Original Article

Exploring the Correlation Between Celiac Disease and Thyroid Ultrasound Findings

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ABSTRACT

Background:
Celiac disease, a prevalent autoimmune disorder, frequently coexists with various syndromes and autoimmune conditions. The leading cause of acquired hypothyroidism, wherein T cells target the thyroperoxidase enzyme, causing irreversible damage to the thyroid gland. According to the conflicting results presented in the studies, we aimed to determine the relationship between celiac disease and thyroid ultrasound findings.

Materials and Methods:
62 patients who were referred to the hospital and suffering from celiac disease were included in the study. After obtaining informed consent from the patients, a questionnaire related to demographic characteristics, including age and sex, was completed, and the patients were subjected to ultrasonography of the thyroid gland. The collected information was entered into SPSS software version 16 for data analysis.

Results:
The mean duration of celiac disease was 6.03 years. No cases of heterogeneity were found in the thyroid ultrasonography of the healthy control group, but in the group of celiac patients, 24 cases (38.7%) had heterogeneous thyroids. In the ultrasound examination, the average volume of the left and right lobes and the thickness of the thyroid isthmus in the group of celiac patients was significantly smaller than that of healthy individuals. ($P<0.05$). In the sonographic examination of the thyroid of patients with celiac disease, six patients who had a heterogeneous appearance also had Hashimoto's. The prevalence of thyroid nodularity was 35.5% in celiac patients and 5.7% in the control group ($P<0.001$).

Conclusion:
Thyroid ultrasonography in patients with celiac disease shows gland shrinkage, diffuse heterogeneity, nodularity, and typical manifestations of Hashimoto's thyroiditis compared with the normal population.

Keywords: Celiac disease, Thyroid, Ultrasound, Hashimoto's

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INTRODUCTION

The prevalence of autoimmune diseases, particularly autoimmune thyroid diseases (AITD), is increasing globally. AITD is a complex disease influenced by both genetic and environmental factors. It encompasses various conditions, including Hashimoto's hypothyroidism and Graves' hyperthyroidism (1). Hashimoto's disease involves autoantibodies targeting thyroid peroxidase (TPO) and thyroglobulin (Tg), while Graves' disease also includes TPO-Ab and Tg-Ab in 70% of patients (2).

Hypothyroidism, often caused by iodine deficiency, affects around 3% of children. On the other hand, Graves' disease is the most common cause of hyperthyroidism in children, with a prevalence of approximately 1 in 5000. Its incidence increases with age, peaking during adolescence at a rate of up to 3 in 100,000 adolescents per year (3,4).

Hashimoto's disease is a destructive autoimmune disorder characterized by T cells targeting thyroperoxidase, leading to permanent damage to the thyroid gland. In contrast, Graves' disease is a non-destructive condition caused by autoantibodies binding to the TSH receptor and stimulating it. Genetic factors contribute to about 70% of AITD cases (5).

Among the environmental factors considered in AITD, obesity deserves special attention. Children with obesity often have elevated levels of leptin, which can enhance cellular immune responses and potentially initiate autoimmune responses in AITD. Additionally, factors such as iodine levels and other environmental influences may also play a role in the development of thyroid disorders (6).

Graves' disease is the primary cause of hyperthyroidism, accounting for 95% of cases (7). It has an annual incidence of 8 per 1,000,000 in children under 4 years old. In patients with celiac disease, thyroid autoimmune disorders are also commonly observed, with thyrotoxicosis occurring in 5.0% and spontaneous hypothyroidism in 5.8% of cases (8). Malnutrition and gluten consumption are believed to contribute to hypothyroidism, and stopping gluten intake can help normalize thyroid function. Iodide malabsorption in the small intestine is a significant factor in non-autoimmune hypothyroidism in celiac disease (CD) (9-13).

CD is a chronic autoimmune disorder triggered by gluten consumption in genetically susceptible individuals (14). The only available treatment is a strict gluten-free diet. It is prevalent worldwide, more common in women, and can occur at any age, although it often starts in early childhood or around the fifth decade of life. Symptoms include gastrointestinal issues, malabsorption, weight loss, and growth delay in children. Adults may be asymptomatic but have positive serological and histological markers (15). Unusual manifestations include dermatitis herpetiformis or amelogenesis imperfecta. Diagnosis involves small bowel sampling and serological tests such as tissue transglutaminase (16).

CD frequently coexists with other conditions, such as Down syndrome, Turner syndrome, type 1 diabetes, and autoimmune thyroid diseases (17-19). The relationship between CD and autoimmune thyroid diseases is likely influenced by shared genetic factors. However, there is no conclusive evidence linking CD to autoimmune thyroid diseases due to gluten-related factors. Ultrasonography has been explored as a non-invasive method for assessing thyroid findings, but previous studies have shown conflicting results. The aim of this study was to investigate the relationship between CD, thyroid ultrasound findings, and antithyroid peroxidase.

METHODS AND MATERIALS

Study design

The present study is a case-control study with a descriptive-analytical approach. The study population consisted of patients with CD and a control group, who were referred to our medical department. All patients who participated in this study were diagnosed with CD via endoscopy and biopsy. The diagnosis of CD was confirmed before they were enrolled in the study. After diagnosis, all participants were advised to follow a diet of strict gluten-free adherence. We noted that the duration of adherence to the gluten-free diet varied among participants in cases where specific information on the duration of adherence to the gluten-free diet was not available. This limitation was confirmed in the study.

Sample Size Determination:

The sample size for this study was determined based on the study conducted by Velluzzi et al (20), considering a confidence level of 95% and a power of 80% to detect a correlation coefficient of 0.21. A total of 86 patients with CD were included in the study. Additionally, 70 individuals from the same age range were randomly selected as the control group.

Information Collection Method:

After obtaining ethical approval from the relevant authorities, 86 patients with CD referred to the hospital were included in the study. Informed consent was obtained from each patient, and a questionnaire was administered to collect demographic characteristics, including age, sex, ethnicity, etc. However, only 62 patients completed the study.

The evaluation of antithyroid peroxidase levels was conducted prior to the study, and patients underwent thyroid gland ultrasound using a 7.5 MHz linear probe. Thyroid ultrasound patterns were classified according to the Thyroid

Imaging Reporting and Data System (TIRADS) criteria. All collected information was entered into the SPSS software version 16 for data analysis.

Eligibility Criteria:

The inclusion criteria for participants were providing consent to enter the study and having CD under care.

Statistical analysis

The collected data were entered into SPSS-16 statistical software. The descriptive statistics, including mean, standard deviation, frequency, and percentage, were used to present the data. The distribution of quantitative data was analyzed using the Kolmogorov-Asimernov and Shapiro-Wilk tests to assess normality. If the data distribution met the conditions of normality, the correlation between CD and antithyroid peroxidase level, thyroid ultrasound findings, sex, ethnicity, and age was investigated using Pearson's correlation test. If the data distribution did not meet the conditions of normality, Spearman's correlation test was employed. A significance level of less than 0.05 was considered statistically significant.

RESULTS

The study involved a total of 132 participants, consisting of 62 individuals with CD and 70 healthy individuals. Among the participants, 52.3% were women, and 47.7% were men, with a mean age of 35.53 years. In terms of sex distribution, 74.2% of patients with CD were women, compared with 52.3% of healthy individuals. The mean age of patients with CD was 38.23 years, while that of healthy individuals was 33.14 years (Table 1).

Table 1. Sex distribution and mean age of the participants in this study

Variables		Group of patients		Abundance
		Celiac disease	Control	
Mean±standard deviation of patients' age		38.23±9.49	33.14±9.55	35.53±9.82
Sex	Male	16 (25.8%)	47 (67.1%)	63 (47.7%)
	Female	46 (74.2%)	23 (32.9%)	69 (52.3%)

The mean duration of CD among the patients included in the study was 6.03 years. Heterogeneous thyroids were found in 38.7% of patients with CD, while no cases of thyroid heterogeneity were observed in the healthy control group (Table 2).

Table 2. Frequency of thyroid heterogeneity in patients with CD and controls and patients with Hashimoto's disease and non-Hashimoto's disease in ultrasonography

Variables	Group of patients		Abundance
Celiac disease	38 (61.3%)	24 (38%)	<0.001
Controls	70 (100%)	0 (0%)	
Hashimoto disease	0 (0%)	6 (100%)	0.002
Non-Hashimoto disease	38 (67.9%)	18 (32.1%)	

The Kolmogorov-Smirnov test revealed that age, disease duration, left and right lobe volume, and thyroid isthmus thickness did not follow a normal distribution. Therefore, the non-parametric Mann-Whitney test was used to compare the means.

Ultrasound examination showed that the mean volume of the left lobe of the thyroid was 3.27±1.61 cubic centimeters in patients with CD, compared with 4.34±1.49 cubic centimeters in healthy individuals. This difference was statistically significant (P<0.001). Similarly, the mean volume of the right lobe of the thyroid was 4.60±2.45 cubic centimeters in patients with CD compared with 4.95±1.58 cubic centimeters in healthy individuals. This difference was also statistically significant (P<0.001). The mean thickness of the thyroid isthmus was 2.79±2.88 mm in patients with CD and 3.03±0.70 mm in healthy individuals, with a statistically significant difference (P=0.017, Table 3).

Table 3. Comparison of mean volume of left and right lobe and thyroid isthmus in thyroid ultrasound between CD patients and controls

Variables	Group of patients	Mean±standard deviation	Man-Whitney test
Left lobe volume	Celiac disease	3.27±1.61	<0.001
	Controls	4.34±1.49	
Right lobe volume	Celiac disease	4.60±2.45	<0.001
	Controls	4.95±1.58	
Isthmus thickening	Celiac disease	2.79±2.88	0.017
	Controls	3.03±0.70	

Among patients with CD, those with heterogeneous thyroids had a significantly lower mean volume of the left thyroid lobe (2.73±0.98 cubic centimeters) compared with those with homogeneous thyroids (4.12±2.02 cubic centimeters) (P=0.012). Similarly, the mean volume of the

right lobe of the thyroid was significantly lower in patients with heterogeneous thyroids (3.71±1.57 cubic centimeters) compared with those with homogeneous thyroids (6±2.93 cubic centimeters) (P=0.001). The mean thickness of the thyroid isthmus was also significantly lower in patients with heterogeneous thyroids (2.82±3.42 mm) compared with those with homogeneous thyroids (3.36±1.72 mm) (P=0.007, Table 4).

Table 4. Comparison of mean age, disease duration, left and right lobe volume, and thyroid isthmus between patients with homogeneous and heterogeneous ultrasound

Variables	Group of patients	Mean±standard deviation	Man-Whitney test
Age	Homogeneity	37.39±9.74	0.064
	Heterogeneity	39.54±9.11	
Disease duration	Homogeneity	4.92±4.08	0.099
	Heterogeneity	6.74±4.73	
Left lobe volume	Homogeneity	4.12±2.02	0.012
	Heterogeneity	2.73±0.98	
Right lobe volume	Homogeneity	6±2.93	0.001
	Heterogeneity	3.71±1.57	
Isthmus thickening	Homogeneity	3.36±1.72	0.007
	Heterogeneity	2.82±3.42	

Among patients with CD with a heterogeneous thyroid appearance, six individuals were also diagnosed with Hashimoto's disease (P=0.002, Table 2). The mean thickness of the thyroid isthmus in patients with Hashimoto's disease (4.01±0.71 mm) was significantly higher than in those without the disease (17.3±0.21 mm) (P=0.003, Table 5).

Table 5. Comparison of mean age, disease duration, left and right lobe volume, and thickness of thyroid isthmus between patients with CD and CD patients with Hashimoto disease

Variables	Hashimoto disease	Mean±standard deviation	Man-Whitney test
Age	Yes	44.4±67.5	0.159
	No	37.74±1.2	
Disease duration	Yes	4.1±5.8	0.271
	No	6±3.62	
Left lobe volume	Yes	4.1±1.74	0.276
	No	3.1±19.59	
Right lobe volume	Yes	6.3±44.46	0.115
	No	4.2±40.26	
Isthmus thickening	Yes	3±96.65	0.002
	No	2.3±92.02	

In the study population, 106 individuals had no nodules, five individuals had one nodule (all in the CD group), and 21 individuals had two nodules (17 in the CD group and four in the control group). Among the participants, Thyroid Imaging Reporting and Data System scores were determined for 25 individuals, with 17 individuals classified as grade 2, five individuals as grade 3, and three individuals as grade 4 (Table 6).

Table 6. Distribution of thyroid nodules frequency and TIRADS grade in the studied subjects

Number of nodules	0	1	2	Pearson k^2 test
Celiac disease	40 (64.5%)	5 (8.1%)	17 (27.4%)	0.001
Controls	66 (94.3%)	0 (0%)	4 (%5.7)	
All homogenous people	94 (87%)	0 (0%)	14 (13%)	0.001
All homogenous CD patients	28 (73.7%)	0 (0%)	10 (26.3%)	0.01
All heterogeneous people	12 (50%)	5 (20.8%)	7 (29.2%)	
Hashimoto disease	2 (33.3%)	4 (66.7%)	0 (0%)	
CD patients without Hashimoto's disease	38 (67.9%)	1 (1.8%)	17 (30.4%)	0.001
All subjects without Hashimoto's disease	104 (82.5%)	1 (0.8%)	21 (16.7%)	0.001
TIRADS	2	3	4	Pearson k^2 test
Celiac disease	17 (68%)	5 (20%)	3 (12%)	0.455
Controls	3 (75%)	1 (25%)	0 (0%)	0.958
All homogenous people	6 (54.5%)	3 (27.3%)	2 (18.2%)	
All homogenous CD patients	3 (42.9%)	2 (28.6%)	2 (28.6%)	
All heterogeneous people	2 (50%)	1 (25%)	1 (25%)	
Hashimoto disease	0 (0%)	0 (0%)	1 (100%)	
CD patients without Hashimoto's disease	5 (50%)	3 (30%)	2 (20%)	
All subjects without Hashimoto's disease	8 (57.1%)	4 (28.6%)	2 (14.3%)	0.117

The presence of nodules in the thyroid was significantly higher in patients with CD with a heterogeneous thyroid

appearance (50%) compared with those with a homogeneous appearance (13%) (P<0.001). Among patients with Hashimoto's disease, 66.7% had thyroid nodules, which was significantly higher than the 17.5% observed in other individuals (P=0.014). The prevalence of nodules was 35.5% in patients with CD and 5.7% in the control group, with a statistically significant difference (P<0.001).

DISCUSSION

CD is frequently associated with thyroiditis, particularly Graves' disease, and Hashimoto's thyroiditis. Increased levels of Endomysial Antibodies antibodies are observed in these thyroid conditions, indicating a significant relationship (21). Abnormal liver enzyme levels are also common in both thyroid disorders and subclinical CD. A recent study found that the prevalence of thyroid disease in CD was 13.6% compared with 3.2% in the control group (22). In terms of thyroid ultrasound findings, the healthy control group showed no heterogeneity, while 38.7% of patients with CD had heterogeneous thyroids (23). A hypoechogenic pattern has been identified as a sensitive marker for thyroid autoimmunity, with 44.4% of CD exhibiting thyroid hypoechogenicity, particularly those with positive anti-TPO (20, 24). This suggests that the presence of a hypoechogenic thyroid pattern in the absence of positive anti-TPO may serve as an early marker for autoimmune thyroid involvement before detectable serum autoantibodies develop. However, further research is required to validate this hypothesis.

In the study conducted by Sahin and colleagues (25), parenchymal heterogeneity was observed in 12.5% of the CD group compared with 2.1% in the control group. Similarly, Ansaldi and colleagues found abnormal ultrasound patterns in 16.8% of patients with CD and only 1.6% of control subjects (11). However, Diamanti and others reported similar rates of positive thyroid ultrasound findings between the CD group (41% treated with a gluten-free diet) and the control group (47%) (19).

The variation in the prevalence of thyroid heterogeneity may be attributed to differences in patient selection, control group, and racial and geographical factors across different studies. Nonetheless, it is noteworthy that patients with CD exhibit a higher prevalence of positive ultrasound findings, specifically heterogeneity, compared with the general population and control group.

Regarding ultrasound examination, the mean volume of the left and right lobes of the thyroid was significantly smaller in the CD group than in healthy individuals. The mean thickness of the thyroid isthmus was also significantly smaller in CD. Sahin and colleagues reported an average thyroid volume of 3.58 mL in the CD group and 3.95 mL in the control group (25). Hakanen and others found the mean thyroid gland volume to be 8.3 mL in CD and 10.4 ml in the control group (26). In Metso and others' study, the volume of the thyroid gland was 6.4 cm3 in CD and 6.6 cm3 in the control group (27).

The smaller mean thyroid gland volume observed in CD suggests that these patients may be more susceptible to autoimmune atrophic thyroiditis (23). In ultrasound examinations, the group of patients with heterogeneous thyroid showed significantly smaller mean volumes of the left and right lobes, as well as a smaller thickness of the thyroid isthmus, compared with the homogeneous group. Oderda and colleagues found various ultrasound findings in children with CD, including normal thyroid glands, multiple hypoechoic foci in a normoechoic gland, and an enlarged gland with diffuse but mild hypoechogenicity (28).

In children, the association between CD and AITD has been established, with prevalence rates ranging from 2% to 7.8%, three times higher than the general population (16). A study conducted on children with CD in Sardinia found a prevalence of AITD of 10.5%, four times higher than the general population (29). Other studies have reported variable percentages between 2.4% and 40.4% of patients with CD being affected by AITD. Two hypotheses have been proposed to explain this association: shared genes between CD and AITD, and the potential role of continued gluten exposure in patients with CD who do not follow a gluten-free diet (GFD) in disrupting the intestinal barrier and triggering autoimmune diseases (21,29). However, the duration of gluten exposure and adherence to a GFD do not consistently correlate with the risk or protection against AITD. Some studies suggest that strict adherence to a GFD is associated with a reduced risk of AITD and the disappearance of antithyroid antibodies, while others show conflicting results (11, 29-31). Additionally, while GFD may have a beneficial effect on other autoimmune diseases, it may not be able to halt the progression of an ongoing autoimmune process (32-34).

The association between gluten exposure and autoimmune disorders in CD may be attributed to molecular mimicry and the production of neo-epitopes. Animal models have demonstrated intermolecular T-cell epitope spreading in autoimmune diseases (35). Other researchers have confirmed the hypothesis that gluten load plays a role in developing autoimmune diseases in CD (36). For instance, untreated patients with CD showed higher rates of anti-insulin antibodies compared with treated patients with CD and the control group (37). Similarly, untreated CD adolescents had a higher prevalence of antibodies against thyroid peroxidase and other endocrine-related

autoantibodies compared to non-GFD adolescents (33).

In thyroid ultrasound examination, a subgroup of patients with a heterogeneous appearance also had Hashimoto's thyroiditis. Previous studies have reported varying rates of Hashimoto's thyroiditis among CD (34). Additionally, another study found a high prevalence of goiter based on ultrasound in CD. The mean thickness of the thyroid isthmus was significantly higher in patients with Hashimoto's disease compared with the non-diseased group (38).

Typically, thyroid ultrasound in patients with Hashimoto's thyroiditis shows gland enlargement, diffuse heterogeneity, hypoechoic appearance, micronodular appearance, and occasionally nodule formation. In this study, the majority of participants had no nodules, while a small number had one or two nodules, with a higher occurrence in the CD. The TIRADS classification was determined for a subset of participants, with most falling into grade 2, followed by grades 3 and 4 (39,40).

In a sonographic examination, 50% of the patients with heterogeneous thyroid had nodules, while in the homogeneous group, 13% had nodules, and this difference was significant based on Fisher's exact test ($P<0.001$). Patients with Hashimoto's had thyroid nodules, which percentage was 17.5% in others; this difference was statistically significant ($P=0.014$). Among the CD, 35.5% and 5.7% in the control group had nodules, which was statistically significant ($P<0.001$). In the study of Sahino and colleagues (11), the prevalence of thyroid nodules was observed in 25% of the CD group and 4.2% of the control group ($P<0.05$). In the adult celiac study by Hakanen and others (26), thyroid nodules were observed in 34% of the cases. Ventura and colleagues reported that long-term gluten load may induce autoimmune disorders in CD (41), and autoantibodies disappear during a GFD (32). In Hakanen et al.'s study, the age at diagnosis of CD roughly coincided with when patients were placed on a GFD. Patients who used such a diet for a longer period of time had hypoechogenic thyroid ultrasound findings (26). This, in part, supports the hypothesis of Ventura and others (41), especially since the age of the patients at the time of examination did not significantly affect the echo pattern. In contrast, the timing of gluten exposure does not seem to have a significant effect on the appearance of overt thyroid disease.

However, it is impossible to estimate when autoimmune thyroid disease will become apparent or when thyroid antibodies will appear. In addition, it is noteworthy that thyroid ultrasound is a more sensitive marker for the diagnosis of autoimmune thyroiditis than thyroid antibodies (42). The limitation of our retrospective study was that, in many cases, the laboratory results of thyroid functional tests of patients were not fully available, so accurate diagnosis of thyroid diseases was not possible. Therefore, checking anti-TTG enzyme to check the activity of CD and anti-TPO to check autoimmune thyroid disease will help to solve the existing ambiguities.

CONCLUSION

This study found that patients with CD had a higher prevalence of positive ultrasonography such as heterogeneity, and smaller thyroid size compared with the normal population. In contrast, patients with Hashimoto's thyroiditis exhibit distinct ultrasound features. The study emphasizes the importance of thorough examination and monitoring for early detection of concurrent autoimmune conditions in patients with CD and AITD. Additionally, it highlights the superior diagnostic sensitivity of thyroid ultrasound compared with thyroid antibodies. Overall, these findings emphasize the need for comprehensive screening and follow-up in individuals with CD and AITD.

Declaration section

Ethical approval and consent to participate: The study and all experimental protocols were approved by the Professional Ethics Committee of the Golestan University of Medical Sciences with the ethical code of IR.GOUMS.REC.1402.073. The informed consent was also obtained from all patients for the implementation of this project. All methods were carried out in accordance with relevant guidelines and regulations.

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Availability of data and materials: The data that support the findings of this study are available from the corresponding author. However, restrictions apply to the availability of these data, which were used under license for the current study and are not publicly available. Data are, however, available in the form of an Excel file from the authors upon reasonable request and with permission from Mehdi Soleimannezhad.

CONSENT FOR PUBLICATION:

Not applicable.

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The authors declare no competing interests.

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AUTHORS' CONTRIBUTION

M.S: Patients visiting and necessary data collection.
A.F: Manuscript writing and Data entry.
S.L: Radiologic analysis and interpretation.
S.B: Supervision

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