

## Autoimmune thyroid disease, thyroid functions, and thyroid ultrasonography in pediatric celiac disease

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### Abstract

**Objective:** To compare thyroid function tests, autoantibodies and ultrasound findings in pediatric celiac patients following a gluten-free diet with the non-celiac control group.

**Material and Methods:** The data of 64 celiac patients (median age 11 years) followed up with a gluten-free diet in the pediatric outpatient clinic and 143 control patients were retrospectively reviewed. The patient group consisted of 18 men, 46 women, and the control group 39 men and 103 women. The age range of the cases was 6-17 years. The duration of gluten-free diet was between three months and 15 years (median four years). The diagnosis of celiac disease was made according to the criteria of the European Society for Paediatric Gastroenterology, Association of Hepatology, and Nutrition. Free thyroxine, thyroid stimulating hormone (TSH), anti-thyroid peroxidase (anti-TPO), and antithyroglobulin (anti-Tg) levels were measured. In the thyroid ultrasound, gland volume, parenchymal structure, and thyroid nodules were evaluated. The positivity of thyroid autoantibodies and a heterogeneous appearance on ultrasound were assessed in favor of thyroiditis. The findings were compared between the celiac and control groups.

**Results:** Autoimmune thyroid disease was seen in 12.5% of celiac patients and 4.2% of the controls ( $p < 0.05$ ). The rate of abnormalities in thyroid function tests was 9.3% in the celiac group and 2.8% in the control group ( $p = 0.05$ ). The mean thyroid volume was 3.58 ml in celiac patients and 3.95 ml in controls ( $p > 0.05$ ). The parenchymal heterogeneity was 12.5% in the celiac group and 2.1% in the control group ( $p < 0.05$ ), and the incidence of thyroid nodules was 25% and 4.2%, respectively ( $p < 0.05$ ).

**Conclusion:** The autoimmune thyroiditis and thyroid dysfunction is more frequent in children with celiac disease. In addition, heterogeneous parenchyma and thyroid nodules are more common than the normal population on ultrasound. Celiac patients should be carefully evaluated for possible thyroid disease.

**Keywords:** Celiac disease, Autoimmune thyroiditis, Ultrasonography

### Introduction

Celiac disease is a chronic inflammatory disease mainly affecting the small intestine caused by gluten sensitivity in patients with genetic tendencies. Increased autoimmunity has been reported in celiac disease. Celiac disease is associated with autoimmune thyroid diseases, especially Hashimoto's thyroiditis (HT) (1). The incidence of Hashimoto's thyroiditis in celiac patients is reported to be between 1.25 and 19% (2). Hashimoto's thyroiditis is diagnosed with autoantibodies. In addition, thyroid dysfunction is not uncommon in celiac patients (1, 3-5). Autoimmune thyroiditis and other causes of thyroiditis can cause a heterogeneous appearance on ultrasound. It has been suggested that heterogeneous thyroid parenchyma is more useful than autoantibodies in determining the risk of developing hypothyroidism in euthyroid cases (6).

However, there are only a limited number of studies on the incidence of thyroid nodules in children with celiac disease.

In this study, we aimed to evaluate the ultrasound findings, antibodies and functions of the thyroid in patients followed up for celiac disease.

### Material and Methods

#### Patients and study design

In this study, the files of the cases followed up with celiac disease diagnosis in the Pediatrics Outpatient Clinic of Adiyaman Research and Education Hospital between September 2016 and August 2019 were evaluated retrospectively. Out of 172 cases, 108 were excluded from the study (68 of them had no ultrasound, 36 of them had missing files and 4 cases had a history of surgery).



The diagnosis of celiac disease was made according to the diagnostic criteria of the European Society for Paediatric Gastroenterology Hepatology and Nutrition. The patients were selected from those following a gluten-free diet. The median duration of the application of gluten-free diet after diagnosis was four years (three months-15 years). Eighteen of the cases were male, 46 were female, the mean age 10.84 and the age range was 6-17 years. The control group consisted of 143 subjects (39 males and 103 females with a mean age of 10.57 years). This group comprised patients that presented to our hospital due to anemia (n = 42), palpitations (n = 38), constipation (n = 24), recent excess weight gain (n = 11), hypertension (n = 8), neurological reasons (n = 7), renal complaints (n = 7), and other reasons (n = 6). The Clinical Research Ethics Committee of Adiyaman University approved the study.

### Laboratory Tests

The serum free thyroxine (fT4), thyroid stimulating hormone (TSH), antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-TG) levels were measured by chemiluminescence immunoassay using a DxI800 autoanalyzer (Beckman Coulter Inc, CA, USA). The lower and upper limit values of the measurement method used in the biochemistry laboratory were accepted as the normal reference range for thyroid function tests, anti-TPO and anti-Tg (sT4: 0.61-1.48 ng/dL, TSH: 0.34-5.6 uIU/L, anti-TPO: 0-9 IU / mL, and anti TG: 0-4 IU/mL). The cases with thyroid autoantibody levels above the specified reference value and those with heterogeneous parenchyma on ultrasound were considered to have autoimmune thyroiditis. Subclinical hypothyroidism was diagnosed based on normal sT4 despite increased TSH levels, and an overt hypothyroidism diagnosis was made if there was increased TSH and decreased sT4 levels. Increased sT4 levels and decreased TSH levels were evaluated as overt hyperthyroidism, whereas increased sT4 levels with normal TSH levels were considered as subclinical hyperthyroidism. Euthyroidism was diagnosed with normal TSH and sT4 levels. Other combinations of TSH and sT4 were excluded. A value outside the normal range in at least one of the serum TSH and sT4 values was noted as an indicator of abnormalities in thyroid functions.

### Ultrasound examination

Thyroid ultrasonography was performed using a real-time Aplio 500 (Toshiba Medical Systems, Tokyo, Japan) and a 7.5 MHz transducer by the same researcher blinded to the thyroid findings of the patients. The volume of the thyroid gland was measured by ultrasonography using a special formula: transverse size x anterior posterior size x craniocaudal size x 0.479 (Figure 1).

This calculation was performed for each lobe, and then the values of both lobes were added to obtain a final value in milliliters. The isthmus volume was disregarded. Thyroid parenchyma was evaluated as heterogeneous or normal. The internal structure, echogenicity, and the size and number of thyroid nodules, if any, were evaluated. Celiac patients without laboratory and ultrasound results were excluded from the study.

### Statistical analysis

All analyses were performed using SPSS for Windows (version 21.0; SPSS/IBM, Chicago, IL). Normality was tested using the Kolmogorov-Smirnov test. Since the thyroid gland volume values were not normally distributed, the Mann-Whitney U test was used for the comparison of the celiac and control groups. The chi-square test was used to compare categorical data. The statistical significance level was accepted as  $p < 0.05$ .

### Results

Celiac disease was more common in women. The incidence of autoimmune thyroiditis was significantly higher in the celiac group than in the control group. Autoimmune thyroiditis was found in 17 cases (26.6%) in the celiac group and six cases (4.2%) in the control group ( $p < 0.05$ , Table 1). In the celiac group, nine of the autoimmune thyroiditis cases had euthyroidism, six had hypothyroidism, and two had hyperthyroidism. Of the patients with hypothyroidism, four had subclinical and two had overt hypothyroidism, while both hyperthyroidism cases were overt. There was no patient with subclinical hyperthyroidism.

There was no significant difference between the celiac group and the control group in terms of the thyroid gland volume ( $p = 0.276$ , Table 2). Heterogeneous parenchyma was seen on ultrasound in eight cases (12.5%) in the celiac group and three (2.1%) in the control group ( $p = 0.004$ ). In the celiac group, only heterogeneous parenchyma was seen in four cases, while both autoantibody positivity and ultrasound heterogeneous parenchyma were observed in a further four cases. Thyroid nodules were found in 16 cases (25%) in the celiac group and six (4.2%) in the control group ( $p < 0.05$ ). In the celiac group, only one nodule was detected in 11 cases and two nodules in five cases. There were no cases with more than two nodules. In the control group, there was one nodule in two cases, two nodules in two cases, and more than two nodules in a further two cases. Most of the detected nodules consisted of hypoechogenic, solid nodules smaller than 1 cm.

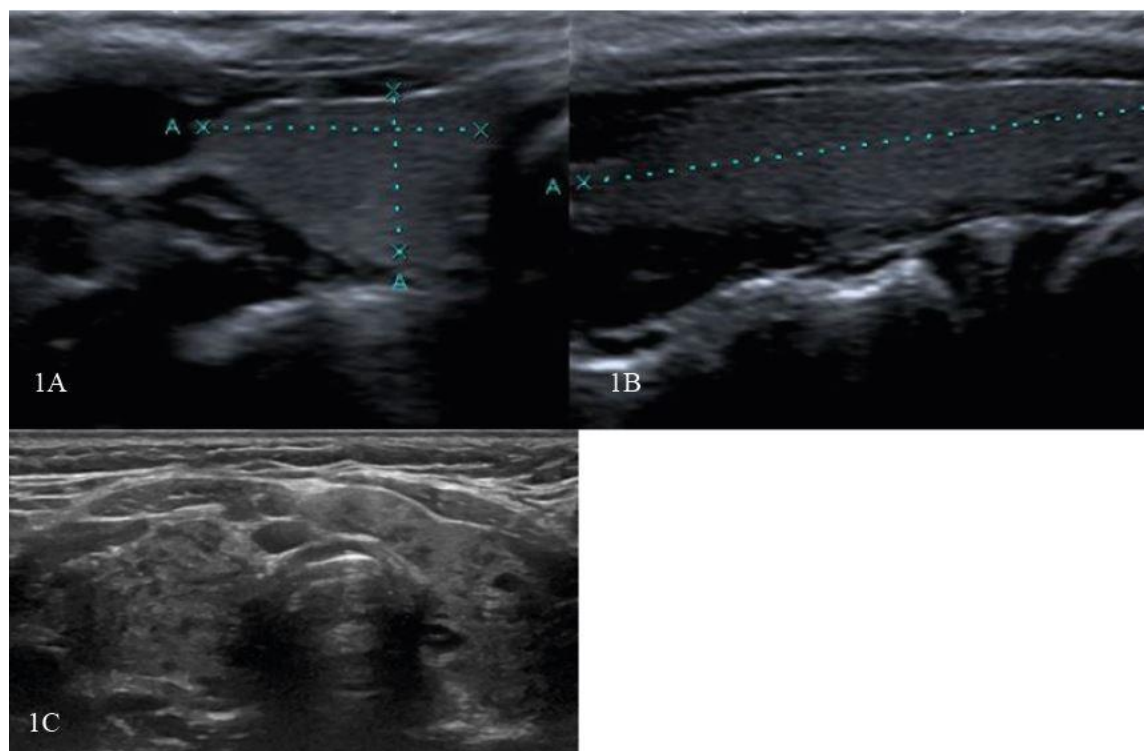
**Table 1:** Thyroid function disorders in the celiac and control groups

	Celiac (N)	Control (N)	p
Autoimmune thyroiditis (%)	17 (26.6)	6 (4.2)	<0.05
<b>Thyroid function</b>			
Euthyroidism	9	2	
Overt hypothyroidism	2	2	
Subclinical hypothyroidism	4	1	
Over hyperthyroidism	2	1	
Subclinical hyperthyroidism	0	0	
Abnormal thyroid functions (%)	8 (12.5)	4 (2.8)	<0.05

**Table 2:** Ultrasound findings in the celiac and control groups

	Celiac (n =86)	Control (n =143)	p
Thyroid gland volume (mean $\pm$ SD)	3,58 $\pm$ 2,18	3,95 $\pm$ 2,39	0,276
Heterogeneous parenchyma (%)	8 (12,5)	3 (2,1)	0,004
Thyroid nodule (%)	16 (25)	6 (4,2)	<0,05
Mean nodule size (SD)	4,93 ( $\pm$ 2,95)	6,71 ( $\pm$ 3,25)	
Nodule size range (mm)	3-12	3-15	
<b>Number of nodules</b>			
One	11	2	
Two	5	2	
Three or more	0	2	
<b>Internal structure of the nodule</b>			
Hyperechoic solid	2	1	
Hypoechoic solid	10	4	
Isoechoic solid	2	1	
Cystic	2	0	
Diabetes mellitus (%)	3 (4,7)	1 (0,7)	
<b>Autoantibody positivity (%)</b>	13 (20,3)	3 (2,1)	0,004
Anti-TPO (%)	12 (18,7)	2 (1,4)	
Anti-Tg (%)	2 (3,1)	1 (0,7)	

SD: Standard deviation, Anti-TPO: Anti-thyroidperoxidase, Anti-Tg: Anti-thyroglobulin.



**Figure 1:** Ultrasound image of the right lobe of the thyroid gland on transverse scan (1A) and longitudinal scan (1B) showing the measurement planes. (1C) Thyroid ultrasound showing heterogeneous parenchyma with poorly defined hypoechoic areas.

## Discussion

The results of this study showed; in pediatric celiac disease, the frequency of autoimmune thyroiditis and thyroid dysfunction increased ( $p < 0.05$ ). While there was no significant increase in thyroid gland volume, the frequency of heterogeneous parenchyma and thyroid nodule increased. Most of the nodules detected are hypoechogenic solid nodules smaller than 1 cm.

The incidence of thyroiditis in celiac patients has been reported to be 5.4% to 26.2% (1, 4, 7, 8). In our study, it was found to be 26.6%. In a case-control study by Hakanen et al., the rates of anti-TPO positivity and anti-Tg positivity were reported as 11.4% and 8.8%, respectively in celiac patients (7).

In that study, while anti-TPO was significantly higher in celiac patients, there was no significant difference in anti-Tg. Although the incidence of anti-TPO was slightly higher in our study, our results were similar in statistical terms. We detected only anti-TPO positivity in 12 cases (18.8%) cases, only anti-Tg positivity in one case, and both in another case. While anti-TPO positivity was significantly higher in the celiac group, there was no significant difference in anti-Tg positivity. In a study by Çağlar et al., the incidence of anti-TPO was found to be 9.7%(9).

Some authors suggest that heterogeneous thyroid parenchyma is more sensitive than thyroid autoantibodies in predicting the development of hypothyroidism (6). Evaluating patients followed up for three years, Rago et al. reported that thyroiditis did not develop in any case with autoantibody positivity and normal ultrasound findings (6). However, hypothyroidism was observed in 58% of euthyroid cases presenting with autoantibody positivity and a heterogeneous thyroid appearance on ultrasound (6). The authors also noted that hypothyroidism developed in 13.7% of patients with autoantibody negativity and heterogeneous thyroid parenchyma (6). In our study, four patients with elevated anti-TPO also had heterogeneous parenchyma on ultrasound. In four other patients, heterogeneous parenchyma was observed without autoantibody positivity. Heterogeneous parenchyma was more common in the celiac group than in the control group ( $p < 0.05$ ). In our study, two of the four cases with heterogeneous parenchyma alone had hyperthyroidism while both cases with heterogeneous parenchyma were euthyroid.

In our study, the incidence of hypothyroidism, hyperthyroidism, and euthyroidism coexisting with thyroid autoimmunity was found to be 9.4%, 3.1%, and 14.1%, respectively. In a study by Ansaldi et al., the incidence of hypothyroidism, hyperthyroidism, and euthyroidism was reported as 8.1%, 1.2%, and 15.7%, respectively (1). In another study, Meloni et al. determined the rate of hypothyroidism as 1.8% and that of euthyroidism as 8.6% (4). The authors noted that there were no cases of hyperthyroidism. Midhagen et al., who evaluated adult celiac patients, detected hypothyroidism at a rate of 5.8% and hyperthyroidism at 5% (3). After a follow-up of 5.5 years, Wessels et al. found the incidence of hypothyroidism as 3.2% and that of hyperthyroidism as 0.5 (5).

In the current study, the number of patients with thyroid nodules was 16 (25%) in the celiac group and six (4.2%) in the control group, indicating a significantly higher incidence of thyroid nodules in the former ( $p < 0.05$ ). In their adult celiac study, Hakanen et al. found thyroid nodules in 34% of cases(7).

The limitation of our retrospective study was that, some cases had to be excluded due to the lack of laboratory or ultrasound results. Therefore, our patient group was not as large as we wished to evaluate.

## Conclusion

The results of this study showed that the incidence of autoimmune thyroiditis, thyroid dysfunction, heterogeneous parenchyma, and thyroid nodule was increased in celiac

cases. Celiac patients should be evaluated in detail for the possibility of thyroid diseases.

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**Author Contributions:** ŞŞ, FDŞ: Review of the literature, Project design, Patient examinations, data collection and analyzes ŞŞ: Writing and Revisions

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