# Serological Tests Assessment in Patients Suspected to have Celiac Disease Attending the Gastroenterology and Hepatology Teaching Hospital in Baghdad

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## Abstract

**Background:** Celiac disease is characterized by small intestinal malabsorption of nutrients after the ingestion of wheat gluten or related proteins from rye and barley, villus atrophy of the small intestinal mucosa, prompt clinical and histologic improvement following strict adherence to a gluten-free diet, and relapse when gluten is retaken.

**Aim of the Study:** Evaluation of patients seeking gastroenterology and hepatology teaching hospital/medical city/Baghdad with suspected celiac disease regarding serological investigation, histological findings and genetic testing, to determine sensitivity, specificity, positive predictive value and negative predictive value for every test.

**Patients and Method:** The study is a cross sectional descriptive analytic study conducted at the teaching hospital of gastroenterology and hepatology/Baghdad/Iraq during a period from the 1st of February 2018 to the 1st of April 2019. After thorough history and Clinical examination patients with suspected celiac disease were sent for serological investigation (TTG IgA and IgG), (antigliadin IgA and IgG), all patients were sent for endoscopic examination for duodenal biopsies with subsequent histological assessment. Patients who failed to be confirmed (positive serology and negative histology or vice versa) were sent either for HLA genotyping or for IgG Deaminated gliadin peptide. Sensitivity & specificity were measured for each test.

**Results:** A total of 140 suspected celiac disease patients involved in this study. Mean age was 18.9 years and ranged from 2 years to 60 years. Male represented 36.4% of the cases while female represented 63.6%. Only 19 patients show positive family history of celiac disease (13.6 %). Regarding associated autoimmune diseases, the majority (111 patients) have no associated diseases (79.3%) while the other patients who have associations most of them show positive association with type 1 DM (16.4%).

Fifty patients (35.7%) presented with short stature, (25.7%) came with diarrhea. The other symptoms vary between bloating and distention, unexplained anemia and weight loss. Constipation was seen in one patient. tTG IgA and tTG IgG showed high sensitivity, specificity, positive predictive value and negative predictive value while antigliadin antibody failed to show these significant results.

**Conclusion:** The use of serologic markers in celiac is easy, direct, noninvasive and reliable and could be benefit in the diagnosis and monitoring of the disease. More specifically, both the tTG-IgA/IgG are very good markers in the diagnostis of CD. This study confirmed the high specificity and sensitivity of tTG, and

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the low results of AGA, but celiac serology does not replace the biopsy in the diagnosis but is useful as an assistant for diagnosis.

***Keywords:*** *Celiac Serological Tests, Transglutaminase Antibody, Antigliadin Antibody, Deamidated Gliadin Antibody, Antiendomysial Antibody, HLA DQ2/DQ8, Marsh Classification, Duodenal Biopsy, Villous Atrophy, Chronic Diarrhea, Malabsorption, Gluten*

## Introduction

**Definition:** Celiac disease is characterized by small intestinal defect of absorption of nutrients after the taking of gluten or proteins from rye and barley, small bowel mucosal villus atrophy, prompt clinical and improvement in histology after adherence to a gluten-free diet, and relapse when gluten is retaken again.[1,2,3].

**Classification:**[4,5, 6]

**Classic disease** —

**Atypical celiac disease** —

**Silent celiac disease** —

**Latent celiac disease** —

**Who should be tested**?

Testing for celiac disease should be considered in the following patients[2,7]:

- Gastrointestinal symptoms
- Extra intestinal signs and symptoms such as iron deficiency anemia, folate or vitamin B12 deficiency, persistent elevation in serum aminotransferases, short stature, delayed puberty,
- Patients with type 1 diabetes mellitus
- Asymptomatic first-degree relatives.

**Serum Antibody Assays:**

A variety of serologic studies have been described to aid in the diagnosis of celiac disease, including:[8,9,10]

- EMA IgA
- tTG IgA
- tTG IgG
- DGP IgA
- DGP IgG

**Anti-tissue transglutaminase antibodies:** The antigen against which antiendomysial antibodies are directed is tissue transglutaminase-2 (tTG)[11]. Anti-tTG antibodies were highly sensitive and specific for the diagnosis of celiac disease in most reports[12,13,14 ].

The accuracy of IgA anti-tTG has been improved more by the use of human in place of the non-human tTG used in earlier kits [15].

**Antigliadin Antibody Assays:** Antigliadin antibody (AGA) tests are not recommended due to their low positive predictive value in a general population [16,17]. The second generation AGA test (deamidated gliadin peptide [DGP]) uses synthetic gliadin peptides that mimic tTG-modified gliadin sequences to capture serum IgA or IgG against DGP [9, 10]. Anti-DGP assays are preferred over anti-AGA due to their higher specificity.

Patients on a gluten-free diet with negative serologies should undergo HLA DQ2/DQ8 testing to determine if the patient is genetically susceptible to celiac disease. If HLA DQ2/DQ8 testing is negative, celiac disease is excluded [17].

**Small Bowel Biopsy:** Patients with a positive serology, and patients with a high probability of celiac disease (>5 percent), regardless of the serology, should undergo an upper endoscopy with small bowel biopsy to confirm the diagnosis of celiac disease.[18] The mucosa of duodenal wallmay appear atrophied with loss of folds, have a nodular appearance or the folds may be scalloped, but such findings are not always present and may be seen with other causes[19][20]. The histologic features range from a mild alteration characterized only by increased intraepithelial lymphocytes (IEL), to a flat mucosa with complete loss of villi, enhanced epithelial apoptosis, and crypt hyperplasia [4,6,21]. The histologic findings in celiac disease can be described using the Marsh-Oberhuber[22]. Quantitative histology (villous height, crypt depth, density of IELs per 100 enterocytes) provides the most sensitive and accurate method to monitor disease activity over time[23,24].

**Suggestive clinical features but negative serologic tests:**

There are four main possibilities in those with suggestive clinical features but negative serologic tests:[25,26,27,28 ]

- IgA deficiency. In such patients, testing for IgG deamidated gliadin peptide antibodies should be performed. Other, less accurate, IgG-based tests include IgG anti-tissue transglutaminase antibodies
- Low gluten diet.
- Falsely negative. IgA or IgG deamidated gliadin peptide antibody testing may be useful.
- Irritable bowel syndrome, nonceliac gluten sensitivity

## Materials and Method

**Participants and study design:** This study was a cross sectional descriptive analytic study conducted at the teaching hospital of gastroenterology and hepatology/ Baghdad/Iraq during a period from 1st of February 2018 to the 1st of April 2019.

**Subjects and sampling method:** After thorough history and clinical examination of the patients referred to the hospital due to variable clinical symptoms and signs compatible with coeliac disease, subjects were recruited according to convenient sampling method and a convenient sample of 140 patients was studied which were sent for serological investigation (TTG IgA and IgG), (AGA IgA and IgG), all patients were send for endoscopic examination for duodenal biopsies with histological assessment. Patients who failed to be confirmed were sent either for the new test IgG DGP or for HLA genotyping.

**Inclusion Criteria:**

1. Chronic diarrhea or loose stools.
2. Abdominal pain, abdominal distention and flatulence not responding to medication.
3. Malabsorption and steatorrhea.
4. Unexplained Wt. loss.
5. Failure to thrive.
6. Unexplained anemia.
7. At-risk family members

**Exclusion Criteria:**

1. Crohn´s disease
2. Chronic liver disease
3. H.pylori gastritis,Peptic ulcer duedenitis
4. Giardiasis
5. Malnourished patients due to chronic debilitating disease

**Blood Sample:** The sample was then analysed for TTG, antigliadin, Some of the patients who showed discrepancy of their results were sent for IgG Deaminated Gliadin peptide in the Central Health Laboratory in Baghdad or for HLA test in the teaching hospital of Alkarama in Baghdad.

**Serological Tests:** Serum tTG and AGA performed by ELISA based to the manufacturers.

**Genotyping:** Coeliac disease-associated HLA genotyping was performed in Alkarama hospital in Baghdad by specialized lab.

**Upper gastrointestinal endoscopy:** Upper gastrointestinal endoscopies with duodenal biopsies were offered regardless of serology results by specialized gastroenterologist.

**Histology:** Biopsies were interpreted in the pathology department in the gastroenterology and hepatology teaching hospital by specialized pathologist to read the small intestinal histological features, according to the modified Marsh criteria:

The reference standard for celiac disease diagnosis was considered Marsh grade ≥2.[29]

**Ethical Aspects:** The Institution's Ethical Committee approval was obtained prior to the enrolment of subjects.

**Statistical Analysis:** Data were analyzed by the statistical package of social sciences version 25. Statistics of the variables was expressed as medians, ranges, frequencies and percentage, as appropriate and calculated by chi-squared test. Odds ratio (OR) and the 95% confidence interval of OR were calculated, Level of significance of $\leq 0.05$, considered as significant difference or association.

## Results

**tTG IgA Serology:** From the patients who were found to be marsh 0 or 1, only 2 patients tested positive for TTG IgA those was sent for IgG DGP or HLA and the results was negatives and so they are regarded as (false positives) while 48 patients tested negative (true negatives). From the patients who were found to be marsh 2 or 3, 84 patients tested positive for TTG IgA (true positives) while only 6 patients tested negative those was sent for IgG DGP or HLA and the results were positives and so they are regarded as (false negatives). From these results we concluded that sensitivity, specificity, PPV and NPV of **TTGIgA** were 93.3%, 96%, 97.6% and 88.8% respectively (Table 1).

**Table 1: Sensitivity, specificity, PPV and NPV of TTG IgA**

| | | Histology | | | |
|---|---|---|---|---|---|
| | | **Marsh 2, 3a,3b and 3c** | **Marsh 0,1** | | |
| TTG IgA | Positive | 84 | 2 | Sensitivity | 93.3 % |
| | | | | Specificity | 96 % |
| | Negative | 6 | 48 | Positive predictive value | 97.6 % |
| | | | | Negative predictive value | 88.8 % |

**tTG IgG Serology:** From patients with marsh 0 or 1 only 4 patients tested positive for TTG IgG so some of those was sent for IgG DGP and another for HLA and the results was negative and so they are regarded as (false positives) while 46 patients tested negative (true negatives).

From the patients who were found to be marsh 2 or 3, 85 patients tested positive for TTG IgG (true positives) while only 5 patients tested negative and those was sent for IgG DGP or HLA and the results were positive and so they are regarded as (false negatives). From these results we concluded that sensitivity, specificity, PPV and NPV of **TTG IgG** were 94.4%, 92%, 95.5% and 90.1% respectively (Table 2).

**Table 2 Sensitivity, specificity, PPV and NPV of TTG IgG**

| | | Histology | | | |
|---|---|---|---|---|---|
| | | **Marsh 2, 3a,3b and 3c** | **Marsh 0,1** | | |
| TTG IgG | Positive | 85 | 4 | Sensitivity | 94.4 % |
| | | | | Specificity | 92 % |
| | Negative | 5 | 46 | Positive predictive value | 95.5 % |
| | | | | Negative predictive value | 90.1 % |

**Antigliadin IgA Serology:** From the patients who were found to be marsh 0 or 1, 13 patients tested positive for antigliadin IgA those was sent for IgG DGP or HLA and the results was negative and so they are regarded as (false positives) while 37 patients tested negative (true negatives). From the patients who were found to be marsh 2 or 3, 33 patients tested positive for antigliadin IgA (true positives) while 57 patients tested negative those was sent for IgG DGP or HLA and the results were positive and so they are regarded as (false negatives). From these results we concluded that sensitivity, specificity, PPV and NPV of **antigliadin IgA** were 36.6%, 74%, 71.7% and 39.3% respectively (Table 3).

**Table 3: Sensitivity, specificity, PPV and NPV of antigliadin IgA**

| | | Histology | | | |
|---|---|---|---|---|---|
| | | **Marsh 2, 3a,3b and 3c** | **Marsh 0,1** | | |
| Antigliadin IgA | Positive | 33 | 13 | Sensitivity | 36.6 % |
| | | | | Specificity | 74 % |
| | Negative | 57 | 37 | Positive predictive value | 71.7 % |
| | | | | Negative predictive value | 39.3 % |

**Antigliadin IgG Serology:** From the patients who were found to be marsh 0 or 1, 7 patients tested positive for antigliadin IgG those was sent for IgG DGP or HLA and the results was negative and so they are regarded as (false positives) while 43 patients tested negative (true negatives). From the patients who were found to be marsh 2 or 3, 22 patients tested positive for antigliadin IgG (true positives) while 68 patients tested negative those was sent for IgG DGP or HLA and the results were positive and so they are regarded as (false negatives). From these results we concluded that sensitivity, specificity, PPV and NPV of **antigliadin IgG** were 24.4%, 86%, 75.8% and 38.7% respectively (Table 4).

**Table 4 Sensitivity, specificity, PPV and NPV of antigliadin IgG**

| | | Histology | | | |
|---|---|---|---|---|---|
| | | **Marsh 2, 3a,3b and 3c** | **Marsh 0,1** | | |
| Antigliadin IgG | Positive | 22 | 7 | Sensitivity | 24.4 % |
| | | | | Specificity | 86 % |
| | Negative | 68 | 43 | Positive predictive value | 75.8 % |
| | | | | Negative predictive value | 38.7 % |

## Discussion

Celiac disease is a common disorder, which affects 1% of individuals [30]. There aremany disorders, with environmental and genetic effects contributing to the etiology of celiac disease [31]. HLA locus is the main influence affect celiac disease [32].

In the present study age distribution of cases showed that celiac disease is more in children than in adults. as shown in table 2 which show that from 90 patients who are proved to be celiac disease the frequency of children is 64 patients versus only 26 adults so that, the results of this study are similar to results that obtained by other researchers, especially with results of AL-Kenzawi, when he showed that children account a large number of celiac patients in Iraq countary[33].

Also these results come in agreement with the results of Al-Saadi and Abid, when they studied patients with celiac disease in Karbala and showed that 64% of patients were children [34] and the results of another study which took 509 patients referred to the immunology department in Baghdad teaching labs and showed that large number of CD cases were children [35].

In general CD in children is more than other ages, might be attributed to introduction of large amount of gluten or exposure to the gluten without breastfeeding might increase the risk of CD in children [36], or might be due to other factors such as infections [37].

In the present study Gender distribution of cases showed that the majority of cases that are proved to be celiac disease were females (72.2 %) and the remaining (27.7 %) were males as shown in table 2 so that, this agrees with Green, when he reported that CD was 2 to 3 times higher in females [30]. Also, agrees with results of Fasano A [38] and Giorgio F [39] showed that the prevalence of celiac disease is 1.5 to 2 times higher in females.

In general, some genetic loci are related to sex, also sex-dependent HLA associations are seen because

female patients are carry DQ2 and/or DQ8 molecules while DQ2/DQ8 negative celiac mostly are males [40], or role of sex hormones in immune regulation which may explain sex varieties [41].

In the present study significant numbers of CD patients have positive family history and this agrees with the results of Vitoria JC showed that the risk of having CD is higher in siblings than in parents of patients with CD[42] and agree with the research done India showed that CD prevalence among first-degree relatives was 8.2% (14/169). CD prevalence between siblings is (15.6%) [43].

CD Prevalence in the first degree relatives vary between 2.8% to 8.2% [42]. The variability can be clarified by study the methodology and the differences of the genetics of the studied population. It is mentioned that this prevalence increases in families with two or more cases of CD [44].

The present study shows significant association between type 1 DM and celiac disease and this comes in agreement with the results of other research that done in British Columbia who confirmed the prevalence of CD in diabetes type one [45] and come in agreement with other research done in Iraq showed that the proportions of patients with CD and type one diabetes who were positive for antigliadin IgA and IgG, tTG IgA IgG were 20%, 23.53%, 20% and 24.71%, respectively, which were higher than those of control subjects significantly[46]

## Conclusion

- Celiac serology does not replace small bowel biopsy in the diagnosis of celiac disease but is useful as an adjunct to biopsy.
- Serological tests are easy, noninvasive and are benefit both for diagnosis and monitoring.
- The study showed the high sensitivity & specificity of tTG, and the low results of the AGA.

**Ethical Clearance:** Taken from The Institution's Ethical Committee approval

**Source of Funding:** Self

**Conflict of Interest:** nil

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