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Association between Level Anti-Tissue Transglutaminase Antibody Titers and Duodenal Histopathology among Patients with Celiac Disease

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ABSTRACT

Background: Celiac disease (CD) is a chronic autoimmune disorder triggered by gluten, diagnosed primarily through serological tests measuring anti-tissue transglutaminase antibodies (anti-tTG) alongside duodenal biopsy. We aimed to explore the relationship between anti-tTG levels and duodenal biopsy findings to improve diagnostic accuracy and management strategies for CD patients.
Methods: This retrospective study analyzed 319 small intestine biopsy results from patients suspected of having celiac disease in Qom Province, central Iran between 2016 and 2023. Serum levels of anti-tTG IgA and IgG were measured by ELISA and compared with duodenal histopathology classified by Marsh criteria. Statistical analysis included one-way ANOVA and Tukey's post hoc test.
Results: Among 226 patients diagnosed with celiac disease, the mean anti-tTG IgA levels increased significantly with Marsh grade severity (Marsh I: 81±93 U/ml; Marsh II: 134.5±97.2 U/ml; Marsh IIIa: 146±121 U/ml; Marsh IIIb: 170±120.2 U/ml; Marsh IIIc: 211.5±116 U/ml; $P<0.002$). Similarly, mean anti-tTG IgG levels rose with increasing Marsh grade (Marsh I: 20±30.3 U/ml; Marsh II: 57.3±70.5 U/ml; Marsh IIIa: 57±79.2 U/ml; Marsh IIIb: 71.3±90.7 U/ml; Marsh IIIc: 113.5±98.5 U/ml; $P<0.006$). There was a statistically significant correlation between antibody titers and histopathological severity.
Conclusion: Higher anti-tTG IgA and IgG antibody titers are significantly associated with greater duodenal tissue damage according to Marsh classification ($P<0.05$). These findings highlight the clinical utility of serological testing not only for initial screening but also for predicting the severity of intestinal involvement in celiac disease. In patients with markedly elevated anti-tTG levels, the necessity for invasive biopsy may be reconsidered, supporting a more individualized diagnostic approach based on serological and histopathological correlation.

Keywords: Celiac disease, Serology, Duodenal histopathology

Introduction

Celiac disease (CD) is a chronic autoimmune condition where the immune system reacts abnormally to gluten, resulting in inflammation and damage to the small intestine (1, 2). The diagnosis of CD typically relies on serological tests, particularly the measurement of anti-tissue transglutaminase antibodies (anti-tTG), in conjunction with histological evaluation through duodenal biopsy (3-5). Recent studies have demonstrated a strong correlation between anti-tTG antibody titers and the severity of duodenal histopathological changes. For instance, research indicates that patients with anti-tTG levels exceeding 10 times the upper limit of normal (≥84 U/mL) are significantly more likely to exhibit Marsh grade III lesions, which indicate severe villous atrophy (6). In a study involving 134 children, 86.5% of those with elevated anti-tTG levels showed histopathological changes consistent with celiac disease, reinforcing the diagnostic value of these antibody measurements (7).

Moreover, in specific populations, particularly those with markedly elevated anti-tTG levels, the need for invasive biopsy procedures may be reduced. For example, an anti-tTG titer of 150 U/L was 100% specific for diagnosing CD in adults, such serological markers could potentially replace biopsy in certain clinical scenarios (8). This shift towards non-invasive diagnostic strategies highlights the importance of understanding the relationship between anti-tTG levels and duodenal biopsy findings.

Continuing this line of research, a recent meta-analysis by Qureshi has synthesized data from multiple studies to explore the correlation between anti-tTG antibody levels and histological severity in adolescents and adults, offering a broader perspective on the diagnostic utility of serological markers (9). To date, limited data exist regarding this association in patients from Qom Province, Iran, a region with unique demographic and clinical characteristics.

Therefore, we aimed to investigate the relationship between anti-tissue transglutaminase antibody titers and duodenal biopsy results, classified by Marsh grade, in patients diagnosed with celiac disease in Qom Province. By elucidating this relationship within this specific population, we hope to enhance diagnostic accuracy and refine management strategies tailored to this region.

Materials and Methods

This study was a retrospective analysis aimed at investigating the association between levels of anti-tissue transglutaminase antibodies (IgA-tTG and IgG-tTG) and duodenal histopathology in patients diagnosed with celiac disease. The data were collected using a researcher-designed checklist, which included demographic information, histopathological findings, and serological results (IgA-tTG and IgG-tTG). Antibody levels were measured using the ELISA method and reported in U/mL. The laboratory cut-off values for considering the results positive were set at greater than or equal to 10 for both IgA-TTG and IgG-TTG. The histological features of celiac disease in the small intestine range from mild changes, characterized only by an increase in intraepithelial lymphocytes, to severe atrophic mucosa with complete loss of villi, increased apoptosis of epithelial cells, and crypt hyperplasia (10, 11). The severity of the lesion in terms of histology is classified using either the Marsh-Oberhuber or Corazza system. We used the Marsh-Oberhuber classification.

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Participants

The study included patients who underwent intestinal biopsy for suspected celiac disease at medical centers in Qom Province from 2016 to 2023. The inclusion criteria for the study were patients who exhibited symptoms suspicious of celiac disease, such as abdominal pain, diarrhea, weight loss, constipation, and bloating. Serological tests for IgA-TTG and IgG-TTG were requested by physicians for these patients, and ultimately, they underwent a duodenal biopsy to confirm the diagnosis. The data were extracted from the medical records of patients with celiac disease registered in medical centers in Qom. Patients with gastrointestinal diseases such as inflammatory bowel disease, gastrointestinal cancers, drug-induced enteropathies, and HIV, who could potentially affect the research results, were excluded from the study.

Data collection

Data collection involved members of the research team visiting medical record departments in Qom after obtaining ethical approvals and introduction letters. They developed a custom checklist to gather relevant data, which included demographic information such as age, gender, and occupation, as well as clinical data regarding the final diagnosis of celiac disease, potential biopsy results, and any other autoimmune disease diagnoses. Additionally, results for antiTTG IgA, and anti-TTG IgG were recorded when available.

Sample Size

The sample size was determined based on the number of eligible patients identified through medical records from 2016 to 2023. All patients meeting the inclusion criteria were included in the final analysis.

Statistical Analysis

Data collected through the checklist were entered into SPSS software (ver. 27) (IBM Corp., Armonk, NY, USA) for statistical analysis. The relationship between antibody titers (anti-TTG IgA and anti-TTG IgG) and histopathological findings was assessed using correlation coefficients. To compare the mean anti-TTG IgA and anti-TTG IgG levels between different Marsh classification groups, we used the one-way analysis of variance (ANOVA). When a statistically significant difference was found by ANOVA, Tukey's Honestly Significant Difference (HSD) post hoc test was performed to determine which specific groups differed from each other. Statistically significant differences among groups were considered at $P<0.05$.

Results

Overall, 319 small intestine biopsy results from patients suspected of having celiac disease were examined. Out of this number, 226 individuals received a final diagnosis of celiac disease, with 223 of them showing pathological findings consistent with celiac disease, and 3 diagnosed based on clinical findings and serological tests. Among the 226 individuals diagnosed with celiac disease, 100 were male (44.2%) and 126 were female (55.8%). The mean age of the patients was 31.8 ± 18.04. The frequency of the pathology types reported in individuals with celiac disease, based on the Marsh-Oberhuber classification, is as follows: for Marsh I, 13 (5.5%); for Marsh II, 25 (11.1%); for Marsh IIIa, 76 (33.6%); for Marsh IIIb, 77 (34.1%); and Marsh IIIc, 32 (14.2%) (Table 1).

Table 1: IgA TTG levels according to Marsh classification

Variable	*Biopsy type*	*Frequency*	*Mean (U/ml)*	*Deviation (U/ml)*	*P-value*
Level of IgA TTG	Marsh I	13	81	93	<0.002
	Marsh II	25	134.5	97.2	
	Marsh IIIa	75	146	121	
	Marsh IIIb	77	170	120.2	
	Marsh IIIc	32	211.5	116	
	Total	222	157	119.2	
Level of IgG TTG	Marsh I	13	20	30.3	<0.006
	Marsh II	24	57.3	70.5	
	Marsh IIIa	71	57	79.2	
	Marsh IIIb	75	71.3	90.7	
	Marsh IIIc	32	113.5	98.5	
	Total	218	67.5	85.7	

The table showed that whether higher serology levels are associated with more severe biopsy results. The mean and standard deviation of serum antiTTG IgA levels in patients with Marsh I biopsies is 81± 93 U/ml. The mean and standard deviation of serum antiTTG IgA levels in patients with Marsh II biopsies is 134.5 ± 97.2 U/ml. For those with Marsh IIIa biopsies, the mean and standard deviation of serum antiTTG IgA is 146 ± 121 U/ml. In patients with Marsh IIIb biopsies, the mean and standard deviation of serum antiTTG IgA is also 170 ± 120.2 U/ml. Lastly, for Marsh IIIc biopsies, the mean and standard deviation is 211.5 ± 116 U/ml. With the increasing severity of the biopsy, the mean antiTTG IgA levels gradually increase in each biopsy type. Given that $P<0.05$, there is a statistically significant correlation between these two variables (antiTTG IgA and biopsy level).

For anti-TTG IgG, the mean and standard deviation in patients with Marsh I biopsies is 20 ± 30.3 U/ml. In those with Marsh II biopsies, it is 57.3 ± 70.5 U/ml. For Marsh IIIa biopsies, the mean and standard deviation is 57 ± 79.2 U/ml. In Marsh IIIb biopsies, it is 71.3 ± 90.7 U/ml, and for Marsh IIIc biopsies, it is 113.5 ± 98.5 U/ml. The increasing biopsy severity, the mean anti-TTG IgG levels also gradually increase to some extent in each biopsy type. Given that $P<0.05$, there is a statistically significant correlation between these two variables (anti-TTG IgG and biopsy level). To further clarify the differences between groups, post hoc analysis using Tukey's HSD test revealed that mean anti-TTG IgA levels were significantly higher in patients with Marsh IIIb and Marsh IIIc compared to those with Marsh I and Marsh II ($P<0.05$ for all comparisons). Similarly, anti-TTG IgG levels were significantly elevated in Marsh IIIc compared to Marsh I and Marsh II ($P<0.05$). No statistically significant differences were observed between Marsh IIIa and Marsh IIIb, or between Marsh IIIb and Marsh IIIc, for either antibody. The most pronounced increases in antibody titers are observed in patients with more advanced histopathological damage (Marsh IIIb and IIIc).

Discussion

Celiac disease is an autoimmune condition triggered by the body's abnormal response to gluten, which is present in wheat, barley, and rye. This condition can lead to damage to the villi of the small intestine and a decrease in

nutrient absorption. The diagnosis of celiac disease (CD) depends on clinical, serological, genetic, and histopathological factors. Among these, duodenal histopathology is regarded as the gold standard. Nevertheless, it has its own set of limitations (6, 12-14). Physicians typically request serological tests in individuals with suspicious clinical manifestations to confirm the diagnosis, which routinely includes testing for anti-TTG IgA and anti-TTG IgG. Tests for antibodies specific to celiac disease (CD) are the first step in identifying individuals who require additional evaluation to diagnose or rule out the disease. A systematic review that compared endomysial antibodies (EMA) and tissue transglutaminase antibodies (TTG) concluded that the human recombinant anti-TTG IgA antibody is the preferred method for screening asymptomatic individuals and for excluding celiac disease in those with symptoms(15). Various studies have been conducted in this area, shown somewhat of a correlation between the level of anti-TTG IgA and the degree of duodenal damage according to the Marsh classification. Below, we will describe and compare these findings with the results of our study.

In a descriptive study conducted on 110 referred patients with gastrointestinal issues visiting a gastroenterology clinic, 83 of them had biopsy results in favor of celiac disease. Among these, 3.6% were classified as Marsh I, 4.8% as Marsh II, 10.8% as Marsh IIIa, 25.6% as Marsh IIIb, and 55.4% as Marsh IIIc(16). In our study, 5.5%, 11.1%, 33.6%, 34.1%, and 14.2% of all biopsy samples were classified as Marsh I, Marsh II, Marsh IIIa, Marsh IIb, and Marsh IIIc, respectively. In a meta-analysis examining 2,505 celiac disease patients across 13 studies, the relationship between anti-TTG antibody levels and their pathological status based on Marsh classification was investigated. As one moves from grade zero of the Marsh classification to higher grades, the levels of anti-TTG antibodies gradually increase. There was a significant correlation between antibody levels and their Marsh grades, with the *P*-value being less than 0.00001 across all Marsh grades (9). In another study, 159 patients with available data on tTG titers and their pathology reports were examined. The mean age of the patients was 35.6 ± 15.2 yr, and 100 of them (62.9%) were women. Among 153 patients, 133 had villous atrophy (Marsh grades IIIa-IIIc). The mean TTG antibody titer in patients with Marsh grade III was significantly higher (P=0.003). The results of the study indicated that tTG antibody titers greater than 9 times the cutoff of the kit had a sensitivity of approximately 97.2% for Marsh II and higher duodenal damage (17). In our study, the mean TTG IgA (Table 1) increases gradually from Marsh I to Marsh IIIc, indicating a significant relationship between the level of TTG IgA and the increase in pathology grade (P<0.002). Additionally, the mean levels of TTG IgG also significantly increase from Marsh I to Marsh IIIc (P<0.006). We can conclude that if serological test levels are high, one can expect that the severity of their pathology reports will also be correspondingly high. In other words, our study demonstrated that, overall, the titers of serological tests have a direct correlation with the severity of biopsy findings.

The relationship between anti-tTG titers and the severity of histological changes was studied in Jordanian children with celiac disease, analyzing medical records of 81 children with elevated anti-TTG titers (≥180 U/mL) who underwent duodenal biopsy. Overall, 94% of these children showed histological evidence of celiac disease. There was a significant positive correlation between high anti-tTG titers and Marsh grading, with 82% of Marsh III patients having high titers (Chi-squared = 18.5; P<0.001; Odds Ratio=8.5). The sensitivity for identifying Marsh III with anti-tTG titers ≥ 180 U/mL

was 81.6%, and the positive predictive value was 78.4%. Overall, an anti-tTG titer of ≥ 180 U/mL is significantly associated with Marsh III histopathological changes in children with celiac disease (7).

In another study, researchers examined the relationship between serum anti-TTG levels and intestinal damage severity in 186 children with suspected celiac disease. All participants had anti-TTG levels above 20 and underwent endoscopy and biopsies for histological evaluation using the Marsh Oberhuber criteria. The findings revealed a significant correlation between anti-TTG levels and degrees of intestinal damage (P=0.01), with greater damage observed in children with gastrointestinal symptoms, classic celiac disease, and growth disorders. The optimal cutoff for Anti-TTG was determined to be 148 IU/ml, with a sensitivity of 46.8%, specificity of 82.4%, a positive predictive value of 91.7%, and a negative predictive value of 27.2%. An Anti-TTG level of 148 IU/ml is a strong predictor for histological changes exceeding grade 1 in the Marsh classification (18).

This study has several limitations that should be acknowledged. First, the retrospective design inherently limits control over potential confounding variables and relies on the completeness and accuracy of existing medical records. Second, although the sample size of 226 diagnosed cases is relatively substantial, it may still be insufficient to generalize the findings to broader populations, especially considering potential regional or demographic differences. Third, HLA typing, which is a valuable tool in confirming celiac disease susceptibility (especially in borderline cases), was not performed. The inclusion of genetic markers like HLA-DQ2 and HLA-DQ8 would have strengthened the diagnostic accuracy and provided additional insights. Future studies with prospective designs, larger and more diverse populations, and the inclusion of genetic testing are recommended to validate and expand upon our findings. The findings of our study were indeed consistent with the results of the mentioned research. The elevated levels of anti-TTG - IgA and anti-TTG IgG antibodies indicate a higher grade of biopsy based on the Marsh classification, which our study results support.

Conclusion

Higher levels of tTG antibodies were strongly associated with the severity of tissue damage according to the Marsh classification. These findings are consistent with previous studies, which suggest that high levels of tTG antibodies can serve as a strong marker for diagnosing and predicting the severity of duodenal damage in patients with celiac disease. Moreover, high anti-TTG antibody levels may be useful in identifying patients who are more likely to have advanced duodenal damage, and in select cases, could potentially reduce the reliance on biopsy for diagnosis. However, this implication should be interpreted with caution, as our study was conducted on a specific population from Qom Province, Iran. Thus, the results may not be generalizable to other populations without further validation.

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Conflict of interest

The authors declare that there is no conflict of interests.

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