Original Article

Diagnostic Significance of Combining Anti-Gliadin IgA and Anti-Tissue Transglutaminase IgA in Suspected Celiac Disease: A Cross-Sectional Study

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ABSTRACT

Objective: To explore the correlation between anti-gliadin IgA and anti-tTG IgA in 384 subjects suspected of celiac disease.

Study Design: Cross-sectional descriptive study.

Place and Duration of Study: This study was conducted at the Laboratories of the Biology Department, College of Education, University of Al-Qadisiyah, Iraq; February to December 2025.

Methods: ELISA testing of sera using commercial kits, with results interpreted against manufacturer-defined cut-off values.

Results: Positivity for anti-gliadin IgA occurred in 13.3% of cases, whereas 15.1% were positive for anti-tTG IgA. Co-positivity for both antibodies was seen in 8.1%, whereas 5.2% and 7.0% were positive only for anti-gliadin IgA and anti-tTG IgA, respectively. Paired analysis disclosed a highly significant correlation (χ^2=91.64, $p<0.001$, φ=0.49). More females were positive for both antibodies, consistent with established sex differences in autoimmune conditions.

Conclusion: Results underscore the combined utility of anti-gliadin IgA and anti-tTG IgA, particularly in discordant cases, supporting multiple-test strategies for improved celiac detection with reduced false negatives.

Key Words: Celiac Disease; Autoimmune Diseases; Transglutaminases; Gliadin; Immunoglobulin A; Gluten Sensitivity.

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INTRODUCTION

Wheat and gluten-containing grains constitute up to half of energy intake in many developing and developed nations. With their increasing dietary inclusion, celiac disease cases have risen dramatically worldwide.1 Celiac disease is now a global concern, no longer limited to those of European descent. Its seroprevalence is 1.4%, with a biopsy prevalence of 0.7%, predominantly among females, with rates increasing over recent decades.[2]

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Celiac disease is an autoimmune enteropathy, in which the body reacts excessively to the consumption of gluten, a protein found in wheat, barley, and rye. Gluten peptides are not completely digested but are deamidated by transglutaminase. Risk factors include early life infection, breast feeding, and changes in gut bacteria.[3] This causes villous atrophy, nutrient malabsorption, and gastrointestinal and extraintestinal manifestations, including diarrhea, bloating, abdominal pain, constipation, anemia, fatigue, and osteoporosis.[4]

Though the diagnosis of celiac disease relies on small bowel biopsy, serologic screening is based on highly sensitive serologic markers, especially IgA anti-tissue transglutaminase antibodies.[5]

The discovery of tTG as an autoantigen clarified that celiac disease was an autoimmune disorder.[6] Celiac disease results from both genetic and environmental factors. The first one is associated with the HLA-DQ2 and HLA-DQ8 alleles in chromosome6, present in 30-40% of patients.[7] The environmental factors include infection with viruses as well as dysbiosis of the gut microbiota. Celiac disease may be manifested in patients of any age and can present itself in various ways, namely, gastroenterologic, extra-intestinal, latent, potential, refractory, and seronegative. Even though the diagnosis is still based on small-bowel biopsy,

serology, such as the measurement of anti-tTG, endomysial, and deamidated gliadin peptide antibodies, are increasingly used in suspected cases.[6]

Recent data have revealed that high titers of IgA antibodies against tissue transglutaminase more than tenfold higher than the upper limit of normal could diagnose celiac disease effectively without a biopsy.[8]

This research was conducted with the purpose of analyzing the diagnostic efficacy of anti-gliadin and anti-tTG IgA antibodies and their relationship in celiac disease suspects.

METHODS

This cross-sectional descriptive study included 384 serum samples from males and females aged 18-55 years suspected of having celiac disease, attending a medical facility in Iraq.

Ethical Considerations: This study was approved by the institution's ethical review board (Approval no. 12284; date: 11-02-2025) and was carried out in accordance with the Declaration of Helsinki (2013). The samples were collected and analyzed in an academic setting under the guidance of qualified academics.

Patient Consent Statement: No direct patient consent was required, as all data were anonymized and collected as part of routine clinical care.

Inclusion criteria: Patients suspected to have celiac disease referred for serological testing based on clinical symptoms (such as weight loss, stunted growth, abdominal pain, lack of appetite, anemia, poor development, or diarrhea).

Exclusion Criteria: Participants previously placed on a gluten free diet, incomplete documentation, and samples unsuitable for testing (hemolyzed or inadequate volume).

Specimen Collection & Handling: 5 mL of venous blood sample was obtained from each participant, after which serum was extracted and stored at -20 degrees Celsius for future analyses.

Serology Assay: Thawed sera were allowed to reach room temperature and were further diluted according to the manufacturers' protocol. Gliadin IgA and tTG IgA antibodies were quantified by sandwich enzyme-linked immunosorbent assay (ELISA) test kit from EASKU (Germany) with cut off values (positive >18 U/mL, equivocal 12-18 U/mL, negative <12 U/mL).

Statistical Analysis: All 384 consecutive eligible patients were included. Statistical analyses were performed using SPSS version 26.0, employing descriptive statistics, chi-square (χ^2) test, and Phi correlation coefficient, with significance set at $p<0.05$.

RESULTS

Out of 384 patients, 13.3% had positive anti-gliadin IgA, while 15.1% had positive anti-tTG IgA. The number of patients who showed both antigens was 8.1%. The complete results are given in Table 1.

Table No. 1: Cross-tabulation between anti-gliadin IgA and anti-tTG IgA among suspected celiac disease cases

	anti-tTG IgA (+)	**anti-tTG IgA (−)**	**Total**
anti-gliadin IgA (+)	31 (8.1%)	20 (5.2%)	51 (13.3%)
anti-gliadin IgA (−)	27 (7.0%)	306 (79.7%)	333 (86.7%)
Total	58 (15.1%)	326 (84.9%)	384 (100%)

A Chi-square test revealed a statistically significant association between anti-gliadin IgA and anti-tTG IgA ($\chi^2 = 91.64$, df = 1, $p < 0.001$). The Phi coefficient ($\varphi = 0.49$) indicated a moderately strong positive correlation between the two antibodies, suggesting that individuals positive for one marker are more likely to be positive for the other.

Gender-Based Distribution: To further explore potential biological differences, gender-based analysis was conducted. Gender-based distribution is detailed in Table 2

Table No. 2: Gender-based distribution of anti-gliadin IgA and anti-tTG IgA results

Category	**Males**	**Females**	**Total**
Both anti-gliadin IgA and anti-tTG IgA (+)	9 (6.7%)	22 (8.8%)	31 (8.1%)
anti-gliadin IgA (+) only	7 (5.2%)	13 (5.2%)	20 (5.2%)
anti-tTG IgA (+) only	5 (3.7%)	22 (8.8%)	27 (7.0%)
Both anti-gliadin IgA and anti-tTG IgA (−)	113 (84.3%)	193 (77.2%)	306 (79.7%)
Total cases	134	250	384
% anti-gliadin IgA (+)	11.9%	14.0%	—
% anti-tTG IgA (+)	10.4%	17.6%	—

Females showed slightly higher positivity rates for both antibodies compared to males, with anti-tTG IgA positivity of 17.6% versus 10.4% respectively.

DISCUSSION

In this research, examining 384 samples produced a moderate correlation between anti-gliadin IgA and anti-tTG IgA ($\varphi=0.49$), which means that if a sample was positive for one, it would also test positive for other, but not necessarily to the same extent. This result has been

proved in other studies as well, in which anti-tTG and anti-endomysium antibodies were described as having a greatest potential as a serological marker for celiac disease, whereas anti-gliadin antibodies have a lower efficiency, though being a sort of early immune alert.[9]

In addition, as shown in previous literature, a combination of TTG testing with gliadin-associated antibodies has been proven to increase sensitivity in the diagnostic tests and make it easier to identify patients who would otherwise test negative for TTG, [10] adding value to our findings as shown in our study where some patients would test positive for anti-gliadin IgA alone, whereas others would test positive for anti-tTG IgA alone.

In addition, it has been shown that dual testing reaches a point of increasing sensitivity without sacrificing a comprehensive evaluation of cases, whereas anti-gliadin antibodies gave rise to occasional false positives that needed confirmation by biopsy of the intestines.[11] Therefore, it becomes important that our results underscore, in a complementary perspective, the role of both antibodies in identifying celiac disease.

Interpretation and Implications: All of these findings reinforce the complementary role of both antibodies in celiac screening. Furthermore, their co-positivity rate of 8.1% indicates that their combined use enhances diagnostic certainty, while their discordant rates of 5.2% for anti-gliadin-only and 7.0% for anti-tTG-only status reveal how differences in disease course, immune mechanism, and antigens exist.

Although anti-tTG IgA has been known for many years for its high sensitivity as well as specificity, anti-gliadin IgA can also be seen as a preliminary immunological marker, particularly in cases with partial villous infiltration and/or with a lack of classical symptoms. These findings also confirm the utility of a two-marker strategy in order to increase the rate of early detection with a low rate of false negatives.

The correlation factor $\varphi = 0.49$ and $p < 0.001$ between anti-gliadin IgA and anti-tTG IgA further strengthens their usage together for celiac screening. When analyzed on the basis of gender, it was found that females showed a higher overall positivity rate, which aligns with known autoimmune patterns. Simultaneous analysis of both provides a broader immunological screening, which further aids in improving the diagnostic acuity and early identification of CD.

A subgroup tested positive for anti-gliadin IgA but negative for anti-tTG IgA. Consistent with Hessinger and Vohra (2021), in which it was found that patients with a positive result for anti-gliadin but negative for anti-tTG were extremely unlikely to be diagnosed with celiac disease when histopathological analysis was done. These cases were commonly linked to other conditions of the gastrointestinal tract, including eosinophilic esophagitis. This indicated that in most cases of isolated anti-gliadin positivity, it can be a false positive result rather than a true manifestation of celiac autoimmune conditions.[12]

Anti-gliadin IgA and anti-tTG IgA positivity was higher in females, consistent with Ludvigsson's large-scale study showing greater celiac prevalence in females.[13] Rossi (2025) reported more extraintestinal manifestations and duodenal lesions in females despite similar dietary compliance between sexes.[14] A Mediterranean cohort similarly showed females presenting more frequently with severe symptoms including anemia, dyspepsia, and genital disorders, while weight loss and low BMI were more common in males.[15] Collectively, these findings support sex-related differences in celiac prevalence and presentation, explaining the higher female seropositivity in our cohort.

The tendency for higher seropositivity in females in our series also corresponds with findings of a genetic predisposition for females as reported in a study by Megiorni et al. in 2009, where celiac disease incidence was found to be almost twice as common in females as in males (F:M = 1.8) This study showed that a high-risk genotype of HLA-DQ2/DQ8 was present in 94% of females compared with 85% in males, which suggests that there may be a higher genetic susceptibility in females for developing this disease. In this study, it also became evident that there was a paternal transmission bias, as 61% of female patients received their HLA-DQ2 from their fathers, which suggests that genetic epigenetics differ between males and females in developing this condition. Thus, it appears that there are different patterns between males and females in developing this condition. Notably, in this study, it was also reported that in DQ2/DQ8-negative celiac cases, most were males with a proportion of F:M=0.7, suggesting that alternate immune mechanisms or non-HLA pathways may be responsible for illness development in some individuals.[16]

This parallels our discordant and dual-negative patterns, possibly reflecting atypical immune reactivity or non-classical HLA pathogenesis. Ciacci (2009) further noted that disease progression may differ by sex due to higher metabolic demands in women from menstruation, pregnancy, and breastfeeding.[15]

The U.S. Preventive Services Task Force systematic review reported sensitivity and specificity above 90% for IgA anti-tTG, with IgA endomysial antibodies also being highly specific. However, sensitivity drops to 57-71% in asymptomatic cases, highlighting the risk of missed diagnoses with single-test screening.[17]

Serological tests continue to play a prominent role in making a clinical diagnosis of celiac disease. According to Volta et al. (2023), anti-tTG IgA has a high sensitivity of 93.4%, with a higher value for endomysial antibodies of 99% for specificity.[18] A biopsy in pediatric patients is unnecessary when, in accordance with the 2020 ESPGHAN management instructions,

there is a concentration of TGA-IgA above ten times over normal values and, in a confirmatory blood test, reactivity with IgA anti-endomysial antibodies (EMA-IgA) is guaranteed. On these bases, with consent from parents, a biopsy can be safely avoided.[19] Although the current investigation focused on anti-tTG IgA and anti-gliadin IgA, other studies, such as that by Anbardar et al. (2022), have shown that adding more sensitive serologic markers, for instance, Immunoglobulin G anti–deamidated gliadin peptide antibodies (IgG anti-DGP), increases diagnostic sensitivity in specific clinical scenarios. This reflects the ever-improving clinical utility of serology and the importance of choosing appropriately adequate antibody panels for accurate, early diagnosis of celiac disease.[20]

This study from a single center involving 384 subjects suspected to have celiac disease using anti-gliadin IgA and anti-tTG IgA offers an interesting contribution to the understanding of antibodies among subjects suspected to be having the condition, albeit without a biopsy diagnosis. though future multi-center studies are warranted for further validation.

CONCLUSION

The current study determined the diagnostic accuracy and association of anti-gliadin IgA and anti-tTG IgA in 384 patients with suspected celiac disease. The former test exhibited greater positivity and moderate to strong correlation with anti-gliadin IgA test, implying that it can be used effectively for screening purposes. Concurrent positivity increased confidence in diagnosis whereas discrepancies were attributed either to early cases or individual immunological reactions. The predominance of females is consistent with previous observations regarding autoimmune diseases.

Author's Contribution:

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Agreement to accountable for all aspects of work:	All the above authors

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