, and the tTG-IgA titre was significantly higher in those who had undergone endoscopic biopsy ($p = 0.014$). Only 11.6% (*n*: 5) of the children diagnosed with CD showed clinical symptoms of CD meanwhile the others were asymptomatic. The mean age of those diagnosed with CD was 9 ± 4.2 years and the diagnosis was made at a median of 1.6 years after the diagnosis of T1D. The rate of diagnosis in the first year after the diagnosis of T1D was 39.5% (*n*:17), 25.6% (*n*:11), in 1–2 years, 25.6% (*n*:11) in 2–5 years, and 9.3% (*n*:4) after 5 years. Concomitant AIT prevalence was significantly higher in the children diagnosed with CD compared to those without CD (14 vs. 5.4%, $p = 0.032$) (Table 1). There was no statistically significant difference between those who were diagnosed with CD and those who were not diagnosed with CD in terms of age, gender, presence of AIT in the family, time of CD screening, diagnosis of T1D and time of first tTG-IgA positivity. The tTG-IgA titre was significantly higher in patients diagnosed with CD compared to those without the disease (Table 2). The

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026

Table 1. Main characteristics of the research group

	N:991
Gender, male, *n* (%)	528 (51.1)
Age at the diagnosis of T1D, years[a]	7.9±4.4
Age at the diagnosis of T1D ≤5 years, *n* (%)	344 (33.3)
Concomitant AIT, %	58 (5.6)
Time to first CD screening after T1D diagnosis[b]	2.1 (0–17)
1–12 months, *n* (%)	654 (66)
13–60 months, *n* (%)	268 (27)
>60 months, *n* (%)	69 (7)
tTG-IgA positivity[a]	101 (10.2)
Time to tTG-IgA positivity after diagnosis of T1D[b]	7.8 (0.2–29.8)
1–12 months, *n* (%)	60 (59.4)
13–60 months, *n* (%)	31 (30.7)
>60 months, *n* (%)	10 (9.9)
Ratio of biopsy, *n* (%)	69 (68.3)
Histopathology	
Marsh 0–1, *n* (%)	26 (37.7)
Marsh 2–3, *n* (%)	43 (62.3)
CD prevalence, *n* (%)	43 (4.3)
Age at diagnosis of CD, years[a]	9±4.2
Time between diagnosis of T1D and diagnosis of CD[b]	1.6 years (4.1 months–3.2 years)
1–12 months, *n* (%)	17 (39.5)
13–24 months, *n* (%)	11 (25.6)
25–60 months, *n* (%)	11 (25.6)
>60 months, *n* (%)	4 (9.3)
Frequency of symptomatic CD, *n* (%)	5 (11.6)

AIT, autoimmune thyroiditis; CD, celiac disease; T1D, type 1 diabetes; tTG-IgA, tissue transglutaminase IgA.
[a]Mean ± SD. [b]Median (25–75%).

rate of tTG-IgA positivity was statistically higher in children diagnosed with TID before the age of 5 years (*n*:331) compared to those diagnosed with TID after the age of 5 years (*n*:660) (14.8 vs. 7.9%, $p = 0.001$). The prevalence of CD was 5.8% in children diagnosed with TID before the age of 5 years, which was higher than that in those diagnosed after the age of 5 years (3.3%), but there was no statistically significant difference between them ($p = 0.058$).

When the cases were analysed according to the frequency of antibody testing and the course of antibodies; in group 1 (*n*:389), tTG-IgA was tested a median of 3 times and was found to be negative each time. In group 2 (*n*:546), tTG-IgA was analysed only once. In 8.2% (*n*:45) of these cases, positivity was detected at a median of 1.8 months after the diagnosis of T1D. In this group, the median tTG-IgA titre was 9.5×ULN, 62.2% (*n*:28) of the group underwent endoscopic biopsy and 86% (*n*:24) of the biopsied children were diagnosed with CD. Group 3 (*n*:32) showed a fluctuating course in terms of tTG-IgA titre, the tTG-IgA antibody was tested a median of 3 times and positivity was detected at a median of 10.6 months after TID diagnosis. In this group, the tTG-IgA titre was 2.2×ULN, 65.6% of the children had undergone endoscopic biopsy and none of them was pathologically diagnosed with CD. Group 4 (*n*:24) consisted of children with negative tTG-IgA titre at baseline and which then became positive. In these cases, antibodies were tested a median of 3 times, positivity was detected at a median of 20.6 months after the diagnosis of TID, and the median tTG-IgA titre was 10.5×ULN. In this group, 83.3% (*n*:20) underwent biopsy and 95% (*n*:19) of the biopsied children were diagnosed with CD. The median antibody titre in group 3 was found to be significantly lower than in

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026

Table 2. Comparison of cases diagnosed and not diagnosed with CD

	CD		*p* value
	negative, *n*:948	positive, *n*:43	
Gender, male, *n* (%)	480 (50.6)	22 (51.2)	0.946
Age at the diagnosis of T1D, years[a]	7.8±4.3	6.6±4.2	0.061
Age at the diagnosis of T1D ≤5 years, *n* (%)	311 (32.8)	20 (46.5)	0.062
Presence of concomitant AIT, *n* (%)	51 (5.4)	6 (14.0)	0.032
Presence of AIT in the family, *n* (%)	32 (3.4)	4 (9.3)	0.066
Time to first CD screening after diagnosis of T1D, months[b]	2.1 (0–18.1)	1 (0–10.3)	0.248
Time to tTG-IgA positivity after diagnosis of T1D, months[b]	7.2 (0.3–27.9)	8 (0.3–31)	0.754
tTG-IgA titres (× ULN)[b]	2.7 (1.5-7.3)[c]	10 (8–12)	<0.001

[a]Mean ± SD. [b]Median (25–75%). [c]The median titres of patients with positive tTG-IgA were only calculated and analysed. AIT, autoimmune thyroiditis; CD, celiac disease; T1D, type 1 diabetes; tTG-IgA, tissue transglutaminase IgA.

groups 2 and 4 ($p < 0.001$ and $p < 0.001$, respectively) (Fig. 1). The characteristics of the groups in terms of the frequency of antibody testing and the course of antibodies are summarized in Tables 3 and 4.

When the relationship between tTG-IgA titre cut-off values and the histopathology of CD was analysed, a tTG-IgA titre of 7×ULN and above was found as the best predictive value with 79.1% sensitivity, 80.8% specificity, 87.2% positive predictive value, and 70% negative predictive value for the diagnosis of CD. The area under the curve was found to be 0.82 (95% confidence interval 0.71–0.93; $p < 0.0001$) by ROC analysis (Fig. 2).

Discussion

Because of the changes in celiac autoantibodies detected by screening in children with T1D not following a gluten-free diet in the follow-up and the possibility that intestinal biopsy may be found normal in antibody-positive cases, the debate on the diagnostic process of CD in children with T1D continues and currently, an intestinal biopsy is recommended in cases with tTG-IgA titres more than 3×ULN [17, 18]. Moreover, families of children with T1D have greater concerns about CD than for their children developing T1D, or, as recently shown, families of tTG-IgA-positive children are highly concerned about their child developing T1D [19]. Therefore, providing evidence-based recommendations regarding the optimal timing of CD screening in children with T1D, interpretation of antibody results, endoscopy decision-making, and subsequent follow-up features will enhance the overall management of the process for both the children and their family.

In this context, the following questions, some of which we tried to find answers with this research, remain on the agenda.

1. What is the frequency of tTG-IgA positivity for CD in children with T1D?
2. What are the characteristics of tTG-IgA positive cases?
3. What is the frequency of transient antibody positivity? What are the characteristics of these cases?
4. Can a cut-off value with higher specificity and sensitivity than the currently accepted cut-off value of 3×ULN be recommended for endoscopy decision?
5. What are the clinical features of CD in children with T1D?

In our study, the tTG-IgA positivity rate in children with T1D was 10.2% and the prevalence of CD was 4.3%, and these figures are very similar with comprehensive international and national studies [2, 4, 5, 7–10]. The fact that 37.7% of biopsies performed in children with tTG-IgA positivity were normal suggests that antibody positivity may be an epiphenomenon of autoimmune activation. In our series, the median time for first screening for CD was 2.1 months and tTG-IgA positivity was detected in 59.4% of the children in the first year after the diagnosis of T1D. The rate of tTG-IgA positivity was significantly higher in children diagnosed with T1D before 5 years of age compared to those diagnosed with T1D after 5 years of age. The rate of diagnosis of CD by intestinal biopsy was 4.3%, 65.1% of whom were diagnosed in the first 2 years and 90.7% in

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026

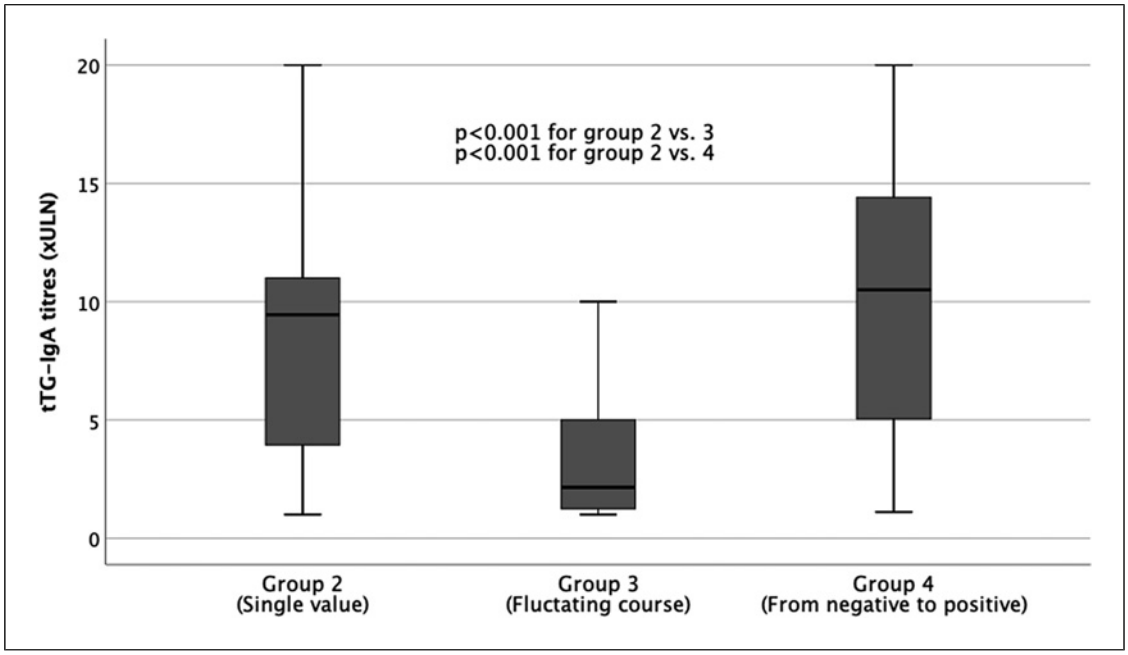


Fig. 1. Comparison of tTG-IgA titres among patient groups with tTG-IgA positivity, based on the course of antibody positivity.

Table 3. Groups in terms of frequency of antibody testing and the course of antibodies

	Group 1 (continuously negative), *n*:389	Group 2 (single value), *n*:546	Group 3 (fluctuating course), *n*:32	Group 4 (– → +), *n*:24
Number of measurements*	3 (2–4)	1	3 (2–5)	3 (2–6)
Age at the diagnosis of T1D, years	7.8±4.1[d,e] 7.5 (4.2–11)*	8±4.4[a,b] 7.6 (4.2–11.4)*	5.4±3.5[b,e] 4.4 (2.7–8.8)*	5.9±4[a,d] 4.2 (2.8–9.6)*
tTG-IgA + and, *n* (%)	–	45 (8.2)	32 (100)	24 (100)
tTG-IgA titres (× ULN)*	–	9.5 (3.8–11)[c]	2.2 (1.2–5)[c,f]	10.5 (4.8–15.6)[f]
Biopsy, *n* (%)	–	28 (62.2)	21 (65.6)	20 (83.3)

[a]$p = 0.017$; [b]$p = 0.004$; [c]$p < 0.001$; [d]$p = 0.023$; [e]$p = 0.009$; [f]$p < 0.001$. *Median (25–75%). Three children diagnosed with CD before T1D were excluded. T1D, type 1 diabetes; tTG-IgA, tissue transglutaminase IgA.

the first 5 years after the diagnosis of T1D. When children with T1D who had CD and those who did not have CD were compared, concomitant AIT was found to be significantly higher in those with CD. In a study comprising approximately 53,000 children with T1D from 3 continents, the prevalence of biopsy-proven CD was reported to be 3.5% and the prevalence of CD was found to be significantly higher in girls and in children in whom the diagnosis of T1D was made before the age of 5 years and similar to our findings, the diagnosis of CD was made in the first 5 years after the diagnosis of T1D in 83% of cases [2]. In a study by Slae et al. [20] covering a 23-year follow-up of 314 children with T1D, a diagnosis of T1D under the age of 4.5 years and serology positivity at the time of diagnosis were defined as risk factors for CD and all cases were diagnosed in the first 6 years after the diagnosis of T1D. Data from the TEDDY study group showed that islet cell and CD autoimmunity were significantly higher in the first 5 years of life (around 30% and 8%), and although the

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026

Table 4. Characteristics of antibody-positive groups

	Antibody test positivity			*p* value
	group 2 (single value), *n*:45	group 3 (fluctuating course), *n*:32	group 4 (− → +), *n*:24	
Cases where the age at the diagnosis of T1D was ≤5 years, *n* (%)	18 (40)	18 (56.3)	13 (54.2)	0.327
Age at the diagnosis of T1D, years	7.4±4.5 6.6 (3.4–10)[a]	5.4±3.5 4.4 (2.7–8.8)[a]	5.9±4 4.2 (2.8–9.6)[a]	0.146
Presence of AIT, *n* (%)	4 (8.9)	2 (6.3)	4 (16.7)	0.436
Time of the antibody positivity, months[a]	1.8 (0.1–11.7)	10.6 (0.2–36.5)	20.6 (8–39.3)	Group 2 versus 3 $p = 0.005$
First 12 months tTG-IgA +, *n* (%)	35 (77.8)	17 (53.1)	8 (33.3)	Group 2 versus 3 $p = 0.023$ Group 2 versus 4 $p < 0.001$
First 3 months tTG-IgA +, *n* (%)	26 (57.8)	11 (34.4)	5 (20.8)	Group 2 versus 3 $p = 0.043$ Group 2 versus 4 $p = 0.003$
First month tTG-IgA +, *n* (%)	17 (37.8)	11 (34.4)	5 (20.8)	0.353
tTG-IgA titres (× ULN)[a]	9.5 (3.8–11)	2.2 (1.2–5)	10.5 (4.8–15.6)	Group 2 versus 3 $p = 0.009$ Group 2 versus 4 $p < 0.001$
Biopsy, *n* (%)	28 (62.2)	21 (65.6)	20 (83.3)	0.193
Characteristics of participants who underwent a biopsy				
Age at the diagnosis of T1D, years[a]	7.8 (4–11.3)	2.9 (1.7–9)	3.9 (2.5–6.8)	Group 2 versus 3 $p = 0.043$ Group 2 versus 4 $p = 0.027$
tTG-IgA titres (× ULN)[a]	10 (8–14)	2.4 (1.1–6.3)	10.5 (5.9–11.8)	Group 2 versus 3 $p < 0.001$ Group 3 versus 4 $p = 0.001$
Time of the antibody positivity, months[a]	1 (0.1–11)	9.9 (0.1–44.3)	23 (11.5–51.1)	Group 2 versus 4 $p = 0.001$
Diagnosis of CD, *n* (%)	24 (86)	0	19 (95)	Group 2 versus 3 $p < 0.001$ Group 3 versus 4 $p < 0.001$

[a]Median (25–75%). AIT, autoimmune thyroiditis; CD, celiac disease; ULN, upper limit of normal; T1D, type 1 diabetes; tTG-IgA, tissue transglutaminase IgA.

prevalence of CD was high in the first 4 years and decreased markedly thereafter, the prevalence of T1D was consistently at the same frequency after a small peak after 2–3 years of age. These data confirm that, due to this overlap between T1D and CD in the first 4–5 years of age, the risk of CD is higher in children with T1D in the first 5 years of age compared to other age groups, and this coincides with the findings of our study [21, 22]. Although different results have been reported in studies investigating the risk of AIT in people with

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026

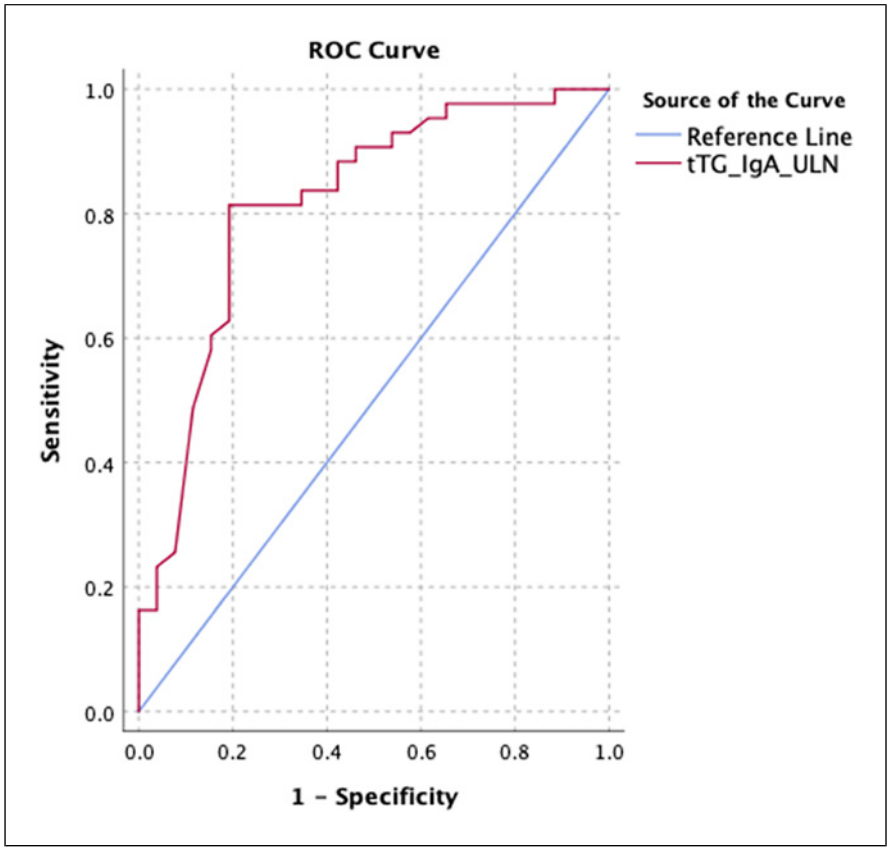


Fig. 2. ROC curve to determine the cut-off value for tissue transglutaminase antibodies to perform diagnostic biopsy for CD in T1D.

T1D and CD, the frequency of AIT was found to be significantly higher in the presence of CD accompanying T1D in our study [8, 23].

In our study, when the cases were evaluated in terms of the frequency and course of tTG-IgA, it was observed that 39.3% of the cases remained negative for tTG-IgA in repeated measurements, 55.1% had antibodies tested once and were found to be positive at high titre and biopsy was performed, 3.2% had a fluctuating course of antibodies examined 3 times, and 2.4% were in the group in which antibodies examined a median of 3 times were first negative and then positive. The rate of endoscopy in groups other than the continuously negative group was 62.2%, 65.6%, and 83.3%, respectively. In children who underwent biopsy, the frequency of CD diagnosis was 86% in the second group and 95% in the fourth group, while no CD was detected in the group with fluctuating antibody course. The median tTG-IgA titre in cases with a fluctuating course was 2.2×ULN, which was significantly lower than in the other two groups in which an endoscopy was performed.

These data suggested that cases with low titre positivity may show a fluctuating course and this feature should be taken into consideration in endoscopy decisions, and that it would be appropriate to monitor with intermittent antibody determinations without endoscopy in cases showing these features and being asymptomatic for CD. Our findings were compatible with other studies on this subject which suggested that antibodies may become negative spontaneously in children with T1D with mildly elevated tTG-IgA and no evidence of CD and recommended follow-up with a normal diet [8, 12, 24].

As is commonly acknowledged, the clinical decision for endoscopy heavily relies on the expertise of the relevant specialist and the tTG-IgA value, particularly in the absence of clinical signs of CD. Endoscopy is mostly conducted in cases where tTG-IgA 3×ULN. The recommendation of Wessels et al. [14] in 2020 to perform an endoscopy at a cut-off value of tTG-IgA >11×ULN to increase the specificity of tTG-IgA exacerbated the debate on this issue. However, this cut-off value was not accepted because waiting for such a high tTG-IgA value to avoid an unnecessary endoscopy would cause some cases to be missed [18]. In our study, a tTG-IgA titre of 7×ULN and above was determined as the best cut-off value for the diagnosis of CD with 79.1% sensitivity, 80.8% specificity,

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026

87.2% positive predictive value, and 70% negative predictive value. Although this value seems to be acceptable in terms of sensitivity and specificity, cases between 3×ULN and 7×ULN should be evaluated for additional risk factors (presence of CD in the family, presence of AIT, etc.). In addition, in cases with tTG-IgA titres between these cut-off values, instead of performing an endoscopy immediately after diagnosis, another option would be to make a decision based on antibody measurements 3–6 months later or to evaluate with anti-endomysial antibody determination.

Recently, "atypical CD," which presents with low antibody titres, has been observed more frequently, with 85% being asymptomatic and/or "silent." The majority of diagnosed cases of CD in children with T1D fall into this group [25, 26]. In the present study, consistent with the literature, the mean age of CD cases was 9 ± 4.2 years and only 11.6% had CD-related symptoms. Recent studies have shown that there is a weak relationship between mucosal damage and symptoms, and mucosal damage has been observed with equal severity in symptomatic CD cases and asymptomatic CD cases [11, 27].

In our series, the diagnosis of CD was made 5 years after the diagnosis of T1D in only 9.3% of the cases, which is consistent with the literature [3, 28, 29]. In a recently published case series, it was reported that celiac antibodies were positive in 33 of 340 children with T1D who were screened, and 33% of them were positive 9 ± 2 years after T1D diagnosis [30]. Considering these data, it is considered important to continue screening children with T1D at an appropriate frequency 5 years after diagnosis, even if they are not symptomatic, and studies focussing on this issue should be conducted.

Although the latest ESPGHAN guidelines do not provide a clear recommendation for CD screening in children with T1D, testing for anti-endomysial antibodies is recommended when tTG-IGA ×10 ULN. However, this test was not available at either of the centres participating in this study, representing one of its limitations. The other limitations of our study include its retrospective nature and the use of different assay types for tTG-IgA measurements in the two participating centres. However, presenting results in multiples of the ULN is currently considered the most optimal approach and has been employed in numerous other studies.

In conclusion, our study unveiled a significant temporal parallelism (overlap) between T1D and CD, the majority of cases diagnosed with CD were asymptomatic, and the frequency of autoantibody positivity was twice as high as that of CD. Approximately 10% of the antibody-positive cases exhibited fluctuating and low-titre positivity, with no CD detected by endoscopic biopsy in the group with fluctuating antibody course; therefore, it was thought that it would be appropriate to follow these cases under normal diet without endoscopy. The results of our study indicate that performing endoscopies in children with tTG-IgA levels 7×ULN or above may prevent both false-positive results and missed cases. We recommend considering endoscopy decisions based on a 3–6-month follow-up for cases with ULN levels between 3 and 7 times, particularly in the absence of symptoms.

Acknowledgments

The authors would like to thank the children and, their families for participating in the study, Alan J. Newson (certified proofreader) for English language editing.

Statement of Ethics

The protocols were conducted according to the Declaration of Helsinki principles and were approved by the Koç University Institutional Research Ethics Committee (2023.298.IRB1.094). Written informed consent was obtained from the parent/legal guardian of participants prior to the study.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

Funding Sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

E.E., S.S., N.U.K., G.Y.M., C.A., B.D., and S.H. designed the study, E.E., S.S., and E.D. collected the data, E.E., S.S., N.U.K., E.D., O.E.G., C.A., and A.B. performed data analysis, E.E., S.S., G.Y.M., O.E.G., A.B., B.D., and S.H. wrote the manuscript. All authors approved the final version of manuscript. All authors read and approved the final article.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material. Further enquiries can be directed to the corresponding author.

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026

References

1 Knip M. Similarities and dissimilarities between type 1 diabetes and coeliac disease. Acta Paediatr. 2023;112(10):2030–1. https://doi.org/10.1111/apa.16940
2 Craig ME, Prinz N, Boyle CT, Campbell FM, Jones TW, Hofer SE, et al. Prevalence of celiac disease in 52,721 youth with type 1 diabetes: international comparison across three continents. Diabetes Care. 2017;40(8):1034–40. https://doi.org/10.2337/dc16-2508
3 Pham-Short ADK, Donaghue KC, Ambler G, Chan AK, Craig ME. Coeliac disease in type 1 diabetes from 1990 to 2009: higher incidence in young children after longer diabetes duration. Diabet Med. 2012;29(9):e286–9. https://doi.org/10.1111/j.1464-5491.2012.03720.x
4 Pham-Short A, Donaghue KC, Ambler G, Phelan H, Twigg S, Craig ME. Screening for celiac disease in type 1 diabetes: a systematic review. Pediatrics. 2015;136(1):e170–6. https://doi.org/10.1542/peds.2014-2883
5 Taczanowska A, Schwandt A, Amed S, Tóth-Heyn P, Kanaka-Gantenbein C, Volsky SK, et al. Celiac disease in children with type 1 diabetes varies around the world: an international, cross-sectional study of 57 375 patients from the SWEET registry. J Diabetes. 2021;13(6):448–57. https://doi.org/10.1111/1753-0407.13126
6 Fröhlich-Reiterer E, Elbarbary NS, Simmons K, Buckingham B, Humayun KN, Johannsen J, et al. ISPAD Clinical Practice Consensus Guidelines 2022: other complications and associated conditions in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2022;23(8):1451–67. https://doi.org/10.1111/pedi.13445
7 Gülcü Taşkın D, Ata A. The screening of celiac serology in pediatric patients diagnosed with type 1 diabetes mellitus. Turk J Gastroenterol. 2023;34(3):293–7. https://doi.org/10.5152/tjg.2023.22775
8 Unal E, Demiral M, Baysal B, Ağın M, Devecioğlu EG, Demirbilek H, et al. Frequency of celiac disease and spontaneous normalization rate of celiac serology in children and adolescent patients with type 1 diabetes. J Clin Res Pediatr Endocrinol. 2021;13(1):72–9. https://doi.org/10.4274/jcrpe.galenos.2020.2020.0108
9 Sari S, Yeşilkaya E, Eğritaş O, Bideci A, Cinaz P, Dalgiç B. Prevalence of Celiac disease in Turkish children with type 1 diabetes mellitus and their non-diabetic first-degree relatives. Turk J Gastroenterol. 2010;21(1):34–8. https://doi.org/10.4318/tjg.2010.0045
10 Simsek DG, Aycan Z, Özen S, Cetinkaya S, Kara C, Abalı S, et al. Diabetes care, glycemic control, complications, and concomitant autoimmune diseases in children with type 1 diabetes in Turkey: a multicenter study. J Clin Res Pediatr Endocrinol. 2013;5(1):20–6. https://doi.org/10.4274/Jcrpe.893
11 Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx C, et al. European society paediatric Gastroenterology, Hepatology and nutrition guidelines for diagnosing coeliac disease 2020. J Pediatr Gastroenterol Nutr. 2020;70(1):141–56. https://doi.org/10.1097/MPG.0000000000002497
12 Castellaneta S, Piccinno E, Oliva M, Cristofori F, Vendemiale M, Ortolani F, et al. High rate of spontaneous normalization of celiac serology in a cohort of 446 children with type 1 diabetes: a prospective study. Diabetes Care. 2015;38(5):760–6. https://doi.org/10.2337/dc14-2890
13 Hatun Ş, Dalgıç B, Gökşen D, Aydoğdu S, Savaş Erdeve Ş, Kuloğu Z, et al. Recommendations for clinical decision-making in children with type 1 diabetes and celiac disease: type 1 diabetes and celiac disease joint working group report. J Clin Res Pediatr Endocrinol. 2022;14(1):1–9. https://doi.org/10.4274/jcrpe.galenos.2021.2021.0139
14 Wessels M, Velthuis A, van Lochem E, Duijndam E, Hoorweg-Nijman G, de Kruijff I, et al. 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. J Pediatr. 2020;223:87–92.e1. https://doi.org/10.1016/j.jpeds.2020.02.086
15 Kamrath C, Tittel SR, Dunstheimer D, Fröhlich-Reiterer E, Freff M, Böttcher C, et al. Early vs late histological confirmation of coeliac disease in children with new-onset type 1 diabetes. Diabetologia. 2022;65(7):1108–18. https://doi.org/10.1007/s00125-022-05701-w
16 Marsh MN. Mucosal pathology in gluten sensitivity. In: Marsh MN, editor. Coeliac disease. Oxford: Blackwell Scientific Publications; 1992. p. 136.
17 Stahl M, Koletzko S, Andrén Aronsson C, Lindfors K; TEDDY Study Group, Liu E, Agardh D, et al. Coeliac disease: what can we learn from prospective studies about disease risk? Lancet Child Adolesc Health. 2024;8(1):63–74. https://doi.org/10.1016/S2352-4642(23)00232-8
18 Guandalini S. The when, why and whom to biopsy of type 1 diabetes mellitus children with positive anti-tissue transglutaminase serology. Saudi J Gastroenterol. 2023;29(5):257–8. https://doi.org/10.4103/sjg.sjg_253_23
19 O'Donnell HK, Rasmussen CG, Dong F, Simmons KM; ASK Study Group; Steck AK, Frohnert BI, et al. Anxiety and risk perception in parents of children identified by population screening as high risk for type 1 diabetes. Diabetes Care. 2023;46(12):2155–61. https://doi.org/10.2337/dc23-0350
20 Slae M, Romem A, Edri S, Toker O, Wilschanski M, Strich D. Celiac disease and celiac antibodies in DM1 patients: when are screening and biopsy recommended? Dig Dis Sci. 2019;64(2):487–92. https://doi.org/10.1007/s10620-018-5353-4
21 Hagopian W, Lee HS, Liu E, Rewers M; TEDDY Study Group; She JX, Ziegler AG, et al. Co-Occurrence of type 1 diabetes and celiac disease autoimmunity. Pediatrics. 2017;140(5):e20171305. https://doi.org/10.1542/peds.2017-1305
22 Goodwin G. Type 1 diabetes mellitus and celiac disease: distinct autoimmune disorders that share common pathogenic mechanisms. Horm Res Paediatr. 2019;92(5):285–92. https://doi.org/10.1159/000503142
23 Li Voon Chong JS, Leong KS, Wallymahmed M, Sturgess R, MacFarlane IA. Is coeliac disease more prevalent in young adults with coexisting Type 1 diabetes mellitus and autoimmune thyroid disease compared with those with Type 1 diabetes mellitus alone? Diabet Med. 2002;19(4):334–7. https://doi.org/10.1046/j.1464-5491.2002.00671.x
24 Waisbourd-Zinman O, Hojsak I, Rosenbach Y, Mozer-Glassberg Y, Shalitin S, Phillip M, et al. Spontaneous normalization of anti-tissue transglutaminase antibody levels is common in children with type 1 diabetes mellitus. Dig Dis Sci. 2012;57(5):1314–20. https://doi.org/10.1007/s10620-011-2016-0
25 Krauthammer A, Guz-Mark A, Zevit N, Marderfeld L, Waisbourd-Zinman O, Silbermintz A, et al. Age-dependent trends in the celiac disease: a tertiary center experience. J Pediatr Gastroenterol Nutr. 2021;72(6):894–9. https://doi.org/10.1097/MPG.0000000000003130
26 Kurppa K, Laitinen A, Agardh D. Coeliac disease in children with type 1 diabetes. Lancet Child Adolesc Health. 2018;2(2):133–43. https://doi.org/10.1016/S2352-4642(17)30172-4
27 Agardh D, Lee HS, Kurppa K, Simell V; TEDDY Study Group, Aronsson CA, Jörneus O, et al. Clinical features of celiac disease: a prospective birth cohort. Pediatrics. 2015;135(4):627–34. https://doi.org/10.1542/peds.2014-3675
28 Cerutti F, Bruno G, Chiarelli F, Lorini R, Meschi F, Sacchetti C. Younger age at onset and sex predict celiac disease in children and adolescents with type 1 diabetes. Diabetes Care. 2004;27(6):1294–8. https://doi.org/10.2337/diacare.27.6.1294
29 Fröhlich-Reiterer EE, Kaspers S, Hofer S, Schober E, Kordonouri O, Pozza SBD, et al. Anthropometry, metabolic control, and follow-up in children and adolescents with type1 diabetes mellitus and biopsy-proven celiac disease. J Pediatr. 2011;158(4):589–93.e2. https://doi.org/10.1016/j.jpeds.2010.09.050
30 Wilkes M, Graber E, Rapaport R. Screening for celiac disease in youth with type 1 diabetes: are current recommendations adequate? J Diabetes. 2021;13(6):525–6. https://doi.org/10.1111/1753-0407.13177

Downloaded from http://karger.com/ddi/article-pdf/43/2/225/4320759/000543168.pdf by Gazi Üniversitesi user on 06 January 2026