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Thyroid Autoantibody Positivity Based on Individual Compliance with a Gluten-free Diet in Pediatric Patients with Celiac Disease

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Abstract

The prevalence of concurrent celiac disease (CD) and autoimmune thyroid disorders is elevated relative to the general population, and it has been proposed that non-adherence to a gluten-free diet (GFD) exacerbates this risk. This study aimed to assess individual adherence to a GFD in children with CD and to examine the correlation between celiac antibody positivity and thyroid autoantibody positivity. Three hundred and thirty-four cases with CD, were retrospectively evaluated in terms of their age at diagnosis, duration of CD, individual compliance with GFD, and celiac [tissue transglutaminase antibody, tissue thyroglobulin (tTG)- immunoglobulin A (IgA)] and thyroid autoantibody (anti-thyroid peroxidase, anti-TG) positivity. The cases were divided into two groups: Group 1, with positive thyroid autoantibodies, and group 2, with negative thyroid autoantibodies. They were compared in terms of the same parameters. Additionally, the relationship between compliance with a GFD, duration of CD, and thyroid autoantibody positivity was examined. The average age of the cases was 10.8±4.1 years, with 63.5% being female. The median age at diagnosis of CD was 6.5 years, and the average time from onset to diagnosis was 2.7 years. In 47% of patients, individual compliance with the diet was poor; 69% tested positive for tTG-IgA, and 7.2% were positive for thyroid autoantibodies. The age at diagnosis of CD in group 1 was greater than that in group 2 (7.4 vs. 6.5 years, p=0.454), and the duration of CD was significantly longer in group 1 compared to group 2 (4.9 vs. 2.5 years, p=0.002). The prevalence of tTG-IgA positivity and inadequate individual adherence to the GFD were greater in group 1 compared to group 2 (79% vs. 68%, p1=0.258, 58% vs. 46%, p2=0.236, respectively). Our research shows that the rising prevalence of thyroid autoantibody positivity correlates with both older age at diagnosis and extended duration of celiac disease, implying that prolonged gluten exposure may play a role in thyroid autoimmunity.

Keywords: Gluten exposure, thyroid autoantibody, celiac autoantibody

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Introduction

Autoimmune thyroid diseases (ATD) rank among the most prevalent autoimmune disorders in pediatric populations, with an incidence of roughly 3%[1]. Hashimoto's thyroiditis (HT) is the most prevalent of these disorders, marked by the infiltration of autoreactive B and T-cells into the thyroid parenchyma, leading to irreversible destruction of thyroid tissue. The primary autoantigens targeted in HT are thyroid peroxidase (TPO) and thyroglobulin (TG)[2-4]. HT occurs most commonly during adolescence[1,5].

Highlights

- Celiac disease (CD) have an increased risk of autoimmune thyroid disease.
- It is thought that shared common genes and/or gluten exposure may cause this.
- In this study, the prevalence of thyroid autoantibody positivity was found to be 7.2% among individuals with CD.
- The age at diagnosis of CD was higher in those with thyroid autoantibody positivity.
- The duration of CD was longer in those with thyroid autoantibody positivity.

Genetically susceptible individuals are at a higher risk of developing celiac disease (CD), a chronic autoimmune disorder triggered by the consumption of gluten, a protein found in cereals such as wheat, barley, and rye. The prevalence is 1% in Western societies. It typically causes gastrointestinal symptoms and findings such as marked malabsorption, weight loss, and/or developmental delay 2. The principal serologic diagnostic is serum tissue transglutaminase (tTG) immunoglobulin A (IgA), and its positivity necessitates further screening for CD[5].

Numerous studies indicate that the prevalence of co-occurrence of CD and ATD is greater in childhood than in adulthood. The reported rate in children varies between 2% and 7.8%, which is around three times higher than that of the general population[1]. A study of children with CD in Italy showed a prevalence of ATD at 10.5%, around four times greater than that of the normal population[6]. In research by Elfström et al.[7] in 2008, this rate was also determined to be between 2 and 4 times 7. The prevalence of CD among patients with ATD varies considerably, with reported percentages between 0% and 9.9%[3].

The correlation between CD and HT has been elucidated through two distinct hypotheses. CD and HT possess one or more shared genes. Although human leukocyte antigen-DQ2 and DQ8 haplotypes are present in 69% of persons with CD, the weak correlation between HT and these haplotypes indicates a shared genetic susceptibility 2. The second hypothesis posits that the degradation of intestinal barrier integrity, resulting from the persistent consumption of gluten by children with CD who are not adhering to a gluten-free diet (GFD), induces a systemic immune response and facilitates the onset of additional autoimmune disorders[1].

This study aims to determine the prevalence of HT among children with CD who are monitored at our center, as well as to evaluate the degree of individual compliance with a GFD and to investigate the correlation between tTG-IgA and thyroid autoantibody positivity.

Materials and Methods

A retrospective analysis was done on the outpatient clinic records of 396 patients diagnosed with CD monitored at the pediatric gastroenterology clinic of Şanlıurfa Training and Research Hospital, from March 2023 to June 2024, and subsequently referred to the pediatric endocrinology clinic for potential thyroid dysfunction. Patients aged 1 to 18 years who tested positive for tTG-IgA, received a histopathological diagnosis of CD, and had thyroid autoantibodies assessed during follow-up were included in the study. Patients with other chronic conditions who declined to participate in the trial and whose data were not accessible were excluded. A total of 334 instances were incorporated into the final analyses. Data regarding age; date of diagnosis of CD; duration of CD; presence of CD symptoms; individual compliance assessments to a GFD; height; height standard deviation score (SDS); body mass index (BMI); BMI SDS; tTG-IgA; thyroid-stimulating hormone (TSH); free T4 (fT4); anti-TPO; and anti-TG values were extracted from outpatient clinic records.

tTG-IgA levels in serum were measured by enzyme-linked immunosorbent assay using commercially available Orgentec (Mainz, Germany) kits. The measurement range of the kit was 20-200 U/mL, and results outside these values were reported as upper or lower limit values. Considering the manufacturer's instructions, a threshold value of 20 U/mL was used as the cut-off for seropositivity. Anti-TPO and anti-TG levels were measured by electrochemiluminescence immunoassay using commercially available Elecsys (Mannheim, Germany) kits. Threshold values of ≥35 IU/mL for anti-TPO and ≥115 IU/mL for anti-TG were considered as thyroid autoantibody positivity[6,7].

Celiac symptoms were deemed present when intestinal symptoms (such as stomach pain, constipation, bloating, weight loss) and/or extraintestinal symptoms (including short stature, delayed menstruation, oral aphthae, exhaustion) were reported in patient histories. Participants were categorized into two groups, "excellent adherence" and "poor adherence", based on their dietary compliance level as reported by the patients themselves in the evaluation of individual adherence to the GFD[8]. The connection between age, presence of celiac symptoms, individual adherence to a GFD, tTG-IgA positivity, duration of CD, and thyroid autoantibody positivity was assessed.

The patients were categorized into two groups based on the presence of thyroid autoantibodies (anti-TPO and anti-TG): Group 1 comprised individuals with positive autoantibodies, whereas group 2 included those with negative autoantibodies. The evaluation assessed differences between the groups regarding age, duration of CD, presence of CD symptoms, individual compliance with a GFD, height, height SDS, BMI, BMI SDS, tTG-IgA positivity, TSH, sT4 should be change as fT4, anti-TPO, and anti-TG.

Statistical Analysis

Analyses were conducted using SPSS version 26 (IBM SPSS Statistics for Windows, Version 26.0, IBM Corp, Armonk, NY, USA). The Kolmogorov-Smirnov test was employed to assess the normality of the variable distributions. Mean ± standard deviation values were employed to characterize normally distributed continuous variables, whereas median and interquartile ranges were utilized for non-normally distributed continuous variables. Categorical variables were described using frequency and percentages. In paired group comparisons, Student's t-test was employed for normally distributed independent continuous variables, while Mann-Whitney U test was utilized for non-normally distributed independent continuous variables. The chi-square test was employed to analyze categorical variables. Spearman correlation analysis assessed the relationships between continuous variables, while point-biserial correlation analysis examined the associations between categorical and continuous variables. A value of p less than 0.05 was accepted as statistically significant. The protocols adhered to the principles of the Declaration of Helsinki and received approval from the Harran University Clinical Research Ethics Committee (approval number: HRÜ/25.07.26, date: 14.04.2025).

Results

The average age of the patients in the study was 10.8±4.1 years, with 63.5% (212) female; and the median age at diagnosis of CD was 6.5 years. At the time of the visit, when they were evaluated for thyroid autoantibody positivity, the median duration of CD was 2.7 years, 52% (151) reported the presence of celiac symptoms, and 47% (156) had poor individual dietary compliance assessments. The median height-SDS was -1.3, BMI was 16.4 kg/m^2, and BMI-SDS was -0.3 in the patients whose demographic parameters are given in **Table 1**.

Celiac antibody (tTG-IgA) positivity was present in 69% (230) of the patients; thyroid autoantibody positivity (anti-TPO and/or anti-TG) was present in 7.2% (24).

The evaluation of patients based on thyroid autoantibody positivity revealed that the mean age of patients in group 1 (n=24) was 12.9±3.7 years, while the mean age in group 2 (n=310) was 10.6±4.1 years. A statistically significant difference was observed between the two groups (p=0.008). The median duration of CD was 4.9 years in group 1 and 2.5 years in group 2, demonstrating a statistically significant difference (p=0.002). No statistically significant differences were observed between the groups in terms of gender, height-SDS, BMI, and BMI-SDS (p1=0.918, p2=0.941, p3=0.135, p4=0.712). While no statistically significant difference was observed, the rate of tTG-IgA positivity was greater in group 1 compared to group 2 (79% vs. 68%, p=0.258). Conversely, the prevalence of celiac symptoms was significantly lower in group 1 than in group 2 (25% vs. 46.8%, p=0.042). The rate of poor individual adherence to the GFD was higher in group 1 compared to group 2, with no statistically significant difference observed (58% vs. 46%, p=0.236) (**Table 2**).

The median duration of CD was 3.5 years for patients exhibiting poor individual dietary adherence (n=156) and 2.1 years for those with good individual dietary adherence (n=178), demonstrating a statistically significant difference (p=0.004). A weak positive correlation was observed between the duration of CD and poor individual dietary adherence, as well as anti-TPO levels (r1=0.141, p1=0.010; r2=0.116, p2=0.034). No significant correlation was observed between individual dietary adherence and anti-TPO and anti-TG levels (r1=0.052, p1=0.346; r2=0.028, p2=0.605). The tTG-IgA antibody showed no correlation with anti-TPO and anti-TG (r1=0.007, p1=0.906; r2=0.008, p2=0.888).

Table 1.
Demographic data in the whole group

n=334	Median (IQR)
Age, years*	10.8±4.1
Gender, F:M, %	63.5:36.5
Duration of CD, years	2.7 (1.2-5.6)
Height, cm	135 (119-150)
Height-SDS	-1.3 (-2 - -0.4)
BMI, kg/m^2	16.4 (14.9-19)
BMI-SDS	-3 (-1.1-0.4)
TSH, uIU/mL	2.1 (1.6-2.8)
fT4, pmol/L*	16.5±2.2
Anti-TPO, IU/mL	11.3 (8.7-14.6)
Anti-TG, IU/mL	14.8 (13.3-16.3)
Thyroid autoantibody positivity rate, %	7.2
tTG-IgA, U/mL	67.4 (14.2-200)
tTG-IgA positivity rate, %	69
Presence of celiac symptoms, %	52
Poor individual adherence to GFD, %	47

*: Mean
± SD, BMI: Body mass index, CD: Celiac disease, GFD: Gluten-free diet, IQR: Interquartile range, SDS: Standard deviation score, F: Female, M: Male, tTG: Tissue thyroglobulin, IgA: Immunoglobulin A, TSH: Thyroid-stimulating hormone, SD: Standard deviation, TPO: Thyroid peroxidase

Table 2.
Demographic data, compliance rates to GFD and laboratory parameters according to thyroid antibody positivity (Anti TPO and anti TG positivity)

	Group 1 (thyroid antibody +) median (IQR) (n=24)	Group 2 (thyroid antibody -) median (IQR) (n=310)	p
Age, years*	12.9±3.7	10.6±4.1	0.008
Gender, F:M, %	62.5:37.5	63.5:36.5	0.918
Age at diagnosis of CD, years	7.4 (5.3-9.4)	6.5 (4.5-9.8)	0.454
Duration of CD, years	4.9 (3-8.4)	2.5 (1.2-5.4)	0.002
Height, cm	143 (134-159.7)	132 (118-150)	0.005
Height-SDS	-1.5 (-2 - -0.06)	-1.3 (-2 - -0.4)	0.941
BMI, kg/m^2	17.8 (15-19.8)	16.3 (14.8-18.7)	0.135
BMI-SDS	-0.27 (-1.3-0.05)	-0.36 (-1.1-0.4)	0.712
TSH, uIU/mL	3.1 (1.9-6.6)	2.1 (1.6-2.7)	<0.001
fT4, pmol/L*	15.8±2.9	16.5±2.2	0.114
Anti- TPO, IU/mL	104 (38.3-226)	11 (8.6-13.9)	<0.001
Anti-TG, IU/mL	166 (76-462.6)	14.6 (13.2-16)	<0.001
tTG-IgA, U/mL	40.6 (21.4-200)	68.1 (14.1-200)	0.960
tTG-IgA positivity rate, %	79	68	0.258
Presence of celiac symptoms, %	25	46.8	0.042
Poor individual adherence to GFD, %	58	46	0.236

*: Mean ± SD, BMI: Body mass index, CD: Celiac disease, GFD: Gluten-free diet, IQR: Interquartile range, SDS: Standard deviation score, F: Female, M: Male, tTG: Tissue thyroglobulin, IgA: Immunoglobulin A, TSH: Thyroid-stimulating hormone, SD: Standard deviation, TPO: Thyroid peroxidase

Discussion

In our study, group 1 showed an older age at the time of CD diagnosis and a poorer individual dietary adherence assessment compared to group 2; nevertheless, the differences were not statistically significant. However, as the duration of CD increased, the rate of poor individual adherence with he GFD increased, and the duration of CD was detected to be longer in group 1.

As age increases during childhood, a gradual decrease in intestinal-related symptoms and malabsorption findings, and an increase in extra-intestinal findings are observed[9]. The change in these clinical findings, especially during adolescence, causes a decrease in compliance with the GFD, along with the decrease in social pressures and the alleviation of symptoms[10]. In our study, the fact that patients with positive thyroid autoantibodies were older, had fewer celiac symptoms and still had higher tTG-IgA levels suggests that compliance with GFD was inadequate in this patient group. This supports the hypothesis that continuous gluten exposure in children with CD who do not follow a GFD may initiate a systemic immune response by compromising intestinal barrier integrity, potentially leading to the onset of additional autoimmune diseases.

Individuals with CD who do not adhere to a GFD are at an elevated risk for developing additional autoimmune diseases. The age at which CD is diagnosed and the presumed duration of gluten exposure are regarded as predictive factors for the onset of additional autoimmune diseases[11]. Various studies have reported differing outcomes concerning the effects of a GFD in individuals with CD and concurrent ATD. The observed effects involve clinical outcomes, including regression of subclinical hypothyroidism, alterations in thyroid autoantibody levels, normalization of thyroid volume, and modifications in thyroxine requirements among patients diagnosed with hypothyroidism[12].

In a study evaluating the age at diagnosis of CD, it was reported that children diagnosed with CD after the age of 10 years had four times higher rates of concomitant autoimmune diseases than those diagnosed after the age of 2 years[13]. In another study, it was found that the age at diagnosis of children with CD with concomitant ATD was higher than that of those children without ATD[14]. In a study by Meloni et al.[15], ATD developed in 34 of 324 children with CD, and the age at diagnosis was 6.6 years in children with CD alone, whereas the age at diagnosis for CD was 10.5 years in patients with CD and autoimmune thyroiditis. In our study, there was no statistically significant difference between group 1 and group 2 in the age at diagnosis of CD; however, similar to the literature, the age at diagnosis was older in group 1.

A study on the age at diagnosis of CD indicated that children diagnosed after the age of 10 showed four times the rates of concurrent autoimmune diseases compared to those diagnosed after the age of 213. A separate study indicated that the age at diagnosis for children with CD and concomitant ATD was greater than for those without ATD[14]. Meloni et al.[15] conducted a study revealing that ATD occurred in 34 out of 324 children with CD. The average age at diagnosis for children with CD alone was 6.6 years, while those with both CD and autoimmune thyroiditis had a diagnosis age of 10.5 years. Our study found no statistically significant difference in the age at CD diagnosis between group 1 and group 2; however, consistent with existing literature, group 1 demonstrated a trend toward an older age at diagnosis.

Gluten exposure is considered a significant predictor of autoimmune disease onset, and the literature examines its impact on the formation of thyroid autoantibodies in patients with CD, with varied conclusions. A study conducted by Metso et al.[16] monitored 27 individuals with CD and 27 healthy controls over the course of one year. While no significant difference in anti-TPO positivity was detected at diagnosis or during follow-up between the two groups, a not statistically significant elevation in anti-TPO titers was noted in the group with CD, despite adherence to a GFD. In another study by Oderda et al.[17], anti-TPO positivity was detected in 6 of 41 children diagnosed with CD. It has been reported that these children were older at the time of diagnosis (mean age 7.5 years; comparison group: 2 years), and thyroid antibody positivity was observed more frequently in children older than 6 years. After 1-5 years of follow-up, antibodies became negative in two of the 6 patients with anti-TPO positivity, and antibody titers increased in the other four patients. The younger age of the children with antibody negativity suggests that delayed diagnosis and longer gluten exposure may be related to the development of thyroid autoantibodies. In line with these findings, it is emphasized that starting a GFD may be insufficient to suppress already developed thyroid autoimmunity, but rapid identification and the early removal of gluten may safeguard against the onset of thyroiditis[17]. In another study with long-term follow-up data, 324 children with CD were followed up for approximately 11 years, during which 34 patients developed thyroid autoantibody positivity. Antibody positivity was observed at diagnosis in 11 cases, while it showed up during GFD treatment in 23 cases. In a follow-up period of 2-9 years, it was observed that anti-TPO and/or anti-TG levels remained elevated in 9 out of 11 patients who were antibody positive at diagnosis, despite adherence to a GFD15.

In a multicenter study by Sategna-Guidetti et al.[18], 241 adult patients with CD were evaluated for thyroid autoantibodies and thyroid functions before and one year after starting a GFD. Initially, euthyroid ATD was detected in 16% of the cases, and subclinical hypothyroidism or hyperthyroidism was reported to develop in 25% of these individuals during the follow-up period. It was emphasized that individual adherence to GFD was poor in these patients. It has been reported that 5.5% of individuals with normal thyroid function tests at the time of diagnosis developed thyroid dysfunction during follow-up despite good compliance with a GFD. In a longitudinal study including 90 university students with CD, high anti-TPO titers were detected in 13 (14.4%) of these cases at the time of diagnosis. Following the GFD, anti-TPO positivity was observed at 11.1%, 6.6% and 2.2% at 6, 12 and 24 months, respectively, and in the two cases where antibody positivity continued at 24 months, anti-TPO titers were found to be quite low. These findings suggest that a GFD may reduce anti-TPO titers over time[19]. Abu Hanna et al.[20] found a significant negative correlation between tTG-IgA levels below three times the upper limit of normal and the accelerated normalization of these levels. Additionally, they noted a correlation with the onset of autoimmune illness. Researchers suggest that a GFD may reduce thyroid autoantibodies by decreasing tTG-IgA levels, hence offering a protective effect against the onset of autoimmune disorders. Likewise, another investigation indicated that sustained tTG-IgA positivity correlated with an elevated risk of irreversible hypothyroidism[21]. Our study's findings indicate that gluten exposure may contribute to thyroid autoimmunity. In group 1, the duration of CD was markedly prolonged, and the incidence of individual non-adherence to the diet and individuals were tTG-IgA positive were elevated but not considerable. The findings, consistent with existing literature, indicate that the length of gluten exposure and adherence to a GFD may significantly influence the development of thyroid autoantibodies.

Our study group found no significant association between tTG-IgA levels and anti-TPO and anti-TG antibodies. However, research by Légeret et al.[22] revealed a small but statistically significant negative connection between anti-TG and tTG-IgA levels. Although this finding points to a possible relationship between serological activity and thyroid autoimmunity, data on this subject in the literature are inconsistent[19,23,24]. Although a possible association between CD and thyroid dysfunction or ATD is thought to exist, the strength and direction of this association remain inconsistent in the literature due to factors such as methodological differences between existing studies, sample sizes and follow-up periods. A certain period of time is required for thyroid autoantibodies to be detected. However, the lack of a clear consensus on this period is the main reason for the inconsistent results in the studies. There is no consensus in the guidelines regarding when patients with CD should undergo screening for autoimmune thyroiditis in children, and the decision regarding the timing of the examination is left to the clinician.

Study Limitations

This study is limited by its retrospective and cross-sectional design. Another important limitation is that neither tTG-IgA levels nor individual dietary adherence assessment are gold standard methods for assessing gluten exposure in the evaluation of GFD compliance[25]. This makes it difficult to draw a definitive conclusion about gluten exposure.

Conclusion

Our study observed that the frequency of thyroid autoantibody positivity increased with age at diagnosis of CD, consistent with existing literature. This finding suggests that prolonged gluten exposure with delayed diagnosis may contribute to thyroid autoimmunity. Therefore, the development of screening strategies to prevent delayed age at diagnosis in CD and early initiation of a GFD may have a potential role in the prevention of comorbidities such as thyroid autoimmunity.

Ethics

Ethics Committee Approval: The protocols adhered to the principles of the Declaration of Helsinki and received approval from the Harran University Clinical Research Ethics Committee (approval number: HRÜ/25.07.26, date: 14.04.2025).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Author Contributions: Eviz E: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Teker Düztaş D: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.

Conflict of Interest: The authors declare no conflicts of interest.

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