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Comparison of Anti-Transglutaminase ELISAs and an Anti-Endomysial Antibody Assay in the Diagnosis of Celiac Disease: A Prospective Study

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Background: **Most studies of anti-transglutaminase (anti-tTG) assays have considered preselected groups of patients. This study compared the sensitivity, specificity, and predictive value of an immunofluorescence method for anti-endomysial antibodies (EmAs) and two anti-tTG ELISAs, one using guinea pig tTG (gp-tTG) and the other human tTG (h-tTG) as antigen, in consecutive patients investigated for suspected celiac disease (CD).**

Methods: **We studied 207 consecutive patients (99 men, 108 women; age range, 17–84 years) who underwent intestinal biopsy for suspected CD. Patients presented with one or more of the following: weight loss, anemia, chronic diarrhea, abdominal pain, dyspepsia, alternating bowel habits, constipation, pain in the joints, and dermatitis. At entry to the study, an intestinal biopsy was performed and a serum sample was taken for IgA EmAs, anti-gp-tTG, and anti-h-tTG.**

Results: **Intestinal histology showed that 24 patients had partial or total villous atrophy; in these patients the diagnosis of CD was confirmed by follow-up. The remaining 183 patients had villous/crypt ratios that were within our laboratory's reference values and were considered controls. Serum EmAs, anti-gp-tTG, and anti-h-tTG were positive in all 24 CD patients; in the control group, none were positive for serum EmAs, but 15 of 183 (8.2%) were positive for anti-gp-tTG, and 6 of 183 (3.3%) were positive for anti-h-tTG. Sensitivity was 100% for all assays, whereas specificity was 100% for the EmA, 92% for the anti-gp-tTG, and 97% for the anti-h-tTG assay. The negative predictive value was 100% for all assays; the positive predictive value was 100% for the EmA, 80% [95% confidence interval (CI), 65–95%] for the anti-h-tTG ($P = 0.03$ vs EmA) and 60% (95% CI, 44–76%) for the anti-gp-tTG assay ($P = 0.0002$ vs EmA). Areas (95% CIs) under the ROC curves were 0.987 (0.97–1.0) for anti-h-tTG and 0.965 (0.94–0.99) for anti-gp-tTG. Most of the patients testing false positive for anti-tTG had Crohn disease or chronic liver disease.**

Conclusions: **Although both anti-tTG ELISAs showed optimum sensitivity, their lack of specificity yielded positive predictive values significantly lower than those for the EmA assay.**

The recent introduction of an anti-tissue transglutaminase (anti-tTG)[4] assay in the diagnostic work-up of celiac disease (CD) has offered a simpler means for evaluating suspected CD and selecting patients to undergo intestinal biopsy *(1)*. Pretreatment of CD sera with tTG eliminated the endomysial staining pattern in human umbilical cord, suggesting that tTG could be the previously unknown endomysium autoantigen *(2, 3)*. Furthermore, reticulin, endomysial, and jejunal antibodies detected transglutaminase in primate tissues, suggesting that these tissue antibodies, and the anti-transglutaminase antibodies themselves, could be identical *(4)*. Consequently, it has been suggested that the simpler and less expensive ELISA developed to detect the presence of serum anti-tTG autoantibodies could replace the immunofluorescence technique traditionally used for the detection of anti-endomysial antibodies (EmAs) *(1–3, 5, 6)*. Recent reports, however, have shown a high frequency of false-positive

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[4] Nonstandard abbreviations: tTG, transglutaminase; CD, celiac disease; EmA, anti-endomysial antibody; gp-tTG, guinea pig tTG; h-tTG, human tTG; IEL, intraepithelial lymphocyte; and CI, confidence interval.

results with the most widely used anti-tTG ELISA, which is based on guinea pig tTG (gp-tTG) as the antigen, in patients with liver diseases *(7, 8)*, and we found false-positive results in patients with lymphoproliferative disease *(9)*. Better results have been reported with a new anti-tTG ELISA based on human tTG (h-tTG) as the antigen *(10)*. However, few studies have evaluated the diagnostic accuracy of this new anti-h-tTG ELISA, and almost all the studies on the anti-tTG assay have considered preselected groups of patients and not consecutive individuals with suspected CD.

The aim of the present prospective study was to compare the diagnostic accuracy of the EmA assay and two commercially available anti-tTG ELISAs, one based on gp-tTG and the other on h-tTG as antigen, in consecutive patients prospectively investigated for suspected CD, all of whom underwent intestinal biopsies.

Patients and Methods

This study included 207 consecutive adult patients (99 males and 108 females; age range, 17–84 years; median, 42 years) who had undergone intestinal biopsies for suspected CD between January 1999 and February 2000 at the outpatient clinics of two different Divisions of Internal Medicine and at a Surgery Department of the University Hospital in Palermo. All patients included in the study were followed as outpatients. The patients presented one or more of the following symptoms: weight loss (86 cases), anemia (81 cases), chronic diarrhea (80 cases), abdominal pain (71 cases), dyspepsia (65 cases), alternating bowel habits (61 cases), constipation (20 cases), pain in the joints (2 cases), and dermatitis (2 cases). Patients who had undergone previous serologic or histologic evaluation for suspected CD were ineligible for the study.

At entry in the study, on the same day as the intestinal biopsy sampling, a serum sample was taken from each patient for IgA anti-tTG and anti-EmA assays. Between January and December 1999, only the gp-tTG ELISA was performed immediately, and all the sera were stored at −80 °C. After December 1999, the new anti-tTG ELISA, based on h-tTG as the antigen, was commercially available, and this assay was performed on the stored sera of the patients recruited from January to December 1999. From January to April 2000, both the gp-tTG and the h-tTG IgA ELISA were performed immediately on entry to the study. Total immunoglobulin values (IgA, IgM, and IgG) were also measured by ELISA.

The diagnosis of CD was based on evidence of clinical symptoms and partial or total intestinal villous atrophy on a gluten-containing diet, disappearance of the symptoms and normalization of the intestinal histology on a gluten-free diet, and reappearance of the symptoms on gluten challenge.

According to the individual clinical presentation and laboratory data, the diagnostic work-up of the patients may also have included abdominal ultrasonography and/or computed tomography, colonoscopy, small intestine barium examination, liver histology, a H_2 breath test, and duodenal fluid microbiological evaluation.

The protocol was approved by the Ethics Committee of the University Hospital of Palermo, and informed consent was obtained from the patients involved in the study.

serum anti-tTG IgA elisa using gp-tTG as antigen

The anti-gp-tTG assay was performed with a commercial ELISA (Eu.tTG IgA; Eurospital) in accordance with the method described by Troncone et al. *(5)*, modified according to Sulkanen et al. *(3)*. The antigen used in the ELISA was gp-tTG (cat. no. T5398; Sigma). Values were expressed as a percentage of the values obtained for positive reference sera [obtained from untreated celiac patients diagnosed according to the criteria of the European Society of Paediatric Gastroenterology and Nutrition *(11)* and which tested positive for EmAs in all cases]. Anti-tTG values greater than the 95th percentile of a control group including >100 healthy controls and negative for serum EmAs were considered positive (7% of the reference serum). The intraassay CV was 8.7% (n = 15), and the interassay CV was 10% (n = 15).

serum anti-tTG IgA elisa using recombinant h-tTG as antigen

The anti-h-tTG ELISA was performed in our laboratory on serum samples from 60 patients immediately after blood collection and on serum samples, from 147 patients, that had been kept frozen at −80 °C. A control test performed in our laboratory on 30 serum samples in which anti-tTG antibodies were first assayed on fresh serum and then 8 months later after storage at −80 °C showed that storage at −80 °C did not significantly alter the results obtained: the mean value (± SD) was 5.23% ± 0.71% for fresh samples and 4.92% ± 0.75% for frozen samples. The interassay CV was 7.9%.

Serum IgA recombinant anti-h-tTG antibody concentrations were determined using a commercially available assay (Eu.tTG IgA umana; Eurospital). The purity of the recombinant protein was assessed by sodium dodecyl sulfate–polyacrylamide gel electrophoresis. Recombinant h-tTG antigen diluted in phosphate-buffered saline was used to coat the wells; serum samples diluted 1:26 (20 μL of serum plus 500 mL of phosphate-buffered saline) in phosphate-buffered saline containing 1 mL/L Tween 20 were incubated for 1 h at room temperature. The plates were washed three times and subsequently incubated for 1 h at room temperature with horseradish peroxidase-labeled sheep anti-human IgA. The excess conjugate was removed by washing, and a chromogenic substrate was added. The absorbance was read in a microplate reader at 450 nm. Results were expressed as a percentage of the positive control serum. Normal values were taken as <7%, which represented a value > 2 SD above the mean of 850 healthy individuals. The intraassay CV for the IgA h-tTG autoantibody ELISA was 2.2% (n = 30), and the interassay CV was 5.8% (n = 30).

serum IgA EmA assay

IgA-class EmA values were determined with a commercially available indirect immunofluorescence method on monkey esophagus (Anti-endomisio; Eurospital Pharma), as described previously *(12, 13)*.

intestinal biopsy and histology

Biopsy specimens were taken during gastroduodenoscopy at the second duodenal portion. In all cases, at least two biopsy specimens were obtained. In accordance with our previous studies *(12–14)*, specimens adequate in size were immediately oriented with the aid of a stereomicroscope and subsequently embedded in paraffin. The slides were stained with hematoxylin and eosin and graded by conventional histology as (*a*) normal, (*b*) partial villous atrophy, or (*c*) subtotal/total villous atrophy. In addition, the villous/crypt ratio was evaluated (reference values in our laboratory ≥2.5 for children, ≥3 for adults), and the number of intraepithelial lymphocytes (IELs) per 100 villous epithelial cells was assessed as described by Ferguson and Murray *(15)*; the upper limit of the reference values in our laboratory is 30 IELs/100 epithelial cells.

In all cases, histologic analysis was performed by an examiner unaware of the clinical condition of the patients and of the laboratory test results.

statistical analysis

We followed standard criteria for methodologic studies on the diagnostic accuracy of tests *(16)*. The sensitivities and specificities of the methods examined and their positive and negative predictive values were calculated by standard statistical methods *(17)*. The Fisher exact test was used to compare the different positive and negative predictive values of the three assays. In addition, ROC curves were plotted to show the discriminative ability of the tests. The model plots sensitivity (the proportion of CD patients attributed by the test to the CD group) vs 1 − specificity (the proportion of control patients attributed by the tests to the CD group). The areas under the ROC curves and their 95% confidence intervals were also calculated using the nonparametric method described by Hanley and McNeil *(18)*, developed as a statistical program.

Results

Intestinal histology showed that 24 patients (10 males and 14 females; age range, 18–80 years; median, 30 years) had a partial (7 cases) or total (17 cases) villous atrophy. In these patients, the diagnosis of CD was confirmed by a positive response to the gluten-free diet, which produced a complete disappearance of the symptoms within 2–15 weeks after the beginning of the diet and a normalization of the intestinal histology after 11–14 months (mean, 12.5 months). In these patients. the IEL count in the intestinal mucosa biopsies ranged from 52 to 79 (median, 66) at the time of the first biopsy. No patients were lost during follow-up, and at the time of the second biopsy, all patients showed villous/crypt ratios >3 and the IEL count ranged from 18 to 29 (median, 24). In all cases, gluten challenge caused the reappearance of the symptoms/signs that had initially led to suspicion of CD. The remaining 183 patients (89 males and 94 females; age range, 17–84 years; median, 46 years) included in the study had an intestinal histology characterized by a villous/crypt ratio ≥3 and, consequently, were considered as controls to evaluate the specificity of the diagnostic tests for CD. Table 1 shows the final diagnoses for these patients.

Table 1. Final diagnoses in 183 non-CD patients included in the study (one or more diagnoses possible for each patient).[a]

Diagnosis	No. of cases
Irritable bowel syndrome	70
Esophagitis	45
Peptic erosions/ulcers (gastric or duodenal)	41
Crohn disease	15
Food intolerance/allergy	10
Chronic liver disease	6
Gastric cancer	2
Right colon cancer	2
Collagenous colitis	1
Intestinal bacterial overgrowth syndrome	1
Psoriasis	1

[a] Patients underwent the serologic assays for CD diagnoses and were considered as controls to evaluate the specificities of the assays studied.

None of the patients included in the study showed serum IgA deficiency. Serum EmAs and anti-tTG antibodies, assayed with both the gp-tTG and the h-tTG ELISA, were positive in all 24 CD patients (Table 2). In the control group (non-CD patients), none were positive for serum EmAs, but 15 of 183 (8.2%) were positive for anti-gp-tTG and 6 of 183 (3.3%) were positive for anti-h-tTG (Table 2). In the 15 controls positive for anti-gp-tTG, values ranged between 9% and 24%; in the controls positive by the anti-h-tTG ELISA, values ranged between 8.5% and 28%. These values were in the same range as the values observed in the 24 CD patients with partial or total mucosa atrophy (range of values, 8–31% for gp-tTG and 9–34% for h-tTG). After performing a cumulative analysis of the data from patients and controls, we plotted the ROC curves for anti-h-tTG and anti-gp-tTG; the areas

Table 2. Number of cases positive for serum EmAs, anti-gp-tTG, and anti-h-tTG in 24 CD patients and in 183 non-CD patients (controls).

	Serum EmAs	Serum anti-gp-tTG	Serum anti-h-tTG
CD patients, n	24/24	24/24	24/24
Controls, n	0/183	15/183	6/183
Sensitivity,[a] %	100 (96–100)	100 (96–100)	100 (96–100)
Specificity,[a] %	100 (99–100)	92 (88–96)	97 (92–100)

[a] Values in parentheses are 95% CIs.

Table 3. Positive and negative predictive values (95% CIs) for the anti-EmA assay, the anti-gp-tTG ELISA, and the anti-h-tTG ELISA in our study population.[a]

	EmA assay	Anti-gp-tTG ELISA	Anti-h-tTG ELISA
Positive predictive value, %	100 (96–100)	60 (44–76)	80 (65–95)
Negative predictive value, %	100 (99–100)	100 (99–100)	100 (99–100)

[a] Values were calculated according to the prevalence of 11.6% of CD observed in this study group.

under curves were 0.987 [95% confidence interval (CI), 0.97–1.0] for anti-h-tTG and 0.965 (95% CI, 0.94–0.99) for anti-gp-tTG.

The patients with false-positive anti-tTG ELISA results based on guinea pig antigen included seven with Crohn disease (diagnosis was confirmed by histologic examination of ileal/colon biopsies and positive barium x-ray of ileum examination and/or colonoscopy), three with multiple food intolerance (intolerance to cow's milk and its derivatives, fish, tomato, chocolate, and/or orange, diagnosed by means of an elimination diet that documented the disappearance of the symptoms and a subsequent blind challenge that demonstrated the reappearance of the symptoms), three with chronic hepatitis attributable to a hepatitis virus C infection (with moderate/severe liver histology damage), one patient with biopsy-confirmed collagenous colitis, and one with psoriasis. False-positive results with human tTG antigen all were in the set of those positive in the anti-gp-tTG ELISA: two patients with ileal Crohn disease, two with chronic hepatitis, one with psoriasis, and one with collagenous colitis. Three false-positive results were obtained on fresh sera and three on samples stored at −80 °C. Further examinations performed on these six patients showed that they did not carry the DQ2 or DQ8 HLA haplotypes, which characterize CD patients, and were negative for serum anti-gliadin antibodies.

Because all three assays had a sensitivity of 100%, without any false-negative results, they all had a negative predictive value of 100% (Table 3). In our series (CD prevalence, 11.6%), the positive predictive value was 100% only for the EmA assay. The two anti-tTG assays that we evaluated had lower positive predictive values. The anti-tTG assay based on guinea pig antigen had a positive predictive value of 60%, significantly lower than that of the EmA assay ($P = 0.0002$, Fisher test), whereas the anti-tTG assay based on human recombinant antigen had a positive predictive value of 80%, also significantly lower than that of EmA assay ($P = 0.03$).

Discussion

After Dieterich et al. *(2)* demonstrated that tTG was the main (or the sole) autoantigen recognized by EmAs in CD patients, the use of an ELISA based on tTG was proposed and widely accepted for the diagnostic evaluation of patients with suspected CD *(1, 3, 5, 6, 19–22)*. Although there is general agreement that anti-tTG antibodies have a good diagnostic accuracy in CD diagnosis, it is noteworthy that almost all the studies published to date have investigated anti-tTG in preselected groups of patients with a known diagnosis *(1, 3, 5, 6, 19–23)*; there has been one prospective study on the clinical usefulness of a serum anti-tTG assay in unselected patients with a clinical suspicion of CD, but this included a limited number of patients *(24)*.

In the present study, we considered a wide group of individuals referred to three different centers and followed as outpatients for clinical symptoms and/or signs compatible with a diagnosis of CD. We compared the anti-tTG ELISAs with the anti-EmA assay, which can be considered the "gold standard" in the serology of CD *(25)*. Although the three assays identified all the CD patients, this cannot be considered a generally reproducible result because we had no patients with a serum IgA deficiency, a condition more common in CD than in the general population, which limits the performance of the serologic tests for CD based on IgA antibody determinations.

The positive predictive value of the anti-gp-tTG assay (60%) is too low to warrant subjecting a patient to intestinal biopsy for suspected CD. This relatively low positive predictive value of anti-gp-tTG, however, cannot be considered completely unexpected. In fact, we obtained false-positive results for seven patients with Crohn disease, a condition in which a high prevalence of anti-tTG antibodies has been reported previously *(26)*, and in four patients with intestinal disease characterized by moderate/severe mucosal inflammation (three patients with multiple food intolerance and one patient with biopsy-confirmed collagenous colitis). Three other patients who were false positive for anti-gp-tTG antibodies had chronic hepatitis attributable to a hepatitis virus C infection, a liver disease in which we have previously demonstrated a 14% frequency of false-positive results *(27)*.

All six false positives in the anti-h-tTG assay were also positive in the anti-gp-tTG assay. Although we had no doubts about excluding a CD diagnosis in the two patients with Crohn disease and in the two with chronic liver disease, both collagenous colitis *(28)* and psoriasis *(29)* have been reported to be associated with CD. However, the intestinal biopsies of these two patients, performed at the second portion of the duodenum, did not show alterations of the villi or crypts (ratio of villi to crypts >3), and serum IgG and IgA anti-gliadin antibodies were negative. Moreover, they did not have the classical *HLA DQ2* or *DQ8* alleles, which are typical of CD patients. The low positive predictive values of the anti-tTG assays will be even lower at lower prevalences of CD, such as those commonly reported in studies of consecutive patients with dyspepsia *(30, 31)*.

The false-positive results observed in our study could arise from impurities in the gp-tTG for the ELISA system

based on this antigen, as we have previously suggested in other studies *(9, 27)*. For the false-positive results obtained with the specific recombinant h-tTG in the ELISA system, the hypothesis of protein impurities in the tTG preparation can also be considered, but we do not exclude the possibility that high serum concentrations of anti-tTG antibodies were really present in some "controls". Immunoblot or immunoprecipitation studies with false-positive sera are needed to determine whether the reactive band is really tTG.

In conclusion, the EmA assay has a higher positive predictive value than the anti-tTG assays in CD diagnosis. On this basis, the simpler anti-h-tTG ELISA could be suggested as a first-step examination, with positive results to be confirmed by the EmA assay. We suggest that discordant anti-tTG/EmA results merit further evaluation, e.g., by means of *HLA DQ* determination.

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