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# Assessment of autoimmune thyroiditis in Turkish children with celiac disease

**Coşkun Fırat Özkeçeci[1], Melike Arslan[1], Edibe Gözde Başaran[1], Semra İnce[2], Sevinç Odabaşı Güneş[3], Necati Balamtekin[1]**

*[1]University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Gastroenterology, Ankara, Türkiye*
*[2]University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Nuclear Medicine, Ankara, Türkiye*
*[3]University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Endocrinology, Ankara, Türkiye*

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**Corresponding Author:**
Coşkun Fırat Özkeçeci, M.D., University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Pediatrics, Division of Pediatric Gastroenterology, Ankara, Türkiye
coskunfirat3@hotmail.com

**ORCID:**
orcid.org/0000-0002-3954-6428

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## ABSTRACT

**Aims:** It has been reported that there is a link between celiac disease and other autoimmune diseases in children. We aimed to compare the presence of autoimmune thyroid disease in children with celiac disease and the ultrasonographic evaluations of these patients with healthy controls.

**Methods:** This cross-sectional, case-control study enrolled pediatric patients diagnosed with celiac disease and healthy children as controls. All patients and controls were tested for celiac antibodies (anti-tissue transglutaminase immunoglobulin A), thyroid function tests (thyroid-stimulating hormone, free thyroxine, free triiodothyronine, thyroid peroxidase antibody, and anti-thyroglobulin antibody), and thyroid ultrasonography. The primary endpoint was the difference in the frequency of autoimmune thyroiditis between patients and controls.

**Results:** The study included 50 children with celiac disease [mean±standard deviation (SD) age: 10.98±3.84, 59% girls] and 50 healthy controls (mean±SD age: 11.36±4.17 years, 65% girls). Five patients (10%) with celiac disease and none of the controls were diagnosed with autoimmune thyroiditis at the time of enrolment (p=0.022). No relationship was identified between the severity of small bowel pathology and autoimmune thyroiditis in patients with celiac disease. Additionally, no significant differences were observed in the ultrasonographic evaluation between celiac patients and controls.

**Conclusions:** In this low-sample study, patients with celiac disease were more likely to have autoimmune thyroiditis than the controls. However, the severity of small bowel damage in celiac disease may not be associated with autoimmune thyroiditis.

## Introduction

Celiac disease is an immune-mediated systemic condition causing pathology in the small intestine mucosa of genetically predisposed individuals, leading to lifelong intolerance to dietary gluten intake (1). Studies have shown that the prevalence of celiac disease in Europe is approximately 0.6-1% (2). Today, it is well-known that celiac disease affects not only the gastrointestinal system but also the extraintestinal systems and it can present with highly variable clinical symptoms (3).

There is a close association between celiac disease, diabetes mellitus, and pubertal disorders. One of the extraintestinal organs affected by celiac disease is the thyroid gland. In patients with celiac disease, the rates of thyroid gland dysfunction, papillary thyroid carcinoma, and autoimmune thyroiditis, including Hashimoto's thyroiditis, and Graves' disease, are higher than in healthy individuals. Therefore, it is recommended to screen patients with celiac disease at certain intervals for thyroid gland pathologies, regardless of their compliance with a gluten-free diet (4).

In this study, we sought to assess autoimmune thyroid disease in children with celiac disease and compare the ultrasonographic assessments of these patients with those of healthy controls.

## Methods

### Study design setting and sample

This cross-sectional, case-control study was conducted between November 2021 and November 2022 at our tertiary hospital's pediatric gastroenterology and general pediatric outpatient clinics. The study included pediatric patients diagnosed with celiac disease based on biopsy reports according to the European Society of Pediatric Gastroenterology Hepatology and Nutrition criteria (3). Patients diagnosed with autoimmune thyroiditis who presented for investigation of celiac disease were not included in the study. The control group consisted of healthy children who visited the pediatrics outpatient clinic annually for routine growth assessment. They had no known chronic illnesses, tested negative for the anti-tissue transglutaminase immunoglobulin A (anti-tTG IgA) marker, and had normal IgA levels for their age. Figure 1 shows the flow chart of the study sample selection.

### Instruments and data collection

We measured the anti-tTG IgA antibody titer during the initial screening using the enzyme-linked immunosorbent assay (ELISA) method. The upper standard limit considered was 10 U/mL. When total serum IgA levels are low, we measured the anti-tTG IgG antibody using the ELISA method, with normal levels defined as <10 U/mL. The participants' thyroid function was evaluated using thyroid-stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), and by measuring thyroid autoantibodies such as anti-thyroid peroxidase antibodies (Anti-TPO) and anti-Tg antibody with the ELISA method. TSH level was used as the primary indicator of thyroid dysfunction. Subclinical hypothyroidism was defined as TSH levels higher than the normal range, while fT4 levels remained within the normal limits for age. Autoimmune thyroid disease was diagnosed using the electrochemiluminescence method when the anti-TPO levels were >9 IU/mL and/or the anti-Tg levels were >4 IU/mL.

### Histopathologic evaluation

Patients underwent at least four biopsies from the distal duodenum and at least one biopsy from the bulb while on a diet containing gluten. An experienced pathologist evaluated biopsies. The degree of histopathologic damage in the small intestine was identified based on the modified Marsh classification, which involves assessing the elevation of intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy (5,6). An increased number of intraepithelial lymphocytes with normal villi morphology characterizes type 1. In addition to the characteristics of type 1, type 2 includes hyperplasia of glandular structures. Type 3 is classified into three groups: type 3a includes mild villous atrophy, type 3b includes moderate villous atrophy; and type 3c includes total villous atrophy.

### Ultrasonographic assessment

An experienced nuclear medicine specialist, blinded to the participants' group allocations and laboratory results, performed the thyroid ultrasonography in both the patient and control groups using a GE Logiq 5 (GE, California, USA), equipped with a 7-11 MHz linear transducer, which utilized continuous, real-time visualization. The echotexture of the thyroid gland was characterized as either homogeneous or heterogeneous compared to the surrounding muscular structures. Thyroid nodules were identified by solid and cystic (fluid-filled) components their size, margins, echogenicity, calcifications, central compartment, and cervical lymph nodes (7). The color Doppler characteristics of the thyroid gland and nodules were also recorded.

### Ethical approval

University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Scientific Research Ethics Committee reviewed and approved this study protocol (decision number: 2021-395, date: 25.11.2021). It was conducted according to the principles outlined in the Helsinki Declaration. All participants and their parents signed the informed consent form.

### Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corporation, Armonk, NY, USA).

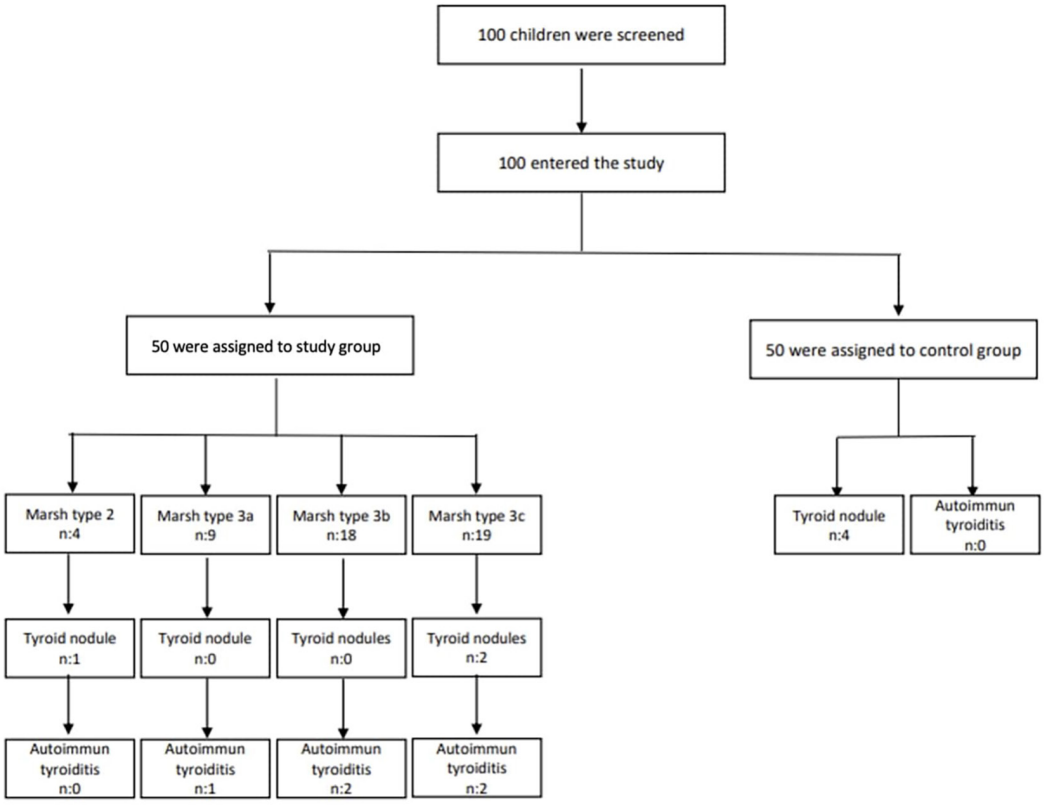


**Figure 1.** Flowchart of the study sample selection

Continuous variables are reported as mean±standard deviation or median [minimum-maximum (min.-max.)], while categorical variables are presented as frequency and percentage values. The normality of continuous variables was assessed using the Kolmogorov-Smirnov goodness-of-fit test. We used the independent-sample t-test for normally distributed data to compare continuous variables between two groups and the Mann-Whitney U test for non-normally distributed data. When necessary, categorical variables were compared using the chi-squared test, Fisher's exact test, or the likelihood ratio. The level of statistical significance was set at $p<0.05$.

## Results

### Socio-demographic and clinical characteristics

The study included 100 children, divided equally into 50 patients and 50 controls. The mean age at diagnosis for the patient and control groups was 10.98±3.84 and 11.36±4.17 years, respectively. There was no significant difference in mean ages between the two groups (p=0.637). The demographic composition of the study population was further characterized by a gender distribution of 63% girls and 37% boys. The socio-demographic characteristics of the patients in both groups are provided in Table 1. The most common presenting symptoms in patients with celiac disease were abdominal pain (34%) and failure to thrive (32%). Surprisingly, two patients visited the hospital, thinking they were overweight. Based on the pathological examination results of the patient group, 8% (n=4) were classified as Marsh type 2, 18% (n=9) as Marsh type 3a, 36% (n=18) as Marsh type 3b, and 38% (n=19) as Marsh type 3c.

### Laboratory findings

Based on blood tests and ultrasound examinations, 10% of patients diagnosed with celiac disease (n=5) were found to have autoimmune thyroiditis. In contrast, there was no autoimmune thyroiditis among the control group participants (p=0.022). It's worth noting that all the patients with autoimmune thyroiditis were female. Among these five patients examined, two exhibited a condition described as "slightly heterogeneous echogenicity" of the thyroid gland, while three presented with "heterogeneous echogenicity" as observed through ultrasonography. Additionally, elevated levels of TSH, anti-Tg, and/or anti-TPO antibodies were detected in all individuals. The mean TSH, anti-TPO, and anti-Tg values for these patients were 7.65 mIU/L (min.: 5.02 mIU/L, max.: 9.75 mIU/L), 350.02 IU/mL (min.: 28.1 IU/mL, max.: 675 IU/mL), and 11.38 IU/mL (min.: 7.1 IU/mL, max.: 33 IU/mL), respectively. Additionally, the fT4 and fT3 levels in all these five

patients were within the normal range for their age; hence, these patients were considered to have subclinical hypothyroidism.

### Ultrasonographic findings

In the patient group, there were no significant differences in the rates of autoimmune thyroiditis and thyroid nodules based on the Marsh scores of the patients. Thyroid nodules were detected in one patient with Marsh type 2, and two patients with Marsh type 3c in the patient group, as well as in a total of four patients from the control group. There was no significant difference between the groups in terms of the presence of nodules (p=0.695), nodule structure (p=1.000), nodule heterogeneity (p=0.956), and the number of nodules (p=0.956) (Table 1). In both groups, there was no significant difference between the volumes of the right and left lobes of the thyroid gland (p=0.934 and p=0.812, respectively). Likewise, the two groups had no notable difference in the thyroid function test results (p=0.495) or thyroid antibodies (p=0.495).

All identified nodules in the patient and control groups had clear margins. All participants had normal free T3 and T4 values. In both groups, none of the participants had microcalcifications, macrocalcifications, central compartment lymph nodes (levels 6-7), or lateral cervical lymph nodes (levels 1-5) (Table 2).

## Discussion

It is well-established that the frequency of celiac disease is higher in patients with autoimmune thyroiditis (1). Conversely, it is believed that the frequency of autoimmune thyroiditis is also higher in patients with celiac disease. Therefore, patients with celiac disease should be monitored for thyroid diseases (4). In our study, we found no significant difference in the prevalence of hyperthyroidism between the patient group and the control group, which aligns with some previous research (4). However, we did observe that five patients with celiac disease had elevated levels of TSH and thyroid autoantibodies, suggesting a potential case of autoimmune thyroiditis. Midhagen et al. (8) reported a prevalence of thyroid dysfunctions in patients with celiac disease at 5.8%, while Volta et al. (9) documented it as 5.7%. In a study by Elfström et al. (10), which examined 15,439 patients with celiac disease from 1964 to 2003, the overall prevalence of thyroid disorders was found to be 3.7%. Additionally, research by Metso et al. (11) compared the rates of autoimmune thyroiditis in patients with celiac disease at diagnosis and one year later against those in a control group. The findings revealed that the patient group had significantly higher rates of autoimmune thyroiditis at both time points than the control group (11). A meta-analysis conducted by Sun et al. (12) found that the prevalence of hyperthyroidism in patients with celiac disease

**Table 1. Socio-demographic, clinical and laboratory characteristics of the groups**

| | Celiac patients (n=50) | Controls (n=50) | p |
|---|---|---|---|
| **Age, years, mean±SD** | 10.98±3.84 | 11.36±4.17 | 0.637* |
| **Age of diagnosis, years, mean±SD** | 9.04±3.55 | - | - |
| **Sex, female, n (%)** | 34 (68.0) | 29 (58.0) | 0.300*** |
| **Autoimmune thyroiditis, n (%)** | 5 (10.0) | 0 (0.0) | **0.022*** ** |
| **Nodule present, n (%)** | 47 (94.0) | 46 (92.0) | 0.695*** |
| **Number of nodules, median (min.-max.)** | 5 (4-8) | 2.5 (1-6) | 0.629** |
| **Nodule heterogeneity, n (%)** | | | |
| **Homogenous** | 35 (70.0) | 36 (72.0) | 0.956*** |
| **Slightly heterogenous** | 7 (14.0) | 6 (12.0) | |
| **Heterogenous** | 8 (16.0) | 8 (16.0) | |
| **Structure of the nodule, n (%)** | | | |
| **Cystic** | 3 (100.0) | 3 (75.0) | 1.000***a |
| **Solid** | 0 (0.0) | 1 (25.0) | |

*Independent samples t-test, **Mann-Whitney U test, ***Chi-square test (aFisher's exact test, likelihood ratio)
min.-max.: Minimum-maximum, SD: Standard deviation

**Table 2. Diagnoses of autoimmune thyroiditis and thyroid nodule across Marsh score groups among patients with celiac disease**

| | Marsh score | | | | p |
|---|---|---|---|---|---|
| | 2 | 3A | 3B | 3C | |
| **Autoimmune thyroiditis, n (%)** | 0 | 1 (11.1) | 2 (11.1) | 2 (10.5) | 0.922* |
| **Thyroid nodule, n (%)** | 1 (25.0) | 0 | 0 | 2 (10.5) | 0.174* |

*Chi-square test

was similar to that in control groups. However, the prevalence of hypothyroidism was significantly higher in patients with celiac disease. Although autoimmune thyroid disease is known to be more common in adult patients with celiac disease, no significant difference was found between patients and controls in the prevalence of hypothyroidism and hyperthyroidism on thyroid function tests (13). There has been increase in the frequency of celiac disease among patients diagnosed with autoimmune thyroiditis (1). However, there is a lack of data on the frequency of autoimmune thyroiditis in patients with celiac disease. A study of Italian children revealed that 32% of those diagnosed with celiac disease also had autoimmune thyroiditis at the time of their celiac disease diagnosis. Furthermore, 68% of patients were diagnosed with autoimmune thyroiditis after the initiation of a gluten-free diet (14). Another study by Diamanti et al. (15) reported that autoimmune thyroiditis was not more prevalent in children with celiac disease on a gluten-free diet than healthy control groups.

The histopathological assessments of patients with celiac disease are currently predominantly performed based on the Marsh classification (6). A literature review revealed no studies that have examined the relationship between autoimmune thyroiditis and intestinal histopathology. In addition, the relationship between Marsh scores and the prevalence of autoimmune thyroiditis was investigated. The findings indicated no significant relationship between the degree of intestinal injury and the severity of thyroid issues. This finding suggests that autoimmune thyroiditis or thyroid pathology cases are not secondary to celiac disease but are associated with it through common genetic factors.

The comorbidity of different autoimmune diseases is a well-known clinical phenomenon. The genetic characteristics of human leukocyte antigen (HLA) DQ2 and DQ8 have been identified as risk factors for celiac disease, with approximately 2-5% of individuals with autoimmune thyroid disease also exhibiting symptoms of celiac disease (16). Furthermore, studies have identified specific HLA antigen alleles, such as HLA-DR 4/5 for autoimmune thyroiditis and HLA-DR3 for Graves disease, associated with autoimmune thyroid disease (17). The observed relationship between celiac disease and autoimmune thyroid diseases may be attributed to a genetic predisposition. A review of the extant literature revealed a paucity of studies in both English and Turkish that examined the prevalence of thyroid nodules and thyroid function among pediatric patients with celiac disease. However, a study by Collin et al. (18) revealed that 25 of the 53 patients with autoimmune thyroid disease presented with solitary nodules; though, only 1 of these patients (4%) was also diagnosed with celiac disease. In contrast, our study identified thyroid nodules in three patients with celiac disease and four participants in the control group. Subsequent analysis revealed no statistically significant differences among the groups concerning nodule structures, heterogeneity, or echogenicity. Moreover, between the patient and control groups, a lack of statistically significant variation was observed in the number and size of nodules, as well as the volume of the right and left thyroid lobes. A previous publication on adult patients with celiac disease noted that the thyroid gland volumes of the patients gradually decreased during their one-year follow-up after they started gluten-free diets (13). This observation suggests that thyroid gland pathologies may manifest in adulthood rather than childhood, emphasizing the need to monitor these patients' thyroid functions closely. Furthermore, as indicated by ultrasound findings, a higher prevalence of heterogeneous echogenicity of the thyroid parenchyma has been observed in patients with celiac disease compared to the healthy population (14). The prevalence of pediatric thyroid carcinomas among all childhood malignancies was reported as approximately 1.4% (19). The ultrasonography assessment of participants in both the patient and control groups revealed no micro-macrocalcifications indicative of precancerous conditions, despite the increasing incidence of malignancies.

While there has been no significant increase in the prevalence of hyperthyroidism or hypothyroidism among patients diagnosed with celiac disease in childhood, the prevalence of autoimmune thyroiditis in this population is high, similar to that observed in adult patients with celiac disease. While there appear to be no issues related to pathologies and malignancies at an early age, it is imperative to address the long-term follow-up of patients. No significant relationship is observed between the degree of intestinal injury assessed by histopathological examinations and the presence of autoimmune thyroiditis. There is no significant relationship between the presence of pediatric celiac disease and the presence of thyroid nodules or thyroid volume. The potential risk factors for thyroid carcinomas in pediatric patients with celiac disease remain to be elucidated, and their long-term follow-ups are of crucial importance.

Due to the low incidence of celiac disease in the region, the study population was small, which significantly constrained the study's execution. Moreover, the study's design, which included data analysis from a single pathologist, constitutes a potential limitation. Prospective studies, re-evaluations, and longitudinal studies with a larger number of patients are necessary following the initiation of a gluten-free diet.

## Conclusion

In conclusion, the present study suggests that autoimmune thyroiditis may be more prevalent in pediatric patients with celiac disease, than healthy controls, though no significant ultrasonographic differences were observed. Further investigation with a more substantial sample size is necessary to ascertain whether pediatric patients are predisposed to autoimmune thyroiditis.

### Ethics

**Ethics Committee Approval:** University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Scientific Research Ethics Committee reviewed and approved this study protocol (decision number: 2021-395, date: 25.11.2021).

**Informed Consent:** Consent form was filled out by all participants.

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: C.F.Ö., M.A., E.G.B., S.İ., S.O.G., N.B., Concept: C.F.Ö., N.B., Design: C.F.Ö., N.B., Data Collection or Processing: C.F.Ö., M.A., E.G.B., S.İ., S.O.G., Analysis or Interpretation: C.F.Ö., S.İ., S.O.G., N.B., Literature Search: C.F.Ö., M.A., E.G.B., S.İ., S.O.G., N.B., Writing: C.F.Ö., M.A., E.G.B., S.İ., S.O.G., N.B.

**Conflict of Interest:** The authors declared no conflict of interest.

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