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ORIGINAL ARTICLE

Evaluation of mucosal status in the follow-up of pediatric patients with celiac disease: the role of serology

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Abstract

Recent guidelines suggest non-biopsy serology–based approach for the diagnosis of celiac disease; however, there is no evidence-based data regarding noninvasive follow-up of mucosal healing. The aim of this study is to investigate the efficacy of serology in reflecting mucosal status in the follow-up of pediatric patients with celiac disease. This is a validation study conducted at a university hospital. Patients who had biopsy proven celiac disease (Marsh III) at diagnosis, and had been followed-up for at least 12 months, were prospectively evaluated with duodenal biopsies. tTG-IgA and EMA tests were performed on the day of endoscopy. One hundred four patients with a mean age of 7.4 ± 4.02 years were included in the study. The sensitivity and specificity of tTG-IgA were 85.2% and 61% respectively, with a high negative predictive value (NPV) of 92.2% but a very low positive predictive value (PPV) of 43.4%. We found that a cutoff value of 68.5 U/mL for tTG-IgA had a sensitivity, specificity of 85.2% and 85.7% respectively. The AUC was 0.891. The sensitivity and specificity of EMA was 77.8% and 87% respectively, with a high NPV of 91.8% but low PPV of 67.7%.

Conclusion: This study suggests that negative tTG-IgA and/or EMA can be used as an indicator of mucosal improvement in the follow-up of pediatric patients with celiac disease. However, positive serology (i.e., $< 10 \times$ ULN) may be misleading in reflecting mucosal status in the follow-up of pediatric patients with celiac disease.

What is Known:

- *The tissue transglutaminase IgA (tTG-IgA) and endomysium IgA (EMA) tests are widely used, sensitive and reliable diagnostic tests, but their role in monitoring adherence to dietary treatment in celiac patients has not yet been demonstrated.*
- *There is still no reliable and non-invasive marker of persistent villous atrophy or mucosal recovery.*

What is New:

- *Negative celiac serology detected in the follow-up of pediatric patients with celiac disease was successful in demonstrating histopathological mucosal healing.*
- *Positive celiac serology, which is highly reliable in the diagnosis of celiac disease, has not been successful in reflecting mucosal status when used in the follow-up of pediatric patients with celiac disease.*

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Keywords Celiac disease · Endomysium IgA · Pediatric · Serology · Tissue transglutaminase IgA

Abbreviations

AUC	Area under curve
CD	Celiac disease
EMA	Endomysium IgA
ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology, and Nutrition
GFD	Gluten-free diet
HT	High titer
LT	Low titer
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operating curve
tTG-IgA	Tissue transglutaminase IgA

Introduction

Celiac disease (CD) is a multi-systemic autoimmune disease triggered by exposure to dietary gluten in genetically predisposed individuals [1]. The prevalence of CD is around 1% in the general population [2–4]. The definitive diagnostic test for CD is still based on examination of endoscopic biopsies of the proximal small bowel [5]. The development of highly sensitive and specific diagnostic tests for CD, namely tissue transglutaminase IgA (tTG-IgA) and endomysium IgA (EMA) tests allow a reliable and cost-effective screening [6]. In the revised diagnostic guidelines for pediatric CD, it has been stated that the likelihood for villous atrophy (Marsh III) is high in symptomatic children with a high anti-tTG2 titer (i.e., > 10 × upper limit of normal) [1]. Furthermore, a positive EMA test in a second blood sample confirms the diagnosis of CD, and a gluten-free diet (GFD) can be initiated even in the absence of an endoscopic biopsy according to this guideline [1]. Moreover, current guideline published in 2020 perpetuated this advice also in asymptomatic children [7].

Treatment of CD is still limited to life-long exclusion of dietary gluten, and the major goal of gluten free diet is amelioration of symptoms as well as complete mucosal remission. Therefore, growth and nutritional biomarkers are monitored during follow-up. Several gastroenterology societies recommend using the serological tests as a marker of dietary adherence and mucosal status; however, serum tTG-IgA and EMA tests have not yet been validated for monitorization of dietary compliance in patients with CD [8–10]. In clinical practice, tTG-IgA is usually measured 6 and 12 months after the initiation of GFD. Regarding the diagnosis and treatment of CD, recently European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) CD working group proposed certain clinical scenarios in which diagnostic small intestinal biopsy can be omitted [1, 7]. But they did not make any recommendations regarding the follow-up of mucosal healing in those who were diagnosed and treated without an intestinal biopsy.

Recent data, analyzing serology as a marker of mucosal recovery is equivocal [5, 6]. It has been demonstrated that mucosal recovery was usually incomplete in adult patients with CD, and it was poorly correlated with serum titers of serologic tests [11–15]. Moreover, a recent meta-analysis of follow-up biopsies of patients with CD on GFD demonstrated that celiac serology (tTG-IgA and EMA) had a low sensitivity in detecting persistent villous atrophy [16]. In this meta-analysis, it was concluded that duodenal biopsy remains the only appropriate test for the assessment of mucosal recovery in the follow-up of both pediatric and adult patients with CD [16]. Furthermore, only 6 of 26 studies in this meta-analysis were performed in pediatric age group, and only one study involving of 53 celiac children evaluated both tTG-IgA and EMA [16, 17].

Although the primary goal of gluten-free diet is mucosal recovery, there is currently no validated non-invasive test to monitor mucosal recovery in the follow-up of patients with CD. Studies evaluating the reliability of serological testing for the assessment of dietary adherence and mucosal healing in adult patients with CD reported conflicting results. Few pediatric reports on this topic are limited to retrospective data and studies done with a small number of patients. In this prospective study, we aimed to investigate whether tTG-IgA and EMA accurately reflect mucosal status in the follow-up of pediatric patients with CD in a relatively large group of patients. The secondary aim of the study was to investigate a reliable cutoff value for tTG-IgA in reflecting mucosal status.

Materials and methods

Study design and patients

This study conducted between July 2017 and July 2019 at a tertiary care university hospital. Patients, who had biopsy proven celiac disease with Marsh III histopathology at diagnosis, were retrieved from the celiac database. Patients with CD between 2 and 17 years of age at diagnosis who had been followed-up for at least 12 months or longer were included in the study. Patients with selective IgA deficiency were excluded. Eligible patients were invited to participate in the study regardless of the presence of any symptom or dietary adherence. Those who consented prospectively underwent a repeat endoscopy between July 2017 and July 2019. A written informed consent was obtained from all parents, and

a written assent was also obtained from patients older than 14 years. Local Ethics Committee of Marmara University School of Medicine approved the study (Reference number: 09.2020.539).

Measurement of serum tTG-IgA and EMA antibodies

Serum IgA (SPA plus, The Binding Site Group Ltd, Birmingham, UK) and IgA-based serologic tests including tTG-IgA antibodies (Euroimmune AG, Germany) and EMA (Euroimmune AG, Germany) were performed on the day of the endoscopy. tTG-IgA antibodies were tested by using commercial enzyme-linked immunosorbent assay kits, and a titer of > 19 U/ml was regarded as positive as per the manufacturer's guidance. EMA was measured by indirect immunofluorescence method using monkey esophagus, at an initial dilution of 1:10 and when positive, titrated up to the end point.

Patients with positive serum tTG-IgA were reclassified according to their serum titer of tTG-IgA antibodies. A titer of tTG-IgA greater than 10 times the upper limit of normal was defined as "high titer (HT) tTG-IgA", while a titer of tTG-IgA less than 10 times the upper limit of normal was defined as "low titer (LT) tTG-IgA".

Specificity, sensitivity, and positive and negative predictive values for tTG-IgA and EMA tests were calculated separately. Then, sensitivity and specificity were recalculated considering patients who were positive or negative for both serological tests.

Endoscopy and histopathologic evaluation

All upper gastrointestinal endoscopies were performed under deep sedation applied by an anesthesiologist in the endoscopy unit. At least four biopsies were obtained from the second part of the duodenum and two biopsies from the bulb in each patient. The same expert gastrointestinal pathologist, who was blind to the clinical and serological information of the patients, evaluated these biopsies. Intestinal histological findings were classified according to the modified Marsh (Oberhuber) classification [18]. Patients with CD whose small intestinal biopsies were compatible with Marsh 0 or Marsh I histopathology on repeat endoscopy were considered as mucosal recovery.

Statistical analysis

Statistical analyses were performed using SPSS software version 22. Data were summarized by descriptive statistics, including counts and percentages for categorical data and medians and ranges for continuous variables. The sensitivity, specificity, and positive and negative predictive values of serology, measuring against duodenal histopathology as the reference standard were calculated in order to investigate the accuracy of serology in assessing mucosal status. Pearson chi-square statistic test were used to compare categorical data. For comparisons, a p value < 0.05 were considered as significant. Receiver operating curve (ROC) analysis was used to determine the optimal cutoff value for tTG-IgA; area under curve (AUC), sensitivity, and specificity were calculated.

Results

During the study period, an endoscopy was recommended to 202 patients with CD with follow-up for at least 1 year, and those 104 (51.5%) accepting the procedure were included into the study. Patients were 7.4 ± 4.02 years old (range 2–16.7 years) at diagnosis, and 65.4% (68) were girls. All of those 104 patients had Marsh III lesions at diagnosis (65% of them had Marsh IIIc). The duration of median follow-up was 3 years ((interquartile range) [IQR]: 1–6 years).

Histopathology of the follow-up biopsies

At the follow-up endoscopy, at least 6 biopsies (range: 6–9) were collected from the bulb and the second part of duodenum in each patient. The histopathologic findings of the follow-up biopsies were consistent with Marsh 0 in 40 and Marsh 1 in 37 patients, mucosal recovery was observed in a total of 77 (74.1%) patients. In the follow-up biopsies, 24 (23%) patients had partial/complete villous atrophy (Marsh III), and the remaining 3 (2.9%) had Marsh II histopathology.

tTG-IgA serology at the time of follow-up endoscopy

At follow-up endoscopy, 53 out of 104 (51%) patients with CD had positive tTG-IgA. Twenty-three patients (43.4%) with positive tTG-IgA serology also had mucosal injury (i.e., Marsh II/III lesion) while 30 (56.6%) patients had mucosal recovery (i.e., Marsh 0/I lesion) in follow-up biopsies.

Twenty-one out of 53 (39.6%) patients with CD with positive serum tTG-IgA had high titer (HT) tTG-IgA. Mucosal injury was detected in 18 out of 21 (85.7%) patients with HT tTG IgA, while remaining 3 (14.3%) patients had mucosal recovery. Besides, 5 out of 32 (15.6%) patients having low titer (LT) tTG-IgA had mucosal injury, while remaining 27 (84.4%) patients had mucosal recovery (Fig. 1).

At follow-up endoscopy, 51 out of 104 (49%) patients with CD had negative tTG-IgA. In this group, 47 (92.2%)

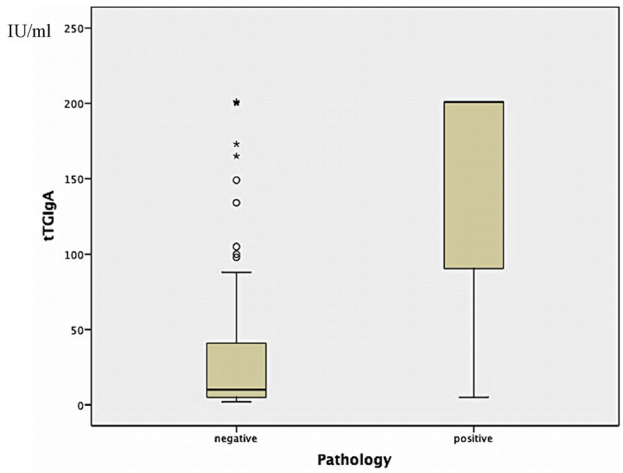

Fig. 1 At the time of follow-up endoscopy, tTG-IgA levels in patients with negative and positive histopathology

patients had mucosal recovery, while 4 (%7.8) patients still had mucosal injury on their follow-up biopsies.

The sensitivity and specificity of tTG-IgA as a marker of mucosal recovery was 85.2% (95% CI: 79–92%) and 61% (95% CI: 53–69%), respectively, with a high negative predictive value (NPV) of 92.2% (95% CI: 87–97%) but a very low positive predictive value (PPV) of 43.4% (95% CI: 35–51%). However, when HT tTG-IgA was tested as a predictor of mucosal injury in the follow-up of patients with CD, the PPV increased to 85.7%.

Furthermore, ROC analysis was used to determine a cut-off value for serum tTG-IgA as a marker of mucosal recovery in the follow-up of patients with CD. A value of 68.5 U/mL (i.e., 3.6 × ULN) for tTG-IgA had a sensitivity, specificity of 85.2% and 85.7%, respectively. The AUC was 0.891 (Fig. 2).

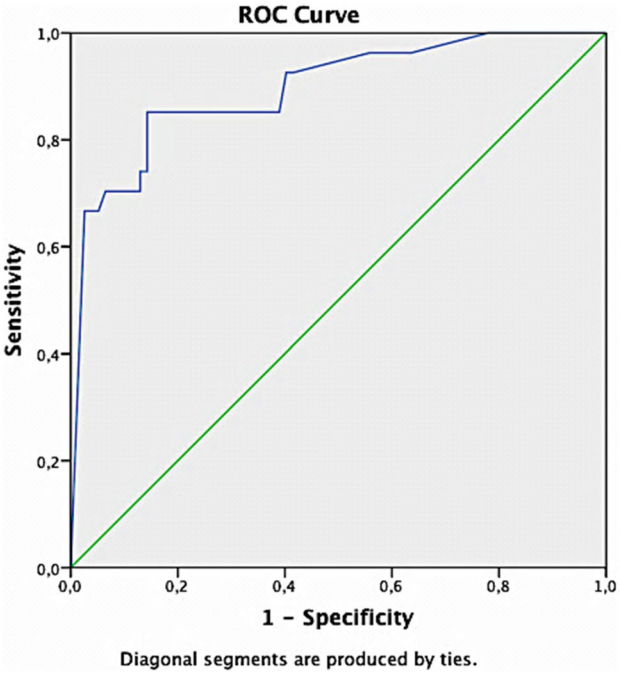

Fig. 2 Receiver operating curve (ROC) for tTG-IgA test. The sensitivity and specificity of a cutoff value ≥ 68.5 U/ml were 85.2% and 85.7% respectively. Area under the curve (AUC) = 0.89 (95%CI: 0.82–0.97)

EMA serology

At follow-up endoscopy, 31 out of 104 (29.8%) patients with CD were positive for EMA. Mucosal injury was found in 21 (67.7%) of these patients, and mucosal recovery was observed in follow-up biopsies of the remaining 10 (32.3%) patients despite positive EMA. Seventy-three (70.2%) patients with CD had negative EMA. Mucosal healing was detected in 67 (91.8%) of these patients whereas 6 (8.2%) patients still had mucosal injury despite negative EMA.

As a marker of mucosal recovery, sensitivity and specificity of EMA was 77.8% (95% CI: 71–85%) and 87% (95% CI: 81–93%) respectively, with a high NPV of 91.8% (95% CI: 87–97%) but low PPV of 67.7% (95% CI: 59–77%). Therefore, EMA per se was an important predictor of mucosal recovery with a specificity of 87% and a NPV of 91.8% in this study. The follow-up histopathology and concurrent serology of all patients with CD were depicted in Table 1.

In order to evaluate the predictive value of both concordant serological tests, 22 patients with CD having discordant serologic test results were excluded for the analysis. Those

Table 1 Follow-up histopathology and concurrent serologies of 104 patients with celiac disease

Serology	Histopathology			
	Marsh 0 ($n=40$)	Marsh I ($n=37$)	Marsh II ($n=3$)	Marsh III ($n=24$)
tTG-IgA				
Negative	24	23	1	3
Positive	16	14	2	21
Positive **tTG-IgA**				
Titer < 10 × ULN	15	12	1	4
Positive **tTG-IgA**				
Titer > 10 × ULN	1	2	1	17
EMA				
Negative	36	31	1	5
Positive	4	6	2	19

remaining 82 patients with CD having either positive or negative results for both tTG-IgA and EMA were analyzed separately. Thirty-one out of 82 (37.8%) patients with CD had positive results for both serological tests, and 21 out of 31 (67.7%) had mucosal injury in their control endoscopic biopsies. Still, mucosal healing was observed in 10 out of 31 (32.3%) patients with CD despite positive serology in both tests. Furthermore, those 31 patients with CD were subdivided according to the serum titer of tTG-IgA (21 HT and 10 LT). While 18/21 patients with CD having HT tTG had mucosal injury, 3/10 patients with CD LT tTG had mucosal injury. Of the 82 patients with CD, 51 (62.2%) tested negative for both serological tests. Mucosal healing was detected in 47 (92.1%) of them, whereas 4 (7.9%) patients with CD had mucosal injury (Table 2).

Sensitivity and specificity of concordant results for both serologic tests were analyzed, and sensitivity and specificity were 84% (95% CI: 76–92%) and 82.5% (95% CI: 74–90%), respectively. PPV of the concordant results was 67.8% (95% CI: 61–75%). Concordant results for both serological tests increased the specificity and PPV of tTG-IgA from 61 to 82% and from 43.4 to 67.8%, respectively. Nevertheless, concordant results for both serologic tests did not further improve NPV (92.2%) (95% CI: 36–98%).

Discussion

The serum tTG-IgA and EMA antibodies are widely used, sensitive, and reliable diagnostic tests for CD. In the recent ESPGHAN guidelines, it has been stated that non-biopsy approach for diagnosis of CD is safe in children with a high serum titer of tTG-IgA combined with a positive EMA in the second serum sample [7]. Despite the widespread use of these non-invasive serological tests in the follow-up of patients with CD, there is no instruction in the guidelines regarding this issue. However, it was recently reported that serum tTG-IgA and EMA are poorly correlated with mucosal outcomes [19–23]. Most of these studies are retrospective, and have been performed in adult patients with CD, and there are only a few pediatric studies [6, 17]. Our study was conducted in pediatric patients with CD, and both serological (tTG-IgA and EMA) tests and endoscopy were performed on the same day. Our findings showed that a positive tTG-IgA was not an accurate marker of mucosal status in the follow-up of patients with CD. A negative tTG-IgA serology is more informative in the follow-up of patients with CD, and can be interpreted as an indicator of mucosal recovery. Regardless of serum titer, positive tTG-IgA per se is not informative; however, high serum titer of tTG-IgA is rather helpful in reflecting persistent villous atrophy compared to low titer tTG-IgA. Contrary to our study, a meta-analysis, including 26 studies reported that serum tTG-IgA levels had high specificity (83%) and low sensitivity (50%) [16]. The authors argued that a negative tTG-IgA is much less informative and should not be interpreted as an indicator of mucosal recovery or as a proxy for GFD adherence. However, only 6 out of 26 studies in this meta-analysis included pediatric patients, and only 2 publications were regarded high in quality. Furthermore, adult and pediatric studies were not analyzed separately; hence, the conclusion should be interpreted with caution [16]. In our study, a negative tTG-IgA test predicted mucosal recovery with a high efficiency. Furthermore, the high NPV (92.2%) value we found revealed that negative test results could be more reliable. Similarly, Leonard et al. [6] found that tTG-IgA was a poor predictor of persistent enteropathy in children with CD receiving GFD regardless of the presence or absence of symptoms whereas a negative serology was closely correlated with mucosal recovery. We also searched for an optimal cutoff value for tTG-IgA using ROC analysis in order to increase the accuracy of this serologic test, and determined a cutoff value of 68.5 U/Ml (3.6 × ULN) with the highest sensitivity and specificity. This cutoff value increased the specificity of tTG-IgA from 61 to 85.7%. This means that if we had used this new cutoff value, false positivity would decrease, and we would have a higher positive predictive value in detecting mucosal injury. In a recently published adult study, the authors calculated an optimal cutoff value of 13.4 U/mL for tTG-IgA using ROC curve to increase sensitivity, specificity, and NPV in predicting persistent villous atrophy [24]. They argued that this new cutoff improved the accuracy of the test in distinguishing

Table 2 The correlation between the follow-up histopathology and concurrent positive or concurrent negative serology of 82 patients with celiac disease

Serology	Histopathology			
	Marsh 0 ($n=28$)	Marsh I ($n=29$)	Marsh II ($n=3$)	Marsh III ($n=22$)
Both negative	24	23	1	3
Both positive	4	6	2	19
Low titer tTG	3	4	1	2
High titer tTG	1	2	1	17

villous atrophy by increasing the NPV of tTG-IgA to 90.8% compared to the manufacturer's diagnostic cutoff value. Our study demonstrated that positive EMA cannot be used as an indicator of mucosal injury in the follow-up of pediatric patients with CD. Several studies, mostly done in adult patients have reported that the sensitivity of EMA is very low in demonstrating mucosal injury in the follow-up of patients with CD receiving GFD [19, 20]. In our study, NPV of both EMA and tTG-IgA were high, indicating that the negative serological tests detected in patients with CD receiving GFD correlated very well with mucosal recovery. Similar to our results, Vécsei et al. [17] found that among the serologic tests they examined, the negative likelihood ratio of EMA alone was low enough (0.097) to effectively rule out mucosal injury. Hence, our findings indicated that the use of EMA along with tTG-IgA in the follow-up of patients with CD increased the specificity of tTG-IgA in detecting mucosal recovery. Nevertheless, analysis of the concordant results for both serologic tests did not further improve the negative predictive value (92%). On the account of these data, we can suggest that negative serological tests are significantly associated with mucosal recovery in follow-up of pediatric patients with CD. Interestingly, there were many patients whose serological tests were still positive despite mucosal recovery in our study. Positive serological tests are much less informative in the follow-up of patients with CD, and may not always be an indicator of mucosal injury.

In contrast to our study, a meta-analysis of patients with CD undergoing follow-up biopsy while on a GFD concluded that the majority of patients with villous atrophy on GFD had normal levels of tTG-IgA or EMA. Thus, a negative antibody test is much less informative, and should not be interpreted as an indicator of mucosal recovery [16]. To our knowledge, there is only one prospective study comparing both tTG-IgA and EMA with follow-up biopsies in 53 pediatric patients with CD receiving GFD [17]. Consistent with our results, they found that negative EMA was the most reliable test predicting mucosal healing, but they did not analyze concordant results for both serological tests in their study.

One of the major strengths of this study was that, it included a larger group of pediatric patients with CD and serological tests were performed on the day of endoscopy in each patient. tTG-IgA and EMA were evaluated both together and separately in the assessment of mucosal status in patients with CD. Another strength of our study was that duodenal biopsies were taken from all patients regardless of celiac serology results or dietary compliance, which allowed the inclusion of false negative cases into the analysis of sensitivity and specificity of serologic tests.

According to the results of our study, we concluded that a negative tTG-IgA and/or EMA results can be used as proxy markers of mucosal healing in the follow-up of children with CD. However a positive tTG-IgA, especially at a low titer can be misleading in terms of mucosal damage, and may cause unnecessary close follow-up and dietary intensification in patients with positive celiac serology despite mucosal healing. Hence, serum tTG-IgA titer should be taken into consideration in the follow-up of patients with CD. The results of our study gain more importance today, when the diagnosis of CD with serological tests without endoscopic biopsy is discussed. False negative and false positive serologic test results in patients, who will be diagnosed without biopsy, will complicate the serologic follow-up of those patients.

Authors' contributions Ozlem Kalaycik Sengul gathered and analyzed the data and wrote the manuscript for publication; Bilge Sahin Akkelle: gathered and analyzed the data; Pınar Ay: gathered and analyzed the data; Burcu Volkan: gathered and analyzed the data; Engin Tutar: drafted and revised the work; Cigdem Ataizi Celikel: revised the work; Deniz Ertem: designed the work, revised the manuscript, and approved the final version of work for publication. All authors read and approved the final manuscript.

Availability of data and material The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethics approval Approval was obtained from the ethics committee of the Marmara University School of Medicine. The procedures used in this study adhere to the tenets of the Declaration of Helsinki (9022.78).

Consent to participate Informed consent was obtained from the parents.

Consent for publication Informed consent was obtained from the parents.

Competing interests The authors declare no competing interests.

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