CLINICAL SCIENCE

AUTOANTIBODY FREQUENCY IN CELIAC DISEASE

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AIM: In our study, we investigated the levels of glutamic acid decarboxylase antibody (anti-GAD), islet cell antibody (ICA), thyroperoxidase antibody (anti-TPO), thyroglobulin antibody (anti-TG), antinuclear antibodies (FANA), antibodies to double-stranded DNA (anti-ds DNA), antibody to Sjögren syndrome A antigen (anti-SSA), antibody to Sjögren syndrome B antigen (anti-SSB), Smith antibody (anti-Sm), smooth muscle antibodies (ASMA), and antimitochondrial antibody liver-kidney microsome (AMA-LKM) in patients with celiac disease as compared to healthy controls and autoimmune hypothyroid patients.
MATERIALS AND METHODS: A total of 31 patients with celiac disease, 34 patients with autoimmune hypothyroidism and 29 healthy subjects were included in this study. Anti-SSA, anti-SSB, anti-Sm, anti-ds DNA, anti-GAD, anti-TPO and anti-TG were studied by Enzyme-Linked Immunosorbent Assay (ELISA), and AMA-LKM, ASMA, ANA and ICA were studied by immunofluorescence. Clinical data and the results of free thyroxine-thyroid stimulating hormone (FT4-TSH) were collected from the patients' files by retrospective analysis. SPSS ver 13.0 was used for data analysis, and the χ^2 method was used for comparisons within groups.
RESULTS: The frequency of anti-SSA, anti-SSB, anti-GAD, anti-Sm, anti-ds DNA, AMA-LKM, ASMA, ANA and ICA were not significantly different between the groups. Levels of anti-TPO and anti-TG antibodies were found to be significantly higher (<0.001) in autoimmune hypothyroid patients when compared with other groups.
CONCLUSION: In previous studies, an increased frequency of autoimmune diseases of other systems has been reported in patients with celiac disease. We found that the frequency of autoimmune antibodies specific for other autoimmune diseases was not higher in celiac disease.

KEYWORDS: Celiac disease; Autoimmune diseases; Autoimmune hypothyroid patients; Autoimmune antibodies; Antinuclear antibodies.

INTRODUCTION

Celiac disease is a disease of autoimmune origin that affects the mucosa of the small intestine. It is characterized by a malabsorption profile that arises as a result of villus damage, which is caused by activation of the cellular and humoral immune system towards gluten, which is present in wheat, barley and rye. Today, it is accepted that individuals with celiac disease have an inborn genetic predisposition that then transforms into the disease under appropriate environmental conditions.[1] At the outset, deterioration of the tight connections among the intestinal cells, which allows the antigenic structures in the lumen to pass, causes excess contact of these antigens with the mucosal immune system (such as antigen-producing cells). It is thought that, as the resulting immune response causes villus damage, it may also cause some other autoimmune diseases to arise.[2] The relationship between celiac and autoimmune diseases has been investigated in various studies. The association of celiac disease with systemic autoimmune diseases, such

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as systemic lupus erythematosus and Sjögren's syndrome, has been shown.[3] Also, it is known that, in celiac disease, there is an increased frequency of endocrinological diseases of autoimmune etiology. Among these, in patients with autoimmune thyroiditis (Hashimoto's thyroiditis, Graves' disease), type I diabetes mellitus and Addison's disease, the frequency of celiac disease is much higher than in the normal population.[4–8] It is known that the above-mentioned association is important in terms of disease treatment. For example, in type I diabetes mellitus that is accompanied by celiac disease, the celiac disease must be treated, particularly good blood glucose regulation, that is, a gluten-free diet must be followed. In individuals with Hashimoto's thyroiditis or Graves' disease, an inadequate treatment response should lead one to consider the presence of celiac disease.[2] One cause of elevated transaminase, which may be present in the same diseases, may be subclinical celiac disease.[1] An association between celiac disease and autoimmune hepatitis and primary biliary cirrhosis, which are autoimmune diseases of the hepatobiliary system, has been shown.[9,10]

The aim of our study was to research the frequency of autoantibodies in celiac disease patients who were monitored in the Gastroenterology Department, College of Medicine of Cerrahpaşa, İstanbul University. In our study, we researched the frequency of anti-GAD, anti-ICA, anti-TPO, anti-TG, FANA, anti-ds DNA, anti-SSA, anti-SSB, anti-Sm, AMA, ASMA, and LKM antibodies in celiac disease patients in comparison with healthy controls and patients with autoimmune hypothyroidism.

PATIENTS AND METHODS

A total of 31 patients with celiac disease who were diagnosed according to histopathological and/or serological criteria and 34 patients with autoimmune hypothyroidism (AHT) who were diagnosed according to serum FT4, TSH, anti-TPO and anti-TG levels[11] participated in the study. The healthy control group consisted of 29 age- and sex-matched healthy subjects. All patients and controls were aged >18 years. All patients were accepted to the study after their approval.

A volume of 10 ml of venous blood were taken from each patient in the morning, after fasting for 8 hours. The collected blood was centrifuged at 2,000 rpm for 10 minutes to obtain sera. The sera were stored at –80°C until the study was completed. Patients and controls were asked about their age, duration of disease and treatment received and their hospital records were examined. We evaluated antibody levels among the diseased control group and healthy control group by using a EUROIMMUN ELISA kits (EUROIMMUN Medizinische Labordiagnostika AG: Germany). Anti-GAD IgG, anti-ds DNA IgG, anti-SSA IgG, anti-SSB IgG, anti-Sm IgG, anti-TPO IgG, anti-TG IgG, AMA-LKM IgG, ASMA IgG, ANA IgG and ICA IgG were studied with the methods described below.

ELISA

Semi-quantitative and quantitative ELISAs were used to measure anti-GAD, anti-ds DNA, anti-SSA, anti-SSB, anti-Sm, anti-TPO, and anti-TG antibody levels in patient serum. In the semi-quantitative analysis, a ratio <1.0 was considered as negative and a ratio ≥1.0 was considered as positive. In the quantitative analysis, the threshold values specified by the kit manufacturer were accepted as positive. An anti-TPO titer ≥50 IU/ml and an anti-TG titer ≥100 IU/ml were each accepted as positive. In the quantitative analysis, the threshold value specified by the kit manufacturer was taken for the GAD values found in the serum samples (an antibody level of ≥10 IU/ml was considered as positive). The ELISA washing steps were performed manually, whereas the reading process was carried out on Tecan Sunrise Touch Screen equipment.

Immunofluorescence

Patient sera were tested for AMA-LKM IgG, ANA IgG, ICA IgG and ASMA IgG. For the ANA test, human Hep 20-10 and monkey hepatic cells were used as the substrate; for the ASMA test, rat gastric cells were used; for the ICA test, monkey pancreatic cells were used; for the AMA-LKM test, rat hepatic cells were used. The biochips were examined with a euroimmun eurostar microscope at 40× magnification. The results were evaluated as being positive or negative.

The main evaluation criterion of the study was the frequency of the autoantibodies. The statistical analyses of the data obtained at the end of the evaluation period were carried out using Statistical Package for the Social Sciences (SPSS) ver. 13.0 for Windows (SPSS, Chicago, IL, USA). Comparisons of continuous variables were made by using Student's t tests and one-way ANOVA followed by posthoc Tukey honestly significant differences (HSD) test and the results are given as mean ± SD, median, and interquartile range (IQR). For the categorical values, the χ^2 test was used.

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RESULTS

The demographic features of the patients with celiac

Table 1 - Demographic features of patients and healthy controls

Groups	Patients with celiac disease	Patients with AHT	Healthy controls	p-value
Sex (M/W)	11/20	10/24	7/22	p=0.629
Age (mean ± STD) years	38.32±12.58	39.79±10.02	36.13±10.02	p=0.525

disease, patients with AHT and healthy controls are summarized in Table 1.

The findings at patients' first outpatient clinic visits are shown in Table 2.

Table 2 - Complaints of patients with celiac disease, prior to diagnosis

Complaint	Number of patients	(%)
Anemia	24	77.4
Diarrhea	24	77.4
Abdominal pain	23	74.2
Arthralgia	19	61.3
Constipation	15	48.4
Oral aphthous ulcer	10	32.3

Median gluten-free diet duration and time elapsed after diagnosis in patients with celiac disease were determined at 18 months [25%–75% IQR; (9–48)] and 30 months [25%–75% IQR; (18–60)], respectively. Median FT4 and TSH levels were determined as 1.04 ng/dL [25%–75% IQR; (0.89–1.12)] and 8.9 mIU/mL [25%–75% IQR; (5.66–21.60)], respectively.

Frequencies of antibody positivity are shown in Table 3.

The additional diseases of patients with celiac disease are shown in Table 4.

DISCUSSION

In our study, we researched the frequency of antibodies that are specific for other autoimmune diseases in patients with celiac disease. Although the association of celiac disease with other diseases of autoimmune origin has been established, the frequency of antibodies that are specific for other autoimmune diseases in patients with celiac disease has not been investigated.

The association of autoimmune thyroid diseases (ATD) with celiac disease is well known. In genetically sensitive individuals, autoimmunity triggered by gluten may also cause the development of ATD. Although a specific influence of an HLA group has not been shown in ATD, it is known that, among the patients with celiac disease, the frequency of ATD is much greater in those with an HLA DQ2 haplotype.[12] Collin et al. determined the frequency of ATD to be 3.5% in patients with celiac disease and 2.7% in a control group; this difference was not significant.[13] On the other hand, Ansaldi et al. found that, in 343 patients with celiac disease and 230 controls, the frequency of ATD was 26.2% in the former and 10% in the latter; this difference was significant ($p<0.001$).[14] In a similar study of 79 patients with celiac disease and 184 healthy controls, which was carried out by Hakanen et al., the respective frequencies of positivity for anti-TPO antibody were 11.4 and 5.1%, respectively. [12] In the same study, the frequency of anti-TG antibody was found to be

Table 3 - Ratio of antibody positivity in groups

	CD N=31	**AHT** N=34	**HC** N=29	x^2	*P*
ANA n (%)	4 (12.9)	9 (26.5)	4 (13.8)	2.536	0.281
ICA n (%)	1 (3.2)	1 (2.9)	-	0.918	0.632
AMA-LKM	2 (6.5)	-	-	4.153	0.125
ASMA n (%)	1 (3.2)	2 (5.9)	2 (6.9)	0.434	0.805
SSA n (%)	2 (6.5)	-	-	4.153	0.125
SSB n (%)	2 (6.5)	-	-	4.153	0.125
TG n (%)	-	23 (67.7)*§	2 (6.9)	40.81	<0.001
TPO n (%)	3 (9.7)	29 (85.3)*§	2 (6.9)	55.72	<0.001
SM n (%)	-	-	-	-	-
GAD n (%)	1 (3.2)	-	-.	2.05	0.358
ds DNA n (%)	-	-	-	-	-

CD: Celiac disease; HC: Healthy controls; AHT: Autoimmune hypothyroid patients; * Comparison between patients with AHT and celiac disease $p\leq0.05$; § Comparison between patients with AHT and healthy controls $p\leq0.05$

Table 4 - Frequency of other diseases in patients with celiac disease

Additional diseases with celiac disease	Number of patients	(%)
Hepatic dysfunction*	6	19.1
Dermatitis herpetiformis	2	6.5
Allergic diseases		
(Bronchial asthma, anaphylaxis)	2	6.5
Endocrinopathy§	2	6.5
Psoriasis	1	3.2
Sarcoidosis	1	3.2
Connective tissue disease#	2	6.4

* Chronic liver disease of unknown etiology was determined in one patient. An increased transaminase level, with unknown origin was later determined in five patients.
§ One patient had hypogonadotropic hypogonadism and the other one had diabetes insipidus.
# One patient had systemic lupus erythematosus and the other had Sjögren's syndrome. The patient with systemic lupus erythematosus was positive for ANA, SSA and SSB antibodies. The patient with Sjögren's syndrome was positive for SSA and SSB antibodies.

8.8% in the patients with celiac disease and 5.1% in the healthy controls; a significant difference was not reached between the groups.[12] For patients with celiac disease and controls, the respective antibody positivity frequencies were as follows: anti-TPO, 9 (11.4%) patients with celiac disease and 9 (5.1%) controls; anti-TG, 7 (8.8%) patients with celiac disease and 9 (5.1%) controls. Importantly, the differences were not statistically significant. The study of Collin et al. was retrospective and the other two studies were case–control studies.[12-14]

In our study, no significant difference was observed between the individuals with celiac disease and healthy controls in terms of the frequency of anti-TPO and anti-TG positivity. Hakanen et al. did not observe a significant difference in terms of antibody positivity, and Collin et al. reported that clinical ATD was not increased in individuals with celiac disease. Therefore, both of these studies support our findings. [12, 13]

In a study of individuals with celiac disease and their close relatives, patients with inflammatory intestinal diseases and healthy controls, Utiyema et al. investigated the frequency of antibodies to AMA, LKM and SMA. They did not find statistically different frequencies of positivity between individuals with celiac disease and healthy controls.[15] In our study, we did not find that these antibodies were significantly increased in patients with celiac disease. In our retrospective analysis, we detected chronic liver disease of unknown etiology in one of our patients with celiac disease and transaminase elevation of undetermined etiology in five patients (6/31 patients, 19%). In another study, hepatic enzyme elevation unrelated to any known hepatic disease was reported in 114 children with celiac disease, for a rate of 32%.[16] Since transaminase elevation at a frequency of 5–10% can be seen in individuals with celiac disease, celiac disease should be investigated in cases of transaminasemia of unknown cause.

The autoimmunity triggered by gluten in genetically sensitive individuals may cause the generation of antibodies (e.g., anti-insulin and anti-B cell) against hidden autoantigens.[1] This hypothesis may explain the high frequency of type 1 diabetes mellitus in individuals with celiac disease. In the literature, the frequency of ICA in patients with celiac disease is approximately 3% on average. In terms of the frequency of this antibody, a significant difference between individuals with celiac disease and healthy controls has not been reported.[17,18] In our study, ICA and anti-GAD positivity were detected in only one patient with celiac disease (3.2%). ICA positivity was detected in one patient with AHT. In healthy controls, ICA and anti-GAD positivity were not detected, and a significant difference was not found in terms of the frequency of either autoimmune antibody among the three study groups. Aygün et al. reported that celiac disease has an increased frequency in patients with type 1 diabetes mellitus when compared with the normal population (2.45%).[19] In our study, type 1 diabetes mellitus was not detected in any of the patients with celiac disease.

In the literature, a high ratio of ANA positivity has been reported in individuals with celiac disease. In a study carried out by Utiyama et al. on 56 patients with celiac disease, their 118 first-degree relatives and 101 healthy controls, ANA was detected at a frequency of 9% in the group with celiac disease, whereas ANA positivity was not seen in any of the healthy controls (p=0.002).[15] In our study, the ANA frequency was 12% (4/31) in the patients with celiac disease and 13.8% (4/29) in the healthy controls. There was no significant difference between the two groups. The results of studies in which ANA frequency in ATD was investigated are contradictory. In some studies, the ANA frequency in individuals with ATD was significantly higher than that in healthy individuals,[20] whereas, in some other studies, the ANA frequency in patients with Hashimoto's disease was not found to be significantly different from that in healthy controls.[21] In our study, we did not detect a significant difference between the ANA frequency in individuals with AHT and healthy controls.

In our study, anti-ds DNA positivity was not seen in any of the groups. Regarding this subject, diverse results have been reported in the literature. Lerner et al. have reported anti-ds DNA positivity of 23% (8/35) in patients with celiac disease.[22] Another study reported an anti-ds DNA frequency

in patients with Hashimoto's to be significantly higher than in the control group (50%, p=0.0001).[23]

In all three groups evaluated in our study, no patients were positive for Sm antibody. As far as we are aware, there have been no previous studies of Sm antibody in patients with celiac disease.

The association of Sjögren's syndrome with celiac disease has been studied frequently. Anti-tTG and anti-SSA/SSB may be found in the circulation of patients with Sjögren's syndrome and celiac disease.[24] Hansen et al. have found that the frequency of anti-SSB antibody frequency is higher in patients with autoimmune thyroidism than in healthy patients; however, they have not found the anti-SSA frequency to be different.[25] In our study, SSA/SSB antibody was detected in 6.4% (2/31) of the patients with celiac disease and no significant difference was found between the groups. We did not detect anti-SSA or anti-SSB in any of the patients with AHT. One of the two patients who had positivity ANA, SSA,SSB antibodies had SLE and the other had Sjögren's syndrome. Patinen et al. detected dry mouth in 40% of the individuals with celiac disease and reported that patients with celiac disease can develop sialadenitis, although it is not accompanied by Sjögren's syndrome.[26] In another study, the frequency of celiac disease was investigated in 34 patients with Sjögren's syndrome and a control group of 28 individuals, and the frequency of celiac disease was found to be 14.7% in patients with Sjögren's syndrome.[24] On the contrary, the frequency of Sjögren's syndrome in individuals with celiac disease was reported as 3.3%. It was specified that this value was higher than the frequency in the group of healthy controls (p=0.0059).[13]

Our study has some limitations. We used a cross-sectional approach and evaluated only patients who attended an outpatient clinic. Patients who had been on a gluten-free diet were checked for autoantibody frequency, which was not checked before switching to a gluten-free diet. A study by Sategna et al. demonstrated that long-term exposure of patients with celiac disease to gluten did not increase the prevalence of autoimmune diseases. Moreover, gluten-free diets were shown not to prevent the development of autoimmune diseases.[27] In another study involving patients diagnosed with late celiac disease, the duration of gluten exposure in adult celiac disease did not correlate with the risk of autoimmune disease, and gluten withdrawal did not protect patients from autoimmune disease.[28] In view of these studies, we consider that it may be appropriate to check for autoantibodies under GFD.

In patients with celiac disease caused by genetic or environmental factors, the frequency of autoimmune diseases has increased. In our study, we determined that the frequency of autoantibodies that are specific for other autoimmune diseases were not elevated in patients with celiac disease. Our results may be explained by the fact that patients with celiac disease followed a gluten-free diet and that we had a small number of patients. However, we noticed an increased frequency of autoimmune disease in individuals with celiac disease when compared with those in the other two groups. Therefore, evaluation of patients with clinical and other laboratory methods is appropriate when existence of an additional autoimmune disease is suspected in patients with celiac disease, as opposed to solely evaluating autoimmune antibodies.

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