

The Screening of Celiac Serology in Pediatric Patients Diagnosed with Type 1 Diabetes Mellitus

Didem Gülcü Taşkın¹ , Aysun Ata² 

¹Department of Pediatric Gastroenterology, Adana City Training and Research Hospital, Adana, Turkey

²Department of Pediatric Endocrinology, Adana City Training and Research Hospital, Adana, Turkey

Cite this article as: 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):293-297.

ABSTRACT

Background: This study aims to detect the rate of celiac antibody test positivity in pediatric patients diagnosed with type 1 diabetes mellitus (T1DM) and determine the characteristics of the patient groups diagnosed with and without celiac disease (CD).

Methods: This study was conducted retrospectively in Adana City Training and Research Hospital, Pediatric Endocrinology Outpatient Clinic with the patients diagnosed with T1DM between September 17, 2017, and January 1, 2022. The patients were examined by 3 different groups. Group 1: celiac patient group, group 2: serology false positive group, and group 3: serology negative group.

Results: The study included 418 patients, 228 (54.5%) males and 190 (45.5%) females. About 6% of the patients (25 patients) were in the celiac patient group, 12.6% (53 patients) in the serology false positive group, and 81.3% (340 patients) in the serology negative group. The age at diagnosis was 10 (7.2-12.9) years in the celiac patient group and 8.8 (6.2-12.00) years in the serology false positive group ($P = .559$). Among 53 patients in the serology false positive group, spontaneous normalization was observed in 66% (35 patients), and positivity was continued during the test follow-up period in 34% (18 patients). There was no significant difference in terms of sex ($P = .101$), and HbA1c values at diagnosis ($P = .557$). Tissue transglutaminase IgA titer was $20\times$ Upper limit of normal (ULN) in the celiac patient group and $2.52\times$ ULN in the serology false positive group.

Conclusion: T1DM and CD are both autoimmune diseases concurrently seen together. CD antibody positivity may be observed at the first presentation of T1DM. While the majority of these antibodies become negative during the follow-up, we wanted to highlight the false positive antibody titers and emphasize that these patients should be followed by endocrinologists and gastroenterologists together.

Keywords: Celiac antibody, pediatrics, type 1 diabetes mellitus

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy caused by immunological mechanisms developing after gluten consumption in genetically susceptible individuals and resulting in villous damage. While the frequency of CD differs by country, it has been reported to be approximately 1%. Similar to CD, type 1 diabetes mellitus (T1DM) is an autoimmune disease due to pancreatic damage resulting from immunological mechanisms. The frequency of CD may be up to 10-fold in T1DM patients (3%-10%) compared to the general population.¹⁻³

Diagnosis is mainly made by villous atrophy shown in small intestine biopsy collected by gastroscopy in patients with clinical suspicion or serologic test positivity.⁴ However, patients diagnosed with T1DM are routinely screened for CD even if they do not have any symptoms at diagnosis. Criteria for definitive diagnosis after screening were developed in 2020 by The European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).

According to these criteria, the diagnosis can be made in individuals with proven genetic susceptibility without biopsy if they have a 10-fold rise in tissue transglutaminase IgA (TTG IgA) titer and anti-endomysium IgA (EMA IgA) antibody positivity.⁵

High rates of false positivity have been reported in CD screening in individuals diagnosed with T1DM.⁶ False positive blood tests lead to additional work-up for the patients and place an additional burden on the healthcare system. This study aims to detect the rate of celiac antibody test positivity in pediatric patients diagnosed with T1DM and determine the characteristics of the patient groups diagnosed with and not diagnosed with CD.

MATERIALS AND METHODS

This study was designed as a single-center, retrospective study and conducted in Adana City Training and Research Hospital, Pediatric Endocrinology Clinic. A total of 418 patients who were diagnosed with T1DM and

Corresponding author: Didem Gülcü Taşkın, e-mail: dgulcu@gmail.com

Received: November 18, 2022 Accepted: January 2, 2023 Publication Date: March 14, 2023

DOI: 10.5152/tjg.2023.22775



treated between January 1, 2008, and January 1, 2022, were included in the study. The antibodies studied during the CD screening of the cases were recorded by date and titer. Patients diagnosed with CD using either ESGHAN 2012⁷ or 2020⁵ guidelines were included in the "celiac patient group" (CPG) (group 1). Patients who had at least 1 positive test result for celiac antibodies after screening but without CD were included in the "serology false positive group" (SFPG) (group 2). Patients who had no positive result for any of the antibodies studied were included in the "serology negative group" (SNG) (group 3). Approval for the study was taken from Adana City Training and Research Hospital Ethics Committee. The study was designed in line with the Helsinki Declaration. An informed consent form was obtained from patients or their legal guardians.

Statistical Analysis

Statistical analysis of the study was performed using Statistical Package for Social Sciences (SPSS) 21.0 software (IBM Corp.; Armonk, NY, USA). Categorical variables were summarized as number and percentage, and continuous variables as mean and standard deviation (median and minimum-maximum, if necessary). For the comparison of categorical variables, chi-square and Fisher's exact tests were used. For the comparison of continuous variables, distribution normality was tested, and Mann-Whitney *U* test was used for non-normally distributed parameters. Statistical significance level, $P < .05$, was used for all tests.

RESULTS

Out of 418 patients included in the study, 228 (54.5%) were males and 190 (45.5%) were females. When the patients were examined by 3 different groups, 6% of the patients (25 patients) were detected to be in CPG,

12.6% (53 patients) in SFPG, and 81.3% (340 patients) in SNG. The mean duration of follow-up was 3.2 ± 2.8 years. Follow-up duration was detected to be 2.3 ± 1.8 years in CPG, 4.1 ± 2.4 years in SFPG, and 3.3 ± 2.9 years in SNG. In the patient groups included in the study, the age at diagnosis was 10 (7.2-12.9) years in CPG with the age at diagnosis in SFPG being similar, 8.8 (6.2-12.00) years ($P = .559$).

Among 53 patients in SFPG, spontaneous normalization was observed in 66% (35 patients), and positivity was continued during the test follow-up period in 34% (18 patients).

When the number of patients diagnosed with Hashimoto's thyroiditis was examined, there were 25 patients (7.4%) in SNG, 2 patients (8%) in CPG, and 8 patients (15.1%) in SFPG ($P = .071$). While the rate of Hashimoto's thyroiditis is higher in SFPG, the difference was not statistically significant. Patient characteristics are summarized in Table 1.

There was no significant difference in terms of sex between 3 groups ($P = .101$). All cases had similar HbA1c values at diagnosis [CPG: 13.2% (10.9-14.5), SFPG: 12.7% (10-14.4), SNG: 12.1% (10.2-13.9)] ($P = .557$).

When 78 patients in SFPG and CPG were evaluated, the median time to the first positive test was 14 days (0-280). In these 2 groups, only 8 patients were observed to have a single antibody study [2 (2.5%) patients TTG IgA, 6 (7.6%) patients EMA IgA]. Forty-five of the other patients had results for all 4 antibodies studied concurrently in Table 2. Among our patients, the median TTG IgA antibody titer was 200 in CPG with titer rates being 20x ULN. Median TTG IgA antibody titer was 25 in SFPG with titer rates of 2.52x ULN as shown in Table 3. Test normalization in SFPG patients occurs after 20 months during the follow-up period (Figure 1).

Of 25 patients diagnosed with CD, 23 had a concurrent diagnosis of T1DM, and the remaining 2 patients got a CD diagnosis within the first year.

DISCUSSION

In our study, the rate of EMA and/or TTG antibody positivity was found to be 18.6% of all the patients; 12.6% (53 patients) were serology positive without CD, and 6% were T1DM patients with CD. We found out that the celiac antibodies may be high up to 2.5x ULN at the first

Main Points

- Celiac disease antibody positivity may be seen as much more common at the first presentation of type 1 diabetes mellitus (T1DM), even if not accompanied by celiac disease.
- The majority of the positive antibodies become negative during the follow-up period. It is crucial to initiate the diabetic diet program of the T1DM patients and follow-up on the symptoms and the antibody normalization.
- The symptoms resolve in a significant proportion of the patients by the time under the diet program. Therefore, we recommend not doing an invasive procedure like an endoscopic examination for those patients early at the first presentation of the disease.

Table 1. Comparison of the Characteristics of the Patient Groups

	Serology Negative Group (SNG) Median (Min-Max)	Celiac Patient Group (CPG) Median (Min-Max)	Serology False Positive Group (SFPG) Median (Min-Max)	P
Age (years)	8.9 (5.6-12.6)	10 (7.2-12.9)	8.8 (6.2-12.00)	.803
HbA1c (%) at diagnosis	12.1 (10.2-13.9)	13.2 (10.9-14.5)	12.7 (10-14.4)	.557
Age	n (%)	n (%)	n (%)	.445
< 10 years	193 (56.9)	12 (48)	28 (52.8)	
≥10	146 (43.1)	13 (52)	25 (47.2)	
Sex (n)	n (%)	n (%)	n (%)	.101
Male	193 (57.1)	13 (52)	22 (41.5)	
Female	145 (42.9)	12 (48)	31 (58.5)	
Hashimoto's thyroiditis (n)	n (%)	n (%)	n (%)	.071
No	314 (92.6)	23 (92)	45 (84.9)	
Yes	25 (7.4)	2 (8)	8 (15.1)	

Table 2. The Distribution Characteristics of Positivity and Negativity of the Celiac Antibodies in Two Patient Groups With Positive Celiac Antibodies

	Celiac Patient Group (CPG)			Serology False Positive Group (SFPG)		
	Positive	Negative	n	Positive	Negative	n
TTG IgA	20	0	20	11	38	49
TTG IgG	12	3	15	6	36	42
EMA IgA	20	1	21	17	31	48
EMA IgG	11	2	13	12	32	44

EMA IgA, anti-endomysium IgA; EMA IgG, anti-endomysium IgG; TTG IgA, tissue transglutaminase IgA; TTG IgG, tissue transglutaminase IgG.

presentation of T1DM diagnosis without CD. The majority of the positive antibodies become negative (66%) during the follow-up of 4.1 ± 2.4 years. We realized that it is crucial to initiate the diabetic diet program of the T1DM

patients, insulin treatment, follow-up the symptoms, and antibody normalization. The symptoms resolve in a significant proportion of the patients by the time under the diet program with the control of the autoimmune activation of the underlying disease and cytokine storm. We did not recommend an invasive procedure like endoscopic examinations for those patients early at the first presentation of the disease.

Although CD is common in diabetics, CD serology false positivity is also common among this patient group.⁸ The rate of EMA or TTG antibody positivity in T1DM patients was found to be 9.8% to 20.6% in different studies, and it was found to be 18.6% (78 patients) in our study.^{2,9,10} In the literature, the rate of spontaneous normalization of antibodies reported by Unal et al¹¹ was 23.3%, and it was found to be approximately 35.4% in the study by Waisbourd-Zinman et al.¹²

Table 3. Median Celiac Antibody Titers of the Subjects and Fold Rise in the Antibody Titers

n (25%-75%)	Celiac Patient Group (CPG), (n = 25)	Serology False Positive Group (SFPG), (n = 53)	P
Age (years)	10 (7.2-12.9)	8.8 (6.2-12.00)	.559
TTG IgA	200 (151-252)	25.2 (14.4-31.22)	<.001*
EMA IgA	200 (150-320)	33.05 (24.7-48.87)	<.001*
TTG IgA fold rise	20 (15.1-25.2)	2.52 (1.44-3.12)	<.001*
EMA IgA fold rise	10 (7.5-16)	1.65 (1.23-2.44)	<.001*
HbA1c (%) at diagnosis	13.2 (10.9-14.5)	12.7 (10-14.4)	.440

EMA IgA, anti-endomysium IgA; TTG IgA, tissue transglutaminase IA.

*Statistical significance level, $P < .05$ was used for all tests.

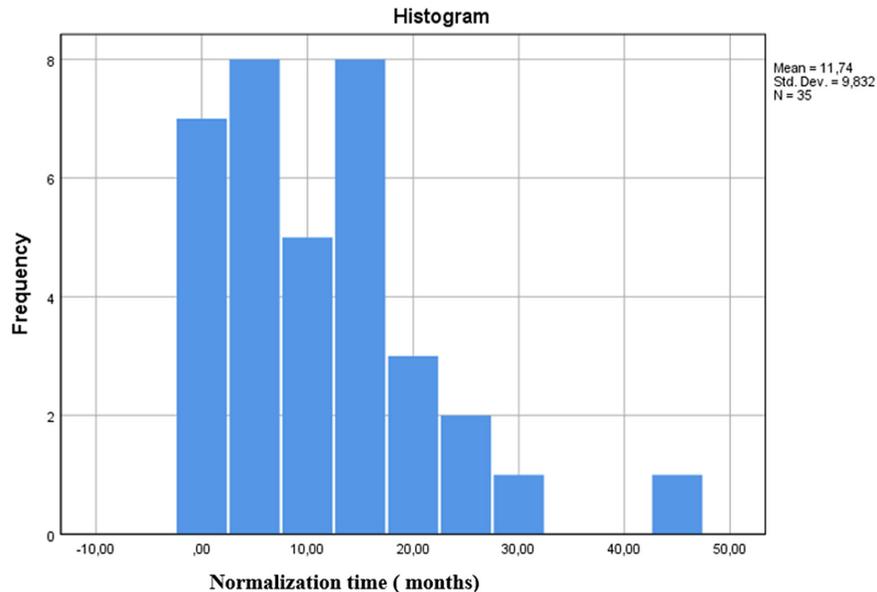


Figure 1. Histogram showing the normalization of serology positivity over time.

We aimed to determine the characteristics of this SFPG but consistent with the literature, no significant difference was found between CPG and SFPG in terms of clinical and laboratory parameters. Also, the median TTG IgA antibody titer was 200 in CPG with titer rates being 20× ULN. In SFPG, the titer rates are 2.52× ULN. In order to diagnose an asymptomatic CD patient without biopsy from one perspective and in order to recognize SFPG and avoid unnecessary procedures and investigations from the other perspective, we should have some criteria for diagnosis and follow-up in this special patient group.

According to the results of 9 cohort studies by Pham-Short et al.⁶ majority of the patients diagnosed with T1DM concurrently get a CD diagnosis, and the probability of CD development substantially decreases after 5 years. While the previous diabetes diagnosis and treatment guidelines recommended CD screening every 1-2 years, the latest changes updated the frequency of CD screening, so as to be performed at diagnosis, year 2, year 5, and every 5 years thereafter.^{8,13} Studies examining the correlation between the age at diagnosis and the frequency of CD have detected that the less the age at diagnosis is, the higher the CD frequency is.¹⁴ As the first screening was at the time of diagnosis of T1DM, patients are under a storm of cytokines, intense autoimmune reactions, and glucotoxicity, which may cause erroneous test results. Therefore, we have to differentiate the picture.

A fold rise in the antibody titers may be a clue for the differentiation of SFPG and CD. In their retrospective study in 2020, Travato et al¹⁵ found the TTG IgA antibody titer being 5-10× ULN and the positive predictive value of EMA IgA positivity to be significant at 0.93. As additional issues such as fasting before anesthesia and difficulty in blood glucose regulation may occur in this patient group during the diagnosis period, we endorse the notion that diagnosis can be made without biopsy in the patient group with serology high positivity as recommended by ESPGHAN 2020 guideline.⁵ A certain titer level should be determined for T1D patients, and serology positivity above that titer should be diagnosed without gastroscopy.

CD screening is performed by endocrinologists in many of the diabetes centers, and it was seen that unnecessary antibody tests are requested in some of them. Although it is not recommended to study TTG IgG and EMA IgG-type antibodies in guidelines, it is noteworthy that TTG IgA and EMA IgA were studied in high percent in our patient group, as it is optional to study these 2 antibodies together in ISPAD guidelines.⁸ As observed in our study, TTG IgG and EMA IgG-type antibody positivity is high in SFPG; therefore, these antibodies should not be used for screening. This notion is supported by the fact that among the patients in 2 groups with celiac antibody positivity in the present study, TTG IgA titer was positive in all

of the patients in CPG patients and the presence of IgG antibody positivity, especially in SFPG.

In conclusion, T1DM and CD developing from a common autoimmune basis are concurrently seen as substantially higher compared to the general population, and positivity of CD antibodies studied for screening may be observed early after diagnosis without the presence of the disease.

While the majority of these false positive cases become negative during the follow-up, we should have criteria for this special patient group either to diagnose CD or to recognize false positive serology. This can avoid unnecessary endoscopic procedures in the future.

The present study has some limitations; even if the number of patients with T1DM is high, the number of patients with both T1DM and CD is insufficient to reach a conclusion. Moreover, when assessing the antibody positivity in SFPG, the high rate of TTG IgG and EMA IgG antibody titers being studied caused a drawback. Since diabetic patients are diagnosed and treated first by pediatric endocrinologists, CD screening is also applied by them. Pediatric gastroenterologists evaluate these patients later. For this reason, different screening antibodies were studied by endocrinologists.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Adana City Training and Research Hospital.

Informed Consent: An informed consent form was obtained from the patients or their legal guardians.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.A., D.G.T.; Design – A.A., D.G.T.; Supervision – A.A., D.G.T.; Funding – A.A., D.G.T.; Materials – A.A., D.G.T.; Data Collection and/or Processing – A.A., D.G.T.; Analysis and/or Interpretation – A.A., D.G.T.; Literature Review – A.A., D.G.T.; Writing – A.A., D.G.T.; Critical Review – A.A., D.G.T.

Acknowledgments: Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

REFERENCES

1. Odeh R, Alassaf A, Gharaibeh L, Ibrahim S, Khdaif Ahmad F, Ajlouni K. Prevalence of celiac disease and celiac-related antibody

status in pediatric patients with type 1 diabetes in Jordan. *Endocr Connect.* 2019;8(6):780-787. [\[CrossRef\]](#)

2. Elfström P, Sundström J, Ludvigsson JF. Systematic review with meta-analysis: associations between coeliac disease and type 1 diabetes. *Aliment Pharmacol Ther.* 2014;40(10):1123-1132. [\[CrossRef\]](#)

3. Imran HA, Cheema HA, Alvi MA, Rehman MU, Ali M, Sarwar HASpectrum of Clinical Presentation of Celiac Disease in Pediatric Population. *Cureus.* 2021;13(6):e15582. [\[CrossRef\]](#)

4. Anderson RP, Henry MJ, Taylor R, et al. A novel serogenetic approach determines the community prevalence of celiac disease and informs improved diagnostic pathways. *BMC Med.* 2013;11:188. [\[CrossRef\]](#)

5. Husby S, Koletzko S, Korponay-Szabó I, et al. European society paediatric gastroenterology, hepatology and nutrition guidelines for diagnosing coeliac disease 2020. *J Pediatr Gastroenterol Nutr.* 2020;70(1):141-156. [\[CrossRef\]](#)

6. Pham-Short A, 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-e289. [\[CrossRef\]](#)

7. Husby S, Koletzko S, Korponay-Szabó IR, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr.* 2012;54(1):136-160. [\[CrossRef\]](#)

8. Mahmud FH, Elbarbary NS, Fröhlich-Reiterer E, et al. ISPAD Clinical Practice Consensus Guidelines 2018: other complications and associated conditions in children and adolescents with type 1 diabetes. *Pediatr Diabetes.* 2018;19(suppl 27):275-286. [\[CrossRef\]](#)

9. Pall H, Newhook LA, Aaron H, Curtis J, Randell E. Young age at diagnosis of Type 1 diabetes is associated with the development of celiac disease—associated antibodies in children living in Newfoundland and Labrador, Canada. *Children (Basel).* 2015;2(4):403-411. [\[CrossRef\]](#)

10. Lewandowska K, Ciepela O, Szybowska A, et al. Celiac antibodies in children with type 1 diabetes - A diagnostic validation study. *Autoimmunity.* 2018;51(2):81-88. [\[CrossRef\]](#)

11. Unal E, Demiral M, Baysal B, 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):72-79. [\[CrossRef\]](#)

12. Waisbourd-Zinman O, Hojsak I, Rosenbach Y, 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):1314-1320. [\[CrossRef\]](#)

13. American Diabetes Association. Children and adolescents. *Diabetes Care.* 2019;42(suppl 1):S148-S164. [\[CrossRef\]](#)

14. Roldán Martín MB, Márquez Romero C, Guerra Vilches E, et al. Celiac disease screening in children and adolescents with type 1 diabetes mellitus: what test should be performed? *Endocrinol Diabetes Nutr (Engl).* 2021;68(3):153-158. [\[CrossRef\]](#)

15. Trovato CM, Montuori M, Anania C, et al. Are ESPGHAN "Biopsy-Sparing" Guidelines for celiac disease also Suitable for Asymptomatic Patients? *Am J Gastroenterol.* 2015;110(10):1485-1489. [\[CrossRef\]](#)