

What Is the Role of Serologic Testing in Celiac Disease? A Prospective, Biopsy-Confirmed Study With Economic Analysis

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See CME exam on page 263.

Background & Aims: The optimal serologic tests for the detection of celiac disease and follow-up assessment remains controversial. Our aim was to evaluate all current immunologic assays for diagnosing celiac disease using the gold standard of duodenal biopsy. We also assessed whether tissue transglutaminase (tTG) antibody is a quantitative marker for histologic severity. **Methods:** Consecutive adult patients referred for gastroscopy without a previous known diagnosis of celiac disease were recruited (group 1). Concurrently, patients with a known diagnosis of celiac disease on a gluten-free diet for more than 1 year undergoing repeat duodenal biopsy were identified (group 2). All patients had duodenal biopsies and serologic analysis performed for immunoglobulin (Ig) A and antibodies to human immunoglobulin (Ig)A-tTG, IgA-gliadin, IgG-gliadin, and IgA-endomysial antibody. **Results:** Two thousand patients were recruited in the first group. Seventy-seven (3.9%) patients were diagnosed with new celiac disease. The sensitivity, specificity, positive predictive value, and negative predictive value for IgA tTG were 90.9%, 90.9%, 28.6%, and 99.6%. When adopting a 2-step approach using tTG first and then EMA the sensitivity, specificity, positive predictive value, and negative predictive value was 85.7%, 98.6%, 71.7%, and 99.7%, respectively. The use of nondeamidated IgA/IgG gliadin antibodies conferred no additional diagnostic benefit when considering the detection of adult celiac disease. In the second group 48 patients with celiac disease on a gluten-free diet were identified. Sixteen of 48 of these patients had persisting villous atrophy, but 7 of 16 (44%) had a normal tTG level. **Conclusions:** IgA tTG alone is a sensitive marker for celiac disease. A normal tTG level does not predict recovery of villous atrophy in patients with celiac disease on a gluten-free diet.

The prevalence of celiac disease in the United States, Europe, and the United Kingdom is between 0.75% and 1%.¹⁻⁴ In addition, we now accept that there may be many associated conditions and symptoms that warrant serologic testing for celiac disease (adopting a case-finding approach). Ultimately, the diagnosis of celiac disease still requires a small-bowel biopsy showing villous atrophy.⁵⁻⁸

There are a number of serologic tests that have been reported to be accurate in identifying patients who then should be referred for a duodenal biopsy. However, the optimal serologic

test or test strategy remains controversial. Previously, anti-endomysial antibody (EMA) had been reported as an accurate test with a sensitivity greater than 90% and a specificity greater than 98%.⁹⁻¹¹ However, it is recognized that EMA requires a subjective immunofluorescence method and has limited substrate resources (either monkey esophagus or umbilical cord).¹² Recently, the introduction of anti-tissue transglutaminase (tTG) antibody testing using either guinea pig or human recombinant tTG has led investigators to suggest that human recombinant tTG may have higher sensitivities than EMA.^{12,13} An advantage of automated tTG testing is higher throughput of samples and also the opportunity to obtain a quantitative titer using the enzyme-linked immunosorbent assay method. However, there are more false-positive results associated with tTG testing.^{14,15} This lower specificity has led some investigators to describe a 2-step method (tTG first and, if positive, followed by EMA—if there is a positive EMA result then proceed to biopsy) to avoid patients undergoing unnecessary duodenal biopsies.^{12,13}

Despite the high accuracy of EMA and tTG, seronegative celiac disease still occurs. This has been reported to account for 6.4% (8 of 126) of all cases of celiac disease,¹⁶ and appears to occur more often with lesser degrees of atrophy.^{17,18} For this reason duodenal biopsy in patients with a high suspicion of celiac disease still is recommended even if the serologic testing is negative.¹⁹ Currently published multicenter trials with large cohorts that have tried to compare EMA and tTG accuracy have taken 1 of 2 approaches. Either they have performed a duodenal biopsy in patients who were antibody positive or they have recruited patients known to have a high risk of celiac disease, for example, iron-deficiency anemia.^{16,20,21} However, we were unable to identify any study that evaluated all of the current antibody tests in a large series of low-risk adult patients with concomitant duodenal biopsy performed in all patients.

Once a diagnosis of celiac disease has been made, there is no single method that allows for assessment of compliance. Questioning patients for symptom response to a gluten-free diet and a dietary assessment can be used as a noninvasive marker, but this may not correlate with intestinal damage.²² However, villous recovery on a gluten-free diet may take up to 24 months or longer in adults.^{23,24} There may be a role for serology in the

Abbreviations used in this paper: EMA, endomysial antibody; IEL, intraepithelial lymphocyte; IG, immunoglobulin; NPV, negative predictive value; PPV, positive predictive value; tTG, tissue transglutaminase.

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assessment of compliance but, to date, EMA has been shown to be a poor predictor of villous recovery.²⁵

For these reasons the aim of our study was to assess which serologic tests or test strategy is optimal for both the recognition and follow-up evaluation of patients with celiac disease.

Methods

Patient Recruitment

Patient recruitment took place in a single endoscopy department at the Royal Hallamshire Hospital in Sheffield (United Kingdom). Consecutive adult patients referred for gastroscopy were recruited by a single endoscopist over a 26-month period (patient group 1 was recruited from January 2004 to April 2006). The Department of Gastroenterology currently uses a policy of taking 4 duodenal biopsy specimens routinely as part of the endoscopic examination. Patient consent was obtained and the gastroscopy examination was performed with 4 biopsy specimens taken from the second part of the duodenum. At the same time a blood sample was obtained from each patient and analyzed for total immunoglobulin A (IgA), IgA-gliadin, IgG-gliadin, IgA-tTG, and IgA-EMA. Patients were excluded from this cohort if they had a known diagnosis of celiac disease, a coagulopathy (international normalized ratio > 1.3 or platelet count of <80), active gastrointestinal bleed or a suspected carcinoma observed during the examination, or refused to participate in the study.

Patients then found to have villous atrophy (on duodenal biopsy) with supportive serology and symptoms were classified as having celiac disease. Patients with villous atrophy (confirmed on a second review of the sample to ensure a well-oriented sample) and a negative antibody profile were classified as having seronegative celiac disease after further assessment. To further support the diagnosis of antibody-negative celiac disease alternative causes of villous atrophy were excluded (such as *Giardia* and *Helicobacter pylori* infection, selective IgA deficiency) and a human lymphocyte antigen profile was checked. To confirm the diagnosis of seronegative celiac disease these patients were required to have the DQ2 or DQ8 pattern consistent with celiac disease and a clinical and histologic response to a gluten-free diet.^{26,27}

Correlation of Tissue Transglutaminase Antibody Titer With Degree of Villous Atrophy

To assess the relationship between tTG and histology we studied both patients diagnosed with celiac disease from group 1 and any patients not in that study but who were newly diagnosed with celiac disease during the same time frame and had the same antibody assessment (in our center).

A second cohort of patients (group 2) formed a *known celiac disease* group. These were patients undergoing gastroscopy and duodenal biopsy for assessment of histologic remission. These patients had been on a gluten-free diet for greater than 1 year. Serology was obtained in an identical manner to that described previously.

Serology and Histology

All duodenal biopsy specimens were fixed in buffered formalin and embedded in paraffin wax. Standard, 3- μ m-thick

sections at 3 levels were stained with H&E. If changes suggestive of celiac disease were present in a biopsy specimen it was graded according to the modified Marsh criteria using the most severe lesion present²⁸: Marsh 0, normal appearance; Marsh 1, normal morphology with raised intraepithelial lymphocytes (IELs); Marsh 2, raised IEL with crypt hyperplasia; Marsh 3a, partial villous atrophy; Marsh 3b, subtotal villous atrophy; and Marsh 3c, total villous atrophy.²⁹

Total IgA was measured on a Behring BN2 nephelometer (Siemens Healthcare, Frankfurt, Germany). IgA gliadin, IgG gliadin, and human tTG antibodies were assayed on enzyme-linked immunosorbent assay kits from Aeskulisa (AESKU. DIAGNOSTICS, Wendelsheim, Germany). Serologic samples with a titer greater than 15 U/mL were taken as positive. IgA EMA was detected by immunofluorescence on primate esophagus sections from The Binding Site (Birmingham, UK).

Ethical approval was obtained from the South Sheffield research and ethics committee. Statistical analysis was performed using SPSS version 10.0 (SPSS Inc, Chicago, IL). All comparisons between sensitivities of tTG and EMA were made using the Fisher exact test, and the mean values of tTG levels and age groups were compared with an independent sample *t* test.

Results

Assessment of the Clinical Performance of Available Serology Tests

In group 1 there were 2000 patients recruited (1167 [58.3%] females; mean age, 55.8 y; range, 16–94 y). From this group a total of 77 patients were diagnosed with new celiac disease, giving a prevalence for celiac disease in all patients attending for gastroscopy of 3.9% (prevalence previously reported by our group¹⁹). The histologic grading of villous atrophy for these 77 patients was as follows: 29 with Marsh 3a, 30 with Marsh 3b, and 18 with Marsh 3c lesions. During the recruitment period a total of 2220 patients had a gastroscopy, and 220 patients were excluded (previous diagnosis of celiac disease, 48; gastrointestinal bleed, 101; probable carcinoma, 12; unable to tolerate gastroscopy, 8; coagulopathy, 12; follow-up gastroscopy during study period, ie, already recruited, 36; refused to be included in the trial, 3).

The indications for performing the gastroscopy for all the examinations and in patients found to have celiac disease are shown in Figure 1.

In group 1, we compared the prevalence of symptoms in patients found to have celiac disease ($n = 77$) with those who did not ($n = 1923$). Patients with celiac disease had a significantly higher prevalence of weight loss (15.6% vs 5.3%) and diarrhea (42.9% vs 5.2%). Patients without celiac disease had a significantly higher prevalence of dyspepsia (17.3% vs 1%), reflux (13.8% vs 1%), and dysphagia (7.2% vs 0%). The celiac disease group was significantly younger (mean age, 48.0 vs 56.1 y) and contained a higher percentage of females (70.1% vs 57.9%) (significance is defined as $P < .05$ for all comparisons).

Table 1 shows the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the individual antibodies and their combinations using tTG and EMA simultaneously or in a 2-step method. Also shown in Table 1 is

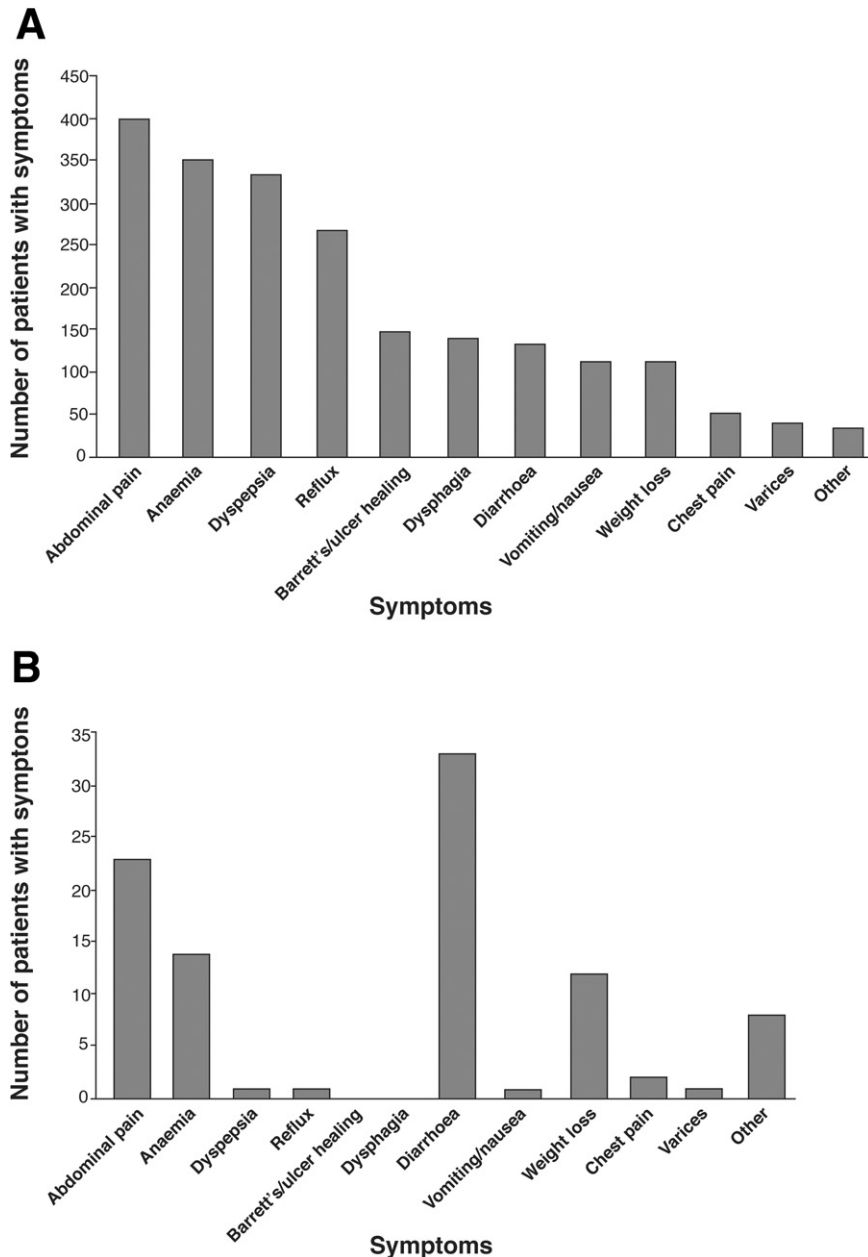


Figure 1. Referral symptoms for gastroscopy. (A) Patient's symptoms that prompted referral for gastroscopy. The total was 2114 as a result of some patients ($n = 2000$) having more than 1 symptom. (B) Patients' symptoms that prompted referral for gastroscopy and were found to have celiac disease. The total was 96 as a result of some patients ($n = 77$) having more than 1 symptom.

the number of patients who would require a duodenal biopsy depending on which serologic strategy is used and the corresponding number of new celiac disease cases that potentially would be missed by taking the different approaches. Table 2 shows a corresponding economic analysis for the different serologic and biopsy strategies.

When specifically considering serology-negative celiac disease there were 6 patients in the cohort of 2000 who had celiac disease but were tTG and EMA negative. All 6 were IgA-gliadin negative; 1 of the 6 patients (who presented with anemia) had an IgA deficiency but, despite this, this patient also had a negative IgG gliadin. Seven celiac disease patients were tTG negative, but 1 of these 7 patients had a positive EMA.

The overall prevalence of IgA deficiency in our series was 0.7% (14 of 2000), of which only 1 patient had celiac disease.

Correlating Serology With Histologic Severity (Newly Diagnosed Patients With Celiac Disease Not on a Gluten-Free Diet)

During the study period we identified a total of 114 patients with newly diagnosed celiac disease. Seventy-seven patients were obtained from group 1 (77 of 2000) and a further 37 who were found to have celiac disease in the department but outside of group 1 recruitment due to being on other endoscopist's lists. The mean age of the whole group ($n = 114$) was 47.3 years (range, 17–85 y), and 69.2% (79 of 114) were female. The findings on histology showed that 37.7% (43 of 114) of these patients had a Marsh 3a lesion, 38.6% (44 of 114) had a Marsh 3b lesion, and 23.7% (27 of 114) had a Marsh 3c lesion.

Patients with partial or subtotal villous atrophy (Marsh 3a or 3b lesion) had a significantly lower average (mean) tTG titer

Table 1. Evaluation of Different Serologic Strategies That Could Be Used for Testing for Celiac Disease

Serologic tests used to refer for biopsy	Sensitivity, (%)	Specificity, (%)	PPV, (%)	NPV, (%)	Resulting number of patients undergoing duodenal biopsy per 2000	Missed cases of celiac disease out of 77
Only tTG positive	90.9 (82.4–94.5)	90.9 (89.5–92.1)	28.6 (23.3–34.5)	99.6 (99.2–99.8)	245	7
Only EMA positive	87.0 (77.7–92.8)	98.0 (97.4–98.6)	64.4 (54.9–73.0)	99.4 (99.0–99.7)	104	10
If tTG positive and then EMA positive (2-step)	85.7 (76.2–91.8)	98.6 (98.0–99.0)	71.7 (61.8–79.9)	99.4 (99.4–99.0)	92	11
Both tTG positive and EMA positive	85.7 (76.2–91.8)	98.6 (98.0–99.0)	71.7 (61.8–79.9)	99.4 (99.4–99.0)	92	11
Either tTG positive or EMA positive	92.2 (84.0–96.4)	90.3 (88.9–91.6)	27.6 (22.5–33.4)	99.7 (99.3–99.8)	257	6
IgG gliadin positive	48.1 (37.3–59.0)	95.8 (94.9–99.6)	31.6 (23.9–40.5)	97.9 (97.1–98.4)	114	40
IgA gliadin positive	49.4 (38.5–60.2)	89.6 (88.2–90.1)	16.0 (11.9–21.2)	97.8 (97.0–98.4)	238	39
Both IgG gliadin and IgA gliadin positive	36.4 (26.5–47.5)	98.8 (98.2–99.2)	54.9 (41.4–67.7)	97.4 (96.7–98.1)	51	49

NOTE. Individual serology is listed and the practice of using both tTG and EMA together or sequentially is shown. If the serology results only are relied on (as the indication for biopsy) the last 2 columns show how many biopsies would be performed in our cohort and how many cases potentially would be undetected. The 95% confidence intervals are shown in parentheses. The “Only tTG positive” data were reported previously by our group.¹⁹

(168.1 U/mL and 165.0 U/mL, respectively) than patients with total villous atrophy (255 U/mL) ($P < .05$). From group 1, when considering patients with changes in the duodenal biopsy suggestive of potential celiac disease, 39 were found to have raised IELs (Marsh 1) and 2 patients had a lesion consistent with a Marsh grade 2. Patients with Marsh 1 or 2 lesions also had a significantly lower average tTG titer (27.7 U/mL and 23.0 U/mL, respectively) than patients with villous atrophy ($P < .05$) (Figure 2).

The sensitivity of EMA increased from 79% in patients with partial villous atrophy to 100% in total villous atrophy ($P < .01$). A similar observation was made for tTG sensitivity (using the standard cut-off level of >15), with 86.0% in Marsh 3a to 100% in Marsh 3c ($P < .05$) (Figure 3).

Correlating Serology With Histologic Severity (Repeat Duodenal Biopsy in Patients With Celiac Disease on a Gluten-Free Diet for More Than 1 Year)

In group 2 there were 48 patients with known celiac disease (gluten-free diet for >1 y). The mean age was 52.7 years (range, 21–78 y), with 68.8% (33 of 48) female patients. The

findings on histology showed that 43.8% (21 of 48) had a Marsh 0 lesion, 12.5% (6 of 48) had a Marsh 1 lesion, 10.4% (5 of 48) had a Marsh 2 lesion, 18.8% (9 of 48) had a Marsh 3a lesion, 10.4% (5 of 48) had a Marsh 3b lesion, and 4.2% (2 of 48) had a Marsh 3c lesion.

Figure 4 shows the percentage of patients with a positive tTG or EMA result for each grade of villous atrophy. The percentage of patients with a positive EMA or tTG both were significantly higher in patients with villous atrophy (EMA, 7 of 16; tTG, 7 of 16) than in those without villous atrophy (EMA, 3 of 32; tTG, 4 of 32) (EMA, $P < .02$; tTG, $P < .05$).

Discussion

This study performed concurrent serologic testing and a duodenal biopsy in all adult patients referred for endoscopy ($n = 2000$). Previous investigators have used either serologic testing as a means of determining which patients should undergo a biopsy or have performed a routine duodenal biopsy without serologic testing in tandem. Our results suggest that tTG is the appropriate first serologic test but thereafter whether a 2-step approach then is taken (with EMA) is likely to remain

Table 2. Proposed Cost of Different Strategies Using tTG and EMA as Listed in Table 1

Serologic test used to refer for biopsy	Resulting number of patients undergoing duodenal biopsy per 2000	Celiac disease cases identified per 2000	Celiac disease cases missed out of a possible 77	Proposed total cost for 2000, \$/£	Cost per celiac disease diagnosis, \$/£
Only tTG positive	245	70	7 (1 in 11)	53,880/28,210	780/403
Only EMA positive	104	67	10 (1 in 8)	38,260/20,032	570/299
If tTG positive and then EMA positive	92	66	11 (1 in 7)	40,200/21,051	610/319
Either tTG positive or EMA positive	257	71	6 (1 in 13)	81,950/42,906	1150/604

NOTE. The cost of a duodenal biopsy in our hospital is converted to US dollars (\$110/£58), and a tTG and EMA antibody test are \$13/£7 each.

subject to individual clinical judgment. If a single antibody test is used in isolation tTG will detect most cases of celiac disease (tTG sensitivity, 90.9%), however, this is offset by the expense of a greater number of endoscopies with duodenal biopsy and the potential discomfort to those patients. This is reflected by tTG having a PPV of only 28.6%. For this reason a 2-step approach may be cost effective (Table 2), but this will result in clinicians missing some cases of celiac disease as a result of the lower sensitivity of EMA. Because of this discordance between EMA and tTG positive results, one could test for both concurrently and opt to biopsy all patients who have any positive antibody. However, in our data set, 1 in 13 cases of undetected celiac disease still would be missed as a result of serology-negative celiac disease. On this basis we cannot make a recommendation on which test is the most cost effective or accurate for different clinical presentations; however, we still would recommend duodenal biopsy in any cases in which a clinician is suspicious of celiac disease irrespective of a negative antibody result.

What is apparent from our evaluation is the poor performance of the gliadin antibodies. In this study, the gliadins gave no extra diagnostic benefit when used specifically to detect adult celiac disease. However, better results for gliadins have been shown in children.²⁰ Variation may occur as a result of the numerous antigliadin assay kits. In addition, they may be a marker of extraintestinal manifestations of gluten sensitivity in the absence of enteropathy (eg, neurologic manifestations).³⁰ Recently, with the emergence of newly developed IgA synthetic gliadin-derived deamidated peptide, investigators have shown promising accuracy when used on its own or combined with tTG.^{31,32}

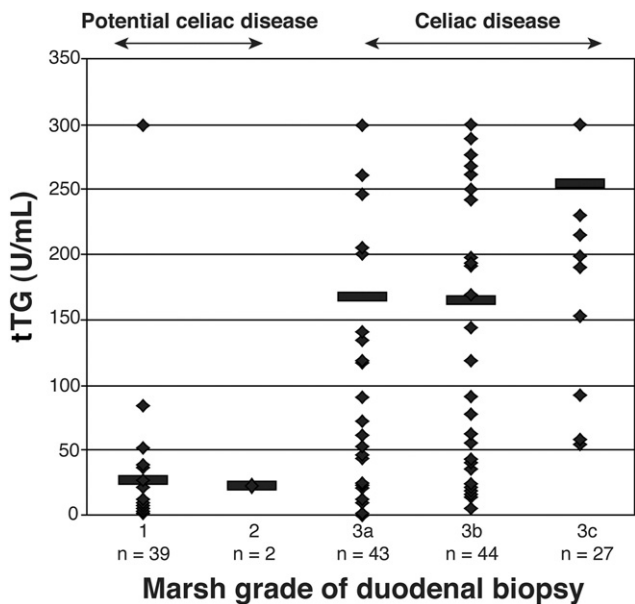


Figure 2. Graph showing patients with newly diagnosed potential and confirmed celiac disease. The tTG titer at presentation was grouped according to the Marsh grade of the duodenal biopsy. The black bars represent the average (mean) tTG values. The average titer for Marsh 3c was significantly higher than that of 3a or 3b ($P < .01$), and the average for Marsh grade 1 and 2 were significantly lower than the average titers for Marsh grades 3a–c. One dot can represent more than 1 patient if the tTG level was identical. tTG, IgA tissue transglutaminase antibody.

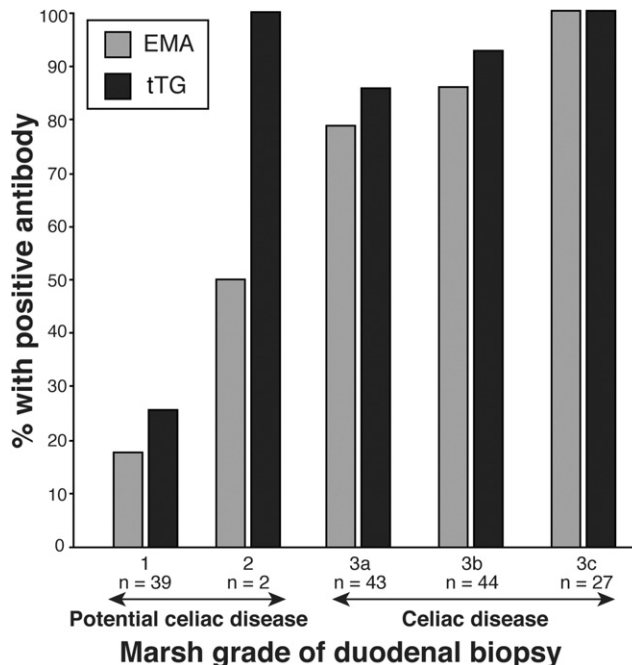


Figure 3. Sensitivity of tTG (cut off >15 U/mL) and EMA antibody for different degrees of villous atrophy in newly diagnosed patients with potential and confirmed celiac disease. Sensitivity for both EMA and tTG was significantly higher in Marsh grade 3c than in Marsh grade 3a ($P < .01$ for EMA and $P < .05$ for tTG).

We have reported a sensitivity for tTG of 90.9% and for EMA of 87.0%. These sensitivities are at the lower end of the spectrum when compared with previously reported studies.¹⁰ Perhaps the reasons for this are as follows: first, our study was a prospective evaluation and other prospective studies also consistently have shown lower sensitivities for tTG and EMA.^{21,26}

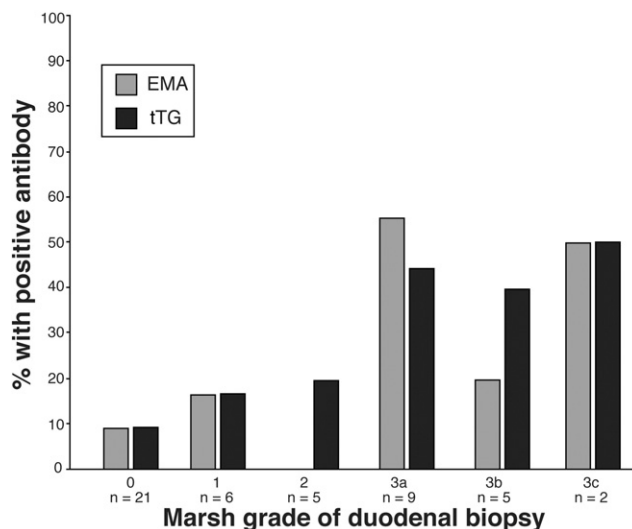


Figure 4. Percentage of positive IgA tTG (cut off >15 U/mL) and EMA results in patients with celiac disease on a gluten-free diet (>1 y) grouped according to Marsh grade. The percentage of patients with a positive EMA or tTG were both significantly higher in patients with villous atrophy (EMA, 7 of 16; tTG, 7 of 16) than in those without villous atrophy (EMA, 3 of 32; tTG, 4 of 32) (EMA, $P < .02$; tTG, $P < .05$).

Second, our study was performed in a low (or lower)-risk group than other biopsy-confirmed studies, which reduced our ascertainment bias. Finally, unlike most previous studies all of our patients underwent a biopsy (irrespective of antibody status), therefore we believe our data truly assesses the prevalence of seronegative celiac disease. It is not surprising that by adopting this strategy this has resulted in a reduced sensitivity by comparison with previously published data.

The PPV of IgA tTG in our study was 28.6% (Table 1). Although disappointing by comparison with other published studies (range, 21.8%–67%),^{33–35} there may be several reasons for this. A high tTG titer has been shown to occur in patients with liver disease, diabetes,^{15,36} and in up to 40% of patients with end-stage heart failure.³⁷ This might be reflected in our cohort, which aimed to be relatively low risk for celiac disease (overall prevalence of celiac disease, 3.9%). However, our cohort might be considered an unwell group (with other comorbidities) because they were coming to the hospital for gastroscopy.

There have been a few reports of a reduced sensitivity for both EMA and tTG in patients with lesser degrees of villous atrophy.^{17,18,38} We found similar results in our cohort of celiac disease patients. The sensitivity of tTG and EMA decreased from 100% and 100%, respectively, in patients with total villous atrophy (Marsh 3c) to 85% and 79%, respectively, in patients with partial villous atrophy (Marsh 3a) (Figure 3). However, despite our observation that the tTG titer in Marsh 3c lesions is significantly higher than in lesser degrees of villous atrophy (Figure 2), conversely others have reported that a high tTG titer can occur in patients without villous atrophy.³⁹ If we used a higher cut-off value than 15 U/mL (manufacturer's recommendation), for example, higher than 100 U/mL, this increased the PPV in our series to 75% (with a corresponding sensitivity, specificity, and NPV of 20%, 97%, and 72.7%, respectively).

We opted for the presence of a Marsh grade 3 lesion to be the gold standard for validating the serologic tests. This approach is concurrent with the majority of previous reports,^{16,20,26,35,38} although there have been a few studies that also incorporated Marsh 2 lesions.^{13,40} The concept of celiac disease or potential celiac disease without villous atrophy is well described.²⁸ Minor mucosal changes (Marsh 1 and 2) may normalize with a gluten-free diet and improvement of symptoms. However, in our study there were only 2 patients with Marsh 2 lesions and thus this would have had a negligible effect on our tTG validation. There are other causes of raised IELs (Marsh 1) in the duodenum (apart from celiac disease) for which we did not assess.²⁸ When trying to detect adult celiac disease using either tTG or EMA, the inclusion of Marsh 1 lesions (by expanding our diagnostic criteria for celiac disease; Figures 2 and 3) in our data set would reduce the sensitivity further. It is unclear which patients with a raised IEL require follow-up evaluation but a repeat biopsy or biopsy after a gluten-free challenge and HLA testing has been suggested.⁴¹ It would perhaps be an option to exclude these patients with a Marsh 1 (n = 39) or Marsh 2 (n = 2) biopsy result completely from both our celiac and control groups and classify them as having potential or unknown celiac disease: in doing so the resulting sensitivity, specificity, PPV, and NPV for tTG from our series would be 90.9%, 91.3%, 30.0%, 99.6%, respectively, and for EMA it would be 87.0%, 98.2%, 66.3%, and 99.5%, respectively.

We consider that tTG offers clear advantages owing to automation (allowing higher throughput of samples) and it is a

quantitative test (using enzyme-linked immunosorbent assay). All patients in our study had a duodenal biopsy; thus, the reduced PPV is perhaps a reflection of real clinical practice. In view of this observation we believe that EMA should not be regarded as an obsolete test. We did not assess IgG tTG in our patients because it was not available in our laboratory at the start of the study. Initial reports of the new IgG-tTG assays have been encouraging.^{21,42}

Our data for the role of tTG in the assessment of histologic remission of celiac patients on a gluten-free diet are concurrent with previous reports.^{43–45} We would not recommend that tTG be used in isolation as a marker of histologic severity or remission. Forty-four percent (7 of 16) of celiac patients at follow-up evaluation (on a gluten-free diet for >1 y) who had villous atrophy (Marsh 3a–c) also had a tTG of less than 15 U/mL. We would recommend that remission should be based on repeat duodenal biopsy, symptom response, dietary questioning, and serologic status as a composite assessment.⁴⁶

In conclusion, IgA tTG alone is a sensitive marker for detecting celiac disease, but because of its poor PPV in clinical practice it has not superseded the use of IgA-EMA testing. The use of nondeamidated IgA/IgG gliadin antibodies confers no additional diagnostic benefit when specifically considering the detection of adult celiac disease. Finally, a normal tTG is unable to predict recovery of villous atrophy in patients with celiac disease (on a gluten-free diet for >1 y) and we would suggest that a duodenal biopsy always should be considered if patients still are symptomatic.

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