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DIAGNOSTIC ACCURACY OF IGA ANTI-TISSUE TRANSGLUTAMINASE ANTIBODY TESTING IN CELIAC DISEASE

DIJAGNOSTIČKA PRECIZNOST ODREĐIVANJA IgA ANTITELA NA TKIVNU TRANSGLUTAMINAZU U CELIJAČNOJ BOLESTI

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Summary: Contemporary guidelines for the first-line diagnosis of celiac disease recommend determination of IgA anti-tissue transglutaminase antibodies or IgA antiendomysial antibodies, as well as total serum IgA antibodies. The aim of our study was to assess the validity and clinical significance of serological testing for IgA anti-tissue transglutaminase antibodies in the diagnosis of celiac disease, and to investigate the presence of malabsorption symptoms in celiac patients. IgA anti-tissue transglutaminase antibody testing was performed in 50 subjects with clinically suspected celiac disease (21 men and 29 women). All subjects underwent endoscopy with small intestine biopsy. Celiac disease was confirmed by histopathological findings in four subjects, whereas the IgA anti-tissue transglutaminase test was positive in three subjects. The IgA anti-tissue transglutaminase test showed sensitivity of 75% and specificity of 100%. There were significant differences between men with biopsy-confirmed and excluded celiac disease in the erythrocyte parameters MCV (96.5±7.7 vs. 78.6 ±11.3; p<0.05), MCH (36.9±4.6 vs. 25.9±4.9; p<0.01), and MCHC (382.5 ±16.3 vs. 326.9±19.1; p<0.005), as well as in the levels of total protein (47.5 ±16.3 vs. 68.3 ± 7.6; p<0.01) and albumins (24.6±9.5 vs. 42.1 ± 6.9; p<0.01). In addition, HDL-cholesterol levels were significantly lower in men with biopsy-confirmed celiac disease (0.42.±0.12 vs. 0.90± 0.30; p<0.05). Our results show a high correlation between IgA anti-tissue transglutaminase testing and endoscopy with biopsy as the gold diagnostic standard.

Keywords: celiac disease, tissue transglutaminase, antibodies, IgA

Kratak sadržaj: Savremeni vodiči u prvostepenoj dijagnostici celijačne bolesti preporučuju određivanje IgA antitela na tkivnu transglutaminazu ili IgA antiendomizijumskih antitela, kao i ukupnog nivoa serumskih IgA antitela. Cilj našeg istraživanja je bio da se proceni validnost i klinička značajnost seroloških testiranja IgA antitela na tkivnu transglutaminazu u dijagnostici celijačne bolesti, kao i da se ispita prisustvo simptoma malapsorpcije kod celijačnih bolesnika. IgA antitela na tkivnu transglutaminazu su određivana kod 50 bolesnika oba pola (21 muškarac i 29 žena) kod kojih je postojala klinička sumnja na celijačnu bolest. Endoskopski im je urađena biopsija tankog creva. Celijačna bolest je potvrđena patohistološkim nalazom bioptata kod 4 pacijenta dok su IgA antitela na tkivnu transglutaminazu bila pozitivna kod 3 ispitanika. U našoj grupi senzitivnost testa je bila 75%, a specifičnost 100%. Kod muškaraca, između onih kod kojih je dokazana celijačna bolest i onih kod kojih nije, signifikantne razlike su ustanovljene za eritrocitne parametre MCV (96,5±7,7 vs. 78,6±11,3; p<0,05), MCH (36,9±4,6 vs. 25,9±4,9; p<0,01) i MCHC (382,5±16,3 vs. 326,9±19,1; p<0,005) kao i za nivoe ukupnih proteina (47,5 ±16,3 vs. 68,3 ± 7,6; p<0,01) i albumina (24,6±9,5 vs. 42,1 ± 6,9; p<0,01). Nivo HDL-holesterola je takođe bio signifikantno niži kod muškaraca sa celijakijom (0,42±0,12 vs. 0,90±0,30; p<0,05). Naši rezultati pokazuju visoku korelaciju IgA antitela na tkivnu transglutaminazu sa zlatnim standardom (endoskopskom biopsijom).

Ključne reči: celijačna bolest, tkivna transglutaminaza, antitela, IgA

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Introduction

Celiac disease, or gluten-sensitive enteropathy, is a chronic inflammatory autoimmune disease caused by ingesting foods that contain gluten, in genetically predisposed persons (1). Strong genetic susceptibility to celiac disease was suggested in a study with monozygotic twins, where celiac disease was found in both twins in 75% of cases (2). Celiac disease is inherited by a two-locus double-recessive model, with the two loci being associated with certain histocompatibility antigens (HLA-DQ/DQ8) (3). Although it was formerly regarded a rare childhood disorder, now it is estimated to affect one in 100 individuals in the USA and other parts of the world (4). However, since most patients do not present classical malabsorption symptoms, the definitive diagnosis is often made on average 9–11 years after the first nonspecific symptoms (5, 6). Women are affected three times more often than men (4, 6).

The pathogenesis of celiac disease involves complex interactions between immune, genetic and dietary factors, the latter being associated with ingestion of gluten (7). After partial degradation by gastric, pancreatic and intestinal brush-border membrane proteases, gluten polypeptides are transported across the mucosal epithelium. In the lamina propria they are deamidated by tissue transglutaminase, and the deamidated gluten polypeptides are recognized by CD4+ lamina propria lymphocytes owing to the HLA-DQ2 or HLA-DQ8 molecules on the surface of antigen-presenting cells. Activated CD4+ lymphocytes stimulate the production of CD8+ lymphocytes and generate cytokines and chemokines, particularly interferon γ, tumor necrosis factor-alpha (TNF-α), interleukin-4 (IL-4), leading to inflammation and damage to intestinal villi. The activated CD4+ cells also stimulate B-cells to produce antigliadin, endomysial and anti-tissue transglutaminase antibodies (8).

Clinical manifestations of celiac disease are diverse, and the symptoms may be classified into classical and atypical. The classical symptoms are mainly gastrointestinal symptoms, such as chronic diarrhea, abdominal distension, recurrent abdominal pain, constipation, exhaustion, fatigue, and weight loss. In an atypical form of the disease, however, gastrointestinal symptoms may be less prominent or absent, and other, extraintestinal manifestations such as anemia, coagulopathy, osteopenia or osteoporosis and arthritis may occur. In women, celiac disease may cause infertility and repeated abortions (9).

Celiac disease is often associated with other autoimmune diseases, such as dermatitis herpetiformis, insulin-dependent diabetes, autoimmune thyroid disease, Adison's disease, Sjögren's syndrome, and selective or total IgA deficiency (9).

Small intestine biopsy is the widely accepted gold standard for the diagnosis of celiac disease (8, 10). However, given the invasiveness of endoscopy, the current guidelines recommend serological testing for celiac disease screening (10). Serological markers of celiac disease known to date are antigliadin (AGA), endomysial (EMA) and anti-tissue transglutaminase (anti-TTG) antibodies (10). AGA are no longer routinely recommended due to their poor sensitivity and specificity and their use is now limited to children younger than 18 months of age (8). EMA and IgA anti-TTG antibodies that target the same endomysial antigen transglutaminase 2 have the highest sensitivity and specificity (11). Although EMA are considered the gold diagnostic standard in routine clinical practice, preference is given to IgA anti-TTG antibodies due to their high sensitivity and specificity in addition to a simpler methodology of production of binding antigens for their determination. On the other hand, since the levels of EMA correlate with the degree of mucosal damage (11, 12), these antibodies are recommended for following the effects of gluten-free dietary compliance, as a more comfortable alternative to endoscopic examination (8). Because of the common association of IgA deficiency with celiac disease, in a person with a negative IgA anti-TTG test and pronounced symptoms total serum IgA testing should be performed, and in the case of confirmed IgA deficiency additional IgG anti-TTG antibody testing is recommended (9, 10). HLA typing is reserved for unclear cases with more pronounced symptoms, given that the negative result for HLA-DQ2, HLA-DQ8, or both, virtually excludes the diagnosis of celiac disease. On the other hand, the presence of these heterodimers is not sufficient for a definitive diagnosis (9).

The aim of our study was to assess the validity and clinical significance of IgA anti-TTG antibody testing for the diagnosis of celiac disease, and to investigate the presence of malabsorption symptoms in celiac patients.

Material and Methods

The study design was retrospective. The study included a total of 50 patients treated at the Clinic for Gastroenterology and Hepatology of the Clinical Center of Vojvodina, in Novi Sad, Serbia, from March 2009 to November 2010. All study subjects underwent IgA anti-TTG antibody testing and duodenal biopsy.

IgA anti-TTG antibodies were determined using a commercially available ELISA kit (BioSystems, Barcelona, Spain) on a ChemWell Awareness analyzer.

Specificity, sensitivity and likelihood ratios for a positive and negative result of the IgA anti-TTG test employed in the study and the prevalence of celiac disease among the study subjects were calculated with the following formulas (13):

Table I Criteria used for evaluation of validity and clinical significance of diagnostic procedures in celiac disease.

IgA anti-TTG		Gold standard (small-intestine biopsy)		Total
		performed	not performed	
IgA anti-TTG test	positive	a	b	a+b
	negative	c	d	c+d
Total		a+b	b+d	a+b+c+d

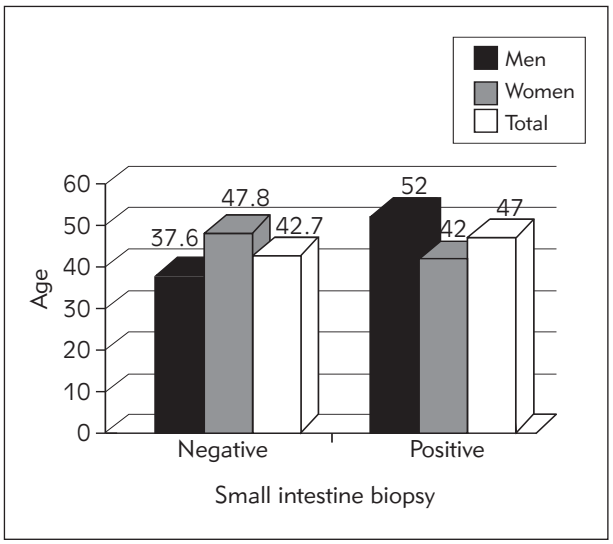

Figure 1 Age structure of study subjects in relation to small-intestine biopsy findings.

– Sensitivity (percentage of sick subjects with a positive test result): a/(a+c) * 100 (%) (see *Table I*)

– Specificity (percentage of healthy subjects with a negative test result): d/(b+d) * 100 (%) (see *Table I*)

– Positive likelihood ratio (i.e. ability to differentiate between true-positive and false-positive results) = sensitivity/(100-specificity)* 100

– Negative likelihood ratio (i.e. ability to differentiate between false-negative and true-negative results) = (100-sensitivity)/specificity *100

– Prevalence in subjects with suspected disease = (a+c)/(a+b+c+d)* 100 (%) (see *Table I*).

Hematological parameters were determined on a Beckman Coulter analyzer using the standard procedures. Biochemical parameters were determined using the standard biochemical methods on an Olympus AU400 biochemical analyzer, using reagents by the same manufacturer. Total serum cholesterol and triglyceride levels were measured using the standard biochemical methods (Technicon RA-XT analyzer and BioMerieux reagents), and HDL cholesterol was measured using a direct method with RANDOX reagents.

Statistical analyses were performed using the Microsoft Excel 2003 software for the functions of arithmetic mean, standard deviation, percentage difference, and Student t-test (14).

Results

There were 21 (42%) men and 29 (58%) women in the study sample. The age structure of the study subjects, divided into those in whom histopathological findings of small intestinal mucosal biopsy confirmed celiac disease (positive) and those in whom the findings excluded celiac disease (negative), is shown in *Figure 1*. There was no significant difference in age between men and women or between subjects with biopsy-confirmed and excluded celiac disease.

Out of the 50 IgA anti-TTG test results, three were positive, two borderline and 45 negative. Histopathological findings were positive for celiac disease in four patients (two women and two men). IgA anti-TTG test was falsely negative in one woman with pronounced hypoproteinemia and hypoalbuminemia (total protein 29 g/L, albumins 16.7 g/L, total serum IgA antibody 0.21 g/L).

We found that the IgA anti-TTG antibody test had sensitivity of 75%, specificity of 100%, a positive likelihood ratio of 75 and a negative likelihood ratio of 25, whereas the prevalence of celiac disease in our study sample was 8.2%.

Among the 50 subjects who underwent small intestine biopsy, the histopathology findings were consistent with gastroduodenitis in 15 (30%) and with colitis of various etiology in five (10%) subjects. Crohn's disease and ulcerative colitis were each found in five (10%) subjects (ulcerative colitis in four (8%) men and one (2%) woman, and Crohn's disease in four (8%) women and one (2%) man). Seven patients had hepatitis.

Hematological parameters in the subjects with biopsy-confirmed and excluded celiac disease are presented in *Table II*. Significantly elevated levels of MCV, MCH and MCHC were found in the men with biopsy-confirmed celiac disease in comparison with the men in whom celiac disease was excluded. There was no similar significant difference in the studied parameters between the women with biopsy-confirmed and excluded celiac disease.

Table II Hematological parameters in subjects with biopsy-confirmed (positive) and excluded celiac disease (negative).

Parameter	Men		Women	
	Negative	Positive	Negative	Positive
	mean ± SD	mean ± SD	mean ± SD	mean ± SD
Er ♂ (4.2–6.0 × 10^{12}) ♀ (3.9–5.4 × 10^{12})	4.51 ± 1.16	3.32 ± 0.41	3.74 ±0.9	4.03±0.14
HCT ♂ (0.40–0.50) ♀ (0.37–0.47)	0.36 ± 0.11	0.32±0.13	0.32 ±0.78	0.36 ± 0.14
Hg ♂ (130–160 g/L) ♀ (120–150 g/L)	117.6 ± 38.9	122.0 ±0	108.4 ± 29.0	127.5 ± 9.2
MCV (82–100 fL)	78.6 ± 11.3	96.5 ± 7.7*	85.3 ± 9.2	90.6 ± 6.7
MCH (27–32 pg)	25.9 ± 4.89	36.9 ± 4.60**	29.1 ± 4.56	31.7 ± 3.5
MCHC (310–350 g/L)	326.9 ± 19.1	382.5 ± 16.3***	339.5 ± 19.2	349.5 ± 12.0

Legend:
* p< 0.05; ** p< 0.01; *** p<0.005; Er– erythrocyte; HCT– hematocrit; Hg–hemoglobin; MCV– mean corpuscular volume; MCH– mean corpuscular hemoglobin; MCHC– mean corpuscular hemoglobin concentration

Table III Biochemical parameters in subjects with biopsy-confirmed (positive) and excluded celiac disease (negative).

	Men		Women	
	Negative	Positive	Negative	Positive
	mean ± SD	mean ± SD	mean ± SD	mean ± SD
Glycemia (3.9–6.1 mmol/L)	5.7 ± 2.7	3.90 ± 0.99	5.01 ± 1.15	4.95 ± 0.21
Fe (10.7–32.2 μmol/L)	10.4 ± 11.7	8.5 ± 5.4	14.9 ± 12.7	5.5 ± 0.78
Total bilir. (3–21 μmol/L)	16.1 ± 18.3	9.5 ± 3.5	21.4 ± 35.5	3.0 ± 0
D. bilir. (0.1–4.2 μmol/L)	4.8 ± 4.6	3.95 ± 1.8	9.33 ± 16.6	0.7 ± 0
AST (5–37 U/L)	24.1 ± 19.9	41.0 ± 24.0	43.9 ± 70.7	56.50 ± 21.9
ALT (5–40 U/L)	30.8 ± 68.6	64.0 ± 45.2	46.8 ± 73.8	79.0 ± 70.7
GGT (1–38 U/L)	29.2 ± 22.6	30.0 ± 5.6	73.2 ± 95.3	38.5 ± 41.7
Amylase (20–100 U/L)	60.4 ± 24.1	45.5 ± 10.6	106.6 ± 202.0	56.5 ± 29.0
Total protein (60–80 g/L)	68.3 ± 7.6	47.50 ± 16.3*	62.3 ± 11.2	44.5 ± 21.9
Albumins (35–56 g/L)	42.1 ± 6.9	24.6 ± 9.5*	37.7 ± 9.5	26.3 ± 13.6

Legend:
* p < 0.01; Fe – serum iron; D. bilir. – direct bilirubin; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase

Table IV Lipid status parameters in subjects with biopsy-confirmed (positive) and excluded celiac disease (negative).

Men	Negative		Positive	
	mean ± SD	range	mean ± SD	range
Total cholesterol (< 5.20 mmol/L)	3.9 ± 1.3	2.04–7.33	2.47 ± 1.4	1.50–3.40
Triglycerides (<1.70 mmol/L)	1.00 ± 0.60	0.30–2.12	0.56 ± 0.07	0.51–0.61
HDL–cholesterol (>1.60 mmol/L)	0.90 ± 0.30	0.51–1.95	0.42 ± 0.12*	0.33–0.50
Women				
Total cholesterol (< 5.20 mmol/L)	4.07 ± 1.14	1.91–6.29	4.55 ± 1.14	3.74–5.36
Triglycerides (<1.70 mmol/L)	0.97 ± 0.33	0.47–1.60	1.10± 0.20	0.90–1.30
HDL–cholesterol (>1.60 mmol/L)	1.04 ± 0.55	0.36–3.08	0.70 ± 0.28	0.50–0.90

Legend:
* $p < 0.05$

Biochemical parameters in the subjects with biopsy-confirmed and excluded celiac disease are presented in *Table III*. Men with biopsy-confirmed celiac disease had significantly lower total protein and albumin levels. There was no similar significant difference in the women.

Lipid status parameters are presented in *Table IV*. Significantly lower HDL cholesterol levels were found in the men with biopsy-confirmed celiac disease, whereas in the women there were no significant differences.

Discussion

Celiac disease was until recently considered a very rare autoimmune disorder. Today, however, it is recognized as one of the most frequent and, due to the unclear symptomatology and often associated gastrointestinal and extraintestinal symptoms, one of the most frequently misdiagnosed autoimmune diseases (15). Histopathological examination of the small-intestinal mucosa is the gold standard for establishing a definitive diagnosis (10). Nevertheless, given the invasiveness of endoscopy, current practice guidelines recommend serological testing as the first-line screening for patients with a suspicion of celiac disease (10, 15).

It is widely accepted that IgA anti-TTG antibody tests have the same, if not better, characteristics compared to IgA-EMA testing which is considered the serological method of choice (16, 17). This is not surprising, since the dominant antigen targeted by endomysial antibodies is tissue transglutaminase 2 and both tests actually determine the presence of antibodies against tissue transglutaminase (18).

In our sample, women made up 52% and were slightly older than men. Epidemiological data about celiac disease in Serbia are virtually non-existent. The age structure of our subjects was similar to those reported for Australian (7) and British (19) populations, but there were fewer women in our sample.

The proportion of our subjects with histopathologically confirmed celiac disease is comparable to the results of a study by Reeves et al. (7), but considerably higher than that reported by Hill et al. (19).

The high sensitivity and specificity of different commercially available IgA anti-TTG assays have already been proven (7, 12, 19, 20). The IgA anti-TTG assay (BioSystems, Spain) used in our study showed specificity of 100%, whereas its sensitivity was somewhat lower (75%), mostly owing to the falsely negative result in one subject with IgA deficiency that is frequently associated with celiac disease.

Cassella et al. (21) in their Italian study found the risk for celiac disease to be lower in individuals with inflammatory bowel disease than in the general population. None of our patients with celiac disease had concomitant inflammatory bowel disease, however, 10% of our subjects in whom celiac disease was excluded had ulcerative colitis and 10% had Crohn's disease.

We found significantly elevated MCV, MCH and MCHC levels in men, which may suggest the presence of megaloblastic changes in erythropoiesis. Unfortunately, our study protocol did not include vitamin B12 and folic acid determination, which would have clarified the nature of macrocytic hyperchromic anemia and confirmed vitamin B12 deficiency in celiac patients, as shown in a study by Dahele and Ghosh (22).

Given that celiac disease is a malabsorption disease characterized by faulty absorption of nutrients, patients with this illness can be expected to have low levels of proteins, fats and carbohydrates (23). Consistently, we found significantly lower total protein and albumin levels in our male subjects with celiac disease, which is in accordance with the results reported by Ciacci et al. (24). In contrast to those authors, however, we did not discover significantly decreased total cholesterol and triglyceride levels in celiac patients, a finding characteristic for malabsorption syndrome.

The results we present have been obtained in a retrospective study on a relatively small study sample. Anti-TTG antibodies showed high sensitivity and specificity in comparison with the gold standard. Still, further research is needed that would include the assessment of anthropometric parameters, biochemical markers of erythropoiesis, and assessment of the thyroid axis.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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