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Alimentary Tract

Utilizing both IgA tissue transglutaminase and IgG-deamidated gliadin peptide antibodies offers accurate celiac disease diagnosis without duodenal biopsy

Fabiana Zingone[a,b], Gary L. Norman[c], Edgardo Smecuol[d], Daria Maniero[a], Antonio Carroccio[e], Federico Biagi[f,g], Juan P. Stefanolo[d], Sonia Niveloni[d], Geoffrey Holmes[h], Vincenzo Villanacci[i], Antonella Santonicola[j,k], Julio C. Bai[d,l], Carolina Ciacci[i,k,*]

[a] Department of Surgery, Oncology, Gastroenterology, University of Padua, Padua, Italy
[b] Gastroenterology Unit, Azienda Ospedale Università di Padova, Padua, Italy
[c] Research and Development, Headquarters & Technology Center Autoimmunity, Werfen, San Diego, CA, USA
[d] Small Bowel Section, Dr. C. Bonorino Udaondo Gastroenterology Hospital, Buenos Aires, Argentina
[e] Unit of Internal Medicine, PROMISE Department, Villa Sofia Cervello United Hospitals - University of Palermo, Palermo, Italy
[f] Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy
[g] Gastroenterology Unit of Pavia Institute, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy
[h] Department of Gastroenterology, Royal Derby Hospital, Derby, UK
[i] Institute of Pathology, Spedali Civili, University of Brescia, Brescia, Italy
[j] Department of Medicine, Surgery, Dentistry, Scuola Medica; Salernitana, University of Salerno, Baronissi (SA), Italy
[k] Center for Celiac disease AOU San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy
[l] Research Institute, Universidad del Salvador, Buenos Aires, Argentina

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ABSTRACT

Background: Gastroenterologists still raise concerns about adopting a non-biopsy strategy for diagnosing celiac disease (CeD) in adults.
Aim: To assess the performance of the concurrent detection of two autoantibodies targeting two independent antigens, tissue transglutaminase (tTG) and deamidated gliadin peptides (DGP).
Methods: This prospective, multicenter, binational study collected consecutive patients with a high pretest probability for CeD. Between 2018 and 2020, adults were enrolled at four Italian and one Argentinian center. Serology was also blindly analyzed by a central laboratory (Werfen, San Diego, USA) for tTG IgA and DGP IgG by Aptiva Particle-based multi-analyte technology (PMAT) assays. CeD diagnosis required histological confirmation of Marsh 3 damage.
Results: 181 adult patients with suspected CeD were enrolled (134 with histological diagnosis of CeD and 47 not histologically confirmed as CeD). Patients positive for both tTG IgA and DGP IgG (double positive) were predictive of CeD in 92.5 % of patients at >1x upper limit of normal (ULN). Double positivity for tTG IgA and DGP IgG, both at >10x ULN, had a 100 % positive predictive value for the presence of Marsh 3 histology.
Conclusions: Incorporating DGP IgG alongside tTG IgA in a single-step approach can be considered a valid confirmatory strategy for definitive non-biopsy diagnosis of CeD.

1. Introduction

Over the past 25 years, celiac disease (CeD) diagnosis has predominantly relied on detecting serum antibodies such as IgA anti-endomysial (EMA) and IgA anti-tissue transglutaminase (tTG) in conjunction with intestinal biopsy, which was long considered the gold standard [1]. Introducing these serology tests has led to a notable increase in the detection and diagnosis of CeD over this period [2]. Recently, there has been renewed interest in anti-gliadin assays targeting synthetic deamidated gliadin-related peptides (DGP). Studies have demonstrated the high sensitivity and specificity of DGP IgG for CeD diagnosis, particularly in patients

* Corresponding author at: Celiac Center, Department of Medicine, Surgery, Dentistry, Scuola Medica Salernitana, Salerno, Italy.
E-mail address: cciacci@unisa.it (C. Ciacci).

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with IgA deficiency [3]. Therefore, we can utilize several highly sensitive tests for CeD diagnosis, the tTG IgA and EMA IgA, which both target the tissue transglutaminase, and the anti-DGP antibodies, which target the gluten itself, precisely the immunogenic fraction of gliadin [4]. EMA IgA is an extremely precise test in an expert setting; however, it is operator-dependent and costly. EMA IgG does not have the same sensitivity and specificity. TTG IgG has also been shown to have low sensitivity. Several studies have demonstrated that DGP IgG has specificity and sensitivity comparable to that of TTG IgA in predicting mucosal damage [4].

Despite accumulating evidence over the past three decades [5], it was only in 2012 that the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) [6] proposed a two-step protocol for non-biopsy serological CeD diagnosis in children, resulting in increased specificity and minimal false positives. Children showing concentrations of tTG IgA $\geq$ 10x the upper limit of normal (ULN), subsequent positivity of EMA in the presence of predisposing HLA and classic symptoms, could safely be diagnosed with CeD without duodenal biopsy. The two-step serology testing increased the specificity of the protocol, minimizing false-positive results and inappropriate diagnosis of CeD. In 2020, updated ESPGHAN guidelines further simplified the two-step diagnosis, removing the presence of symptoms and the HLA testing as requirements for omitting the biopsy in children [7].

While widely accepted in Europe, extending this protocol to adult patients has faced resistance [5] due to concerns that without biopsy other diseases or complications might be missed, despite evidence suggesting otherwise [8,9].

The present study aimed to evaluate the positive predictive value (PPV) of combining tTG IgA and DGP IgG for predicting CeD in adults. The study tested the hypothesis that combining tTG IgA and DGP IgG may provide augmented evidence for relying solely on serology to diagnose CeD in a high-risk population.

2. Methods

Consecutive patients attending CeD clinics in five centers (four from Italy: Padua, Palermo, Salerno, and Pavia) and one from Argentina (Buenos Aires) for suspicion of CeD gave their informed consent to participate in a prospective study. The cases and controls reported here are part of a *post hoc* novel data analysis from the recently published *Bi.A.CeD study* [10].

In the current study, we analyzed novel data obtained by central laboratory testing from the five centers mentioned above. Individuals with high suspicion of CeD were recruited from February 2018 to December 2020 if they were >18 years old and signed a written consent. The suspicion of CeD was defined in the *Bi.A.CeD study* based on the report of at least one of the following findings: weight loss, gastrointestinal symptoms (diarrhea, constipation, vomiting, irritable bowel syndrome-like symptoms, dyspepsia, bloating), anemia, vitamin deficiency, fatigue, infertility, osteoporosis, depression, neurological problems, hypertransaminasemia, Hashimoto's thyroiditis, type I diabetes mellitus, autoimmune liver disease or other autoimmune disorder, or family history of CeD. Exclusion criteria were IgA deficiency, previous CeD diagnosis, treatment with gluten-restricted diet, diagnosis of cancer, the lack of local data on serum tTG IgA, the lack or the withdrawal of the written consent, unreadable duodenal histology, or duodenal villous atrophy with negative tTG IgA and negative HLA-DQ2/DQ8.

2.1. Endoscopic procedure and biopsies

Upper gastrointestinal endoscopy to obtain duodenal biopsies was performed at the local centers. Specifically, two samples were taken from the duodenal bulb, and four samples were taken from the second portion of the duodenum. The mucosal samples were then fixed in formalin and subsequently transferred to the local pathology department for further processing and diagnosis [10].

2.2. Diagnosis of celiac disease for categorization of patients and controls

In each local institution, the diagnosis of CeD was established using conventional histologic criteria and CeD-specific tTG IgA serology [11]. For the purposes of this study, we required histologic evidence of damage consistent with a Marsh 3 lesion [12] or grade B enteropathy according to the Corazza/Villanacci [13] categorization. Patients with Marsh 1 or Marsh 2 lesions or grade A enteropathy were not considered to have a diagnosis of CeD in this study and considered as controls for all assay performance calculations.

2.3. Definition of patients with discrepancies between histology and local or central serology

Patients with positive serum tTG IgA, but who did not show duodenal villous atrophy, as well as those who tested negative for serum tTG IgA, but exhibited duodenal villous atrophy, were categorized as discordant cases based on the local test results. To ensure an unbiased assessment, pictures of the duodenal histology slides from the discordant cases were re-evaluated by a central reference pathologist (VV) who was blinded to the patient's clinical history and test results. However, the non-discordant cases did not undergo re-evaluation by the central reference pathologist as they were considered consistent with the initial diagnoses made by the local institutions. For the aim of this study, we only used histological results after central revaluation.

2.4. Clinical categorization of participating patients

In terms of clinical presentation, the patients were divided into three groups [14]. The first group consisted of patients with a classical presentation of CeD, characterized by symptoms such as anemia, weight loss, or diarrhea, which are considered indicative of malabsorption. The second group included patients with a non-classical presentation, exhibiting symptoms other than those typically associated with classical presentation (fatigue, fertility issues, for example). Lastly, there were asymptomatic patients who were suspected to have CeD based solely on their family history of the condition or the presence of associated autoimmune diseases.

2.5. Serology testing at the central laboratory

Two frozen serum aliquots were prepared by the local center's laboratory from a venous blood sample. These aliquots were then sent to Werfen (San Diego, CA, USA). The blind central laboratory testing involved the measurement of serum tTG IgA and DGP IgG by particle-based multi-analyte technology (PMAT) using the FDA-cleared Aptiva instrument (Werfen, San Diego, CA, USA, FDA K193604). Only central laboratory tests were evaluated in this study.

2.6. Ethics, processing of data, and statistics

The study was approved by the Ethical Committee of the University of Salerno (Approval Number 21, February 15, 2018), as well as by the local Ethical Committees of all participating centers. For the present study, the analysis used data exclusively from the five centers listed above, as indicated (Fig. 1). Notably, data on the central IgG DPG testing presented here has not been used in previous analyses. The teams of the local centers collected and recorded

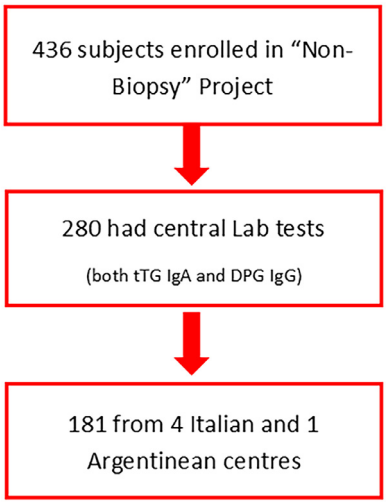

Fig. 1. Flowchart of patients included in the study.

data online, ensuring anonymity by using a unique code for each patient.

The data collection process included key variables such as gender, age, anthropometry, local serum antibody concentrations, and the results of the duodenal histology. Serum tTG IgA and DGP IgG concentrations were expressed as multiples of the assay-specific ULN. Positive serology of a given test was defined as a value above the ULN, while negative serology was defined as a value below that. The reliability of serum tests for the prediction of duodenal Marsh 3 damage was evaluated by analyzing the following: true positive cases, false positive cases, true negative cases, and false negative cases for different cut-offs (1xULN, 3xULN, 5xULN, and 10xULN). Thus, we derived sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). We also estimated the area under the receiver operating characteristic curve (ROC) for each test. All analyses were done after the central re-evaluation of serology. Categorical variables were reported as counts or % prevalence, numerical variables as mean ± standard deviation (SD). Comparisons among groups were done using chi-square analyses for categorical variables and ANOVA *t*-test for numerical variables. Median tTG IgA and DGP IgG values of patients by Marsh scores were plotted and compared by *t*-test (Mann Whitney) or 1-way ANOVA (Krustal-Wallis) using GraphPad Prism 5, version 5.0 (San Diego, CA) or DataLab (Werfen, San Diego, CA). All the authors had access to the study data and approved the final manuscript.

3. Results

Among the 436 subjects composing the study population, 280 had a central laboratory analysis (both tTG IgA and DGP IgG), and of these, 181 were from the five centers taking part in this study (Fig. 1). As reported in Table 1, our study population (mean age: 38.7 ± 13.7 years; 70.7 % females) was composed of 134 patients with confirmed Marsh 3 histological diagnosis of CeD and 47 suspected but, not confirmed as CeD (non-confirmed CeD). No differences in age, gender and symptoms were reported ($p > 0.05$) between the two groups. All CeD patients had a Marsh 3, while 38 individuals not confirmed as CeD had Marsh 0 and 9 individuals Marsh 1 ($p < 0.0001$).

Table 2 presents the sensitivity, specificity, and PPV for each test at different cut-offs (1x, 3x, 5x, and 10x ULN). As expected, increasing the cut-off value resulted in a progressive reduction in sensitivity, but an increase in specificity and higher PPV. Higher cut-offs improved the ability to correctly identify true positive cases, while minimizing false positive results. The central laboratory testing showed that 98.5 % (132/134) of the confirmed (Marsh 3 required) CeD patients had positive tTG IgA tests (>1xULN), indicating high sensitivity. Twenty-three CeD patients scoring Marsh 3 at histology had positive tTG IgA with a concentration <10x ULN, but six of these (6/23, 26.1 %) had strong positive DGP IgG values at >10x ULN. The IgG DGP test was positive at 1xULN in 93.3 % (125 out of 134) of the CeD patients and 12.8 % (6 out of 47) of the non-confirmed CeD. Supplementary Figures 1 and 2 show the ROC for tTG IgA and DGP IgG for CeD (Marsh 3).

The analyses of patients with two positive tests showed that double positive tests at >1xULN cut-off were predictive of Marsh 3 histology in 92.5 % (124/134). When using the >10x ULN cut-off, 60 of the 134 patients (44.7 %) had double positive results and all had Marsh 3 histology, giving the combination assays a PPV of 100 % (Table 1).

Compared to the diagnostic strategy of using only positive tTG IgA as an indicator of CeD, the double positive test strategy identified a similar number of CeD patients across all cut-off values examined (1x, 3x, and 5x ULN). However, at the ≥10x ULN cut-off, the double positive testing approach demonstrated an absolute PPV of 100 %, indicating that all patients identified as positive truly had CeD.

When we considered the combination of the two tests (tTG IgA and DGP IgG), we found high accuracy for higher cut-offs independently of the clinical presentation (Table 3).

3.1. Potential CeD patients

Among the non-confirmed CeD (Marsh<3), only 4.3 % (2 out of 47) had positive tTG IgA tests, indicating high specificity (Fig. 2). Regarding the 2 non-confirmed CeD patients, one had >10xULN of tTG IgA, 5xULN IgG DGP, and had a family history of CeD. The second non-confirmed CeD was ~6xULN for tTG IgA and10xULN IgG DGP. These patients are considered "potential CeD" as they had positive serology and negative histology (Fig. 2).

3.2. Seronegative CeD patients

One patient with Marsh 3 enteropathy was only positive by DPG IgG. One CeD patient (Marsh 3) had double negative serology. This patient was considered a truly seronegative CeD case, as it was confirmed as CeD based on the response to the gluten-free diet (GFD) and the exclusion of IgA deficiency as established by the protocol.

3.3. Serology trend by intestinal abnormalities

Levels of tTG IgA varied with levels of intestinal abnormality and are graphically illustrated in Figure S3. As expected, mean levels of tTG IgA were very low in patients with Marsh 0 or 1 and about 50x higher in patients with Marsh 3 histology. There was a significant trend of increasing median levels of tTG IgA from Marsh 0 to Marsh 3c (Figure S3). Similar to tTG IgA, DGP IgG levels increased with increasing histological abnormality from Marsh 0 to 3c (Supplementary Figure 4).

4. Discussion

The results of the present study indicate that the combined serology testing for two different gluten-related antigens (tTG IgA + DGP IgG) is highly sensitive in predicting mucosal damage and allows a safe CeD diagnosis in adults. The combination of tTG IgA and DGP IgG at 1xULN has a 98.3 % PPV and reaches a PPV of 100 % when both tests are > 10x UNL. The results indicate that about 45 % of adults in our series could have reasonably avoided

Table 1
Demographic and some clinical characteristics of patients and controls enrolled in the study.

Characteristic	All subjects	Celiac disease (M3)	Non-confirmed celiac disease (M0, M1)
Overall number of cases (%)	181	134	47
Female sex. Number (%)	128 (70.7)	92 (68.7)	36 (76.6)
Mean age at entry, years Mean (SD)	38.7 ± 13.7	39.8 ± 13.5	36.1 ± 14.1
Mean body mass index. Kg/m2 Mean (SD)	22.9 ± 3.8	23.2 ± 4.1	22.0 ± 2.9
Clinical presentation N. of cases (%)			
Classical	86 (47.5)	58 (43.3)	28 (59.5)
Non-classical	78 (43.1)	62 (46.3)	16 (34.1)
Asymptomatic	17 (9.4)	14 (10.4)	3 (6.4)
Mucosal histology. N of cases (%)			
Marsh 0	38 (21)	–	38 (80.9)
Marsh 1	9 (5.0)	–	9 (19.1)
Marsh 2	–	–	–
Marsh 3	134 (74)	134 (100)	–

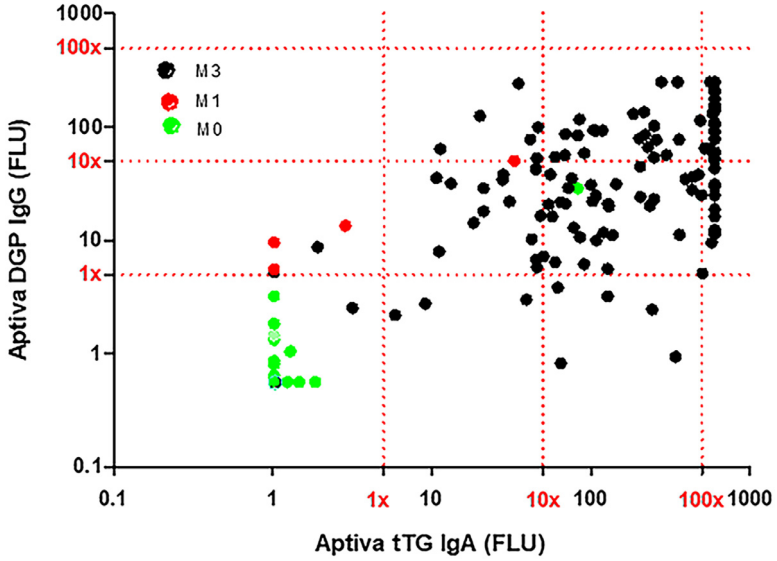

Fig. 2. Logarithmic representation of the concurrent determination of tTG IgA and DGP IgG concentrations in biopsy-confirmed (Marsh 3) celiac disease and non-confirmed celiac disease (M0 & M1, high pre-test probability) patients. Green Dots: Marsh 0, Red Dots: Marsh 1, Black Dots: Marsh 3. Dotted lines indicate concentrations above the upper limit of normal (xULN) for each antibody test (1x, 10x, and 100xULN).

duodenal biopsy with strong confidence in the presence of mucosal atrophy.

The results could encourage those clinicians who remain uncomfortable with a non-biopsy strategy for diagnosing adult CeD based on just one test to use the double-test strategy. The present findings align with previous literature that explored the omission of biopsy for the diagnosis of CeD [15]. In particular, our multinational study showed that tTG IgA at >10x ULN correctly predicted villous atrophy in 97.5 % of the patients [10]. The results of the present study showed that using the concurrent determination of tTG IgA and DGP IgG, the accuracy became absolute in our cohort. Consequently, concurrent testing of both tTG IgA and DGP IgG, instead of sole tTG IgA testing, may guide and accelerate treatment decisions with less diagnostic delay, a problem frequently reported in literature [16,17].

The recent systematic review and meta-analysis reported above, supported the option of non-biopsy diagnosis of celiac disease in patients with moderate to high pre-test probability [15]. The accompanying editorial confirms that such a strategy can be an acceptable choice for patients with high pretest probability [18].

The present data provides a novel and practical application of high-quality serology for diagnosis of CeD. The observation that we can confidently use a combination of two tests to diagnose CeD in high-risk individuals should be seen as an opportunity to ease the economic and the emotional burden of the diagnosis and potentially importantly reduce the delay in diagnosis resulting from some patient's reluctance to undergo the biopsy procedure.

Since the first study by Valdimarsson et al. [19] exploring the non-biopsy diagnosis of CeD, the primary concern with the omission of the biopsy in CeD diagnosis has been the possibility of "false-positive" results (i.e. patients with positive serology and negative histology, thus potential CeD, leading to the imposition of a lifelong gluten-free diet and its impact on an individual's, as well as their family's quality of life. In our study, 2 out of 181 participants (3.6 %) had positive serology and negative histology and thus were considered potential CeD. The destiny of the patient classified as potential CeD is still a matter of debate; in this case, both patients had gastrointestinal symptoms that reverted by adopting GFD. Similarly, a previous study from Penny reported that 5/740 potential CeD patients were all symptomatic, and the tTG titers decreased after GFD [20]. Moreover, a very recent study showed that in CeD patients with mucosal damage limited to the duodenal bulb, tTG IgA levels were lower compared to those with conventional CeD (1.8x ULN) [21], further potential CeD is rarely found at high levels of tTG IgA.

Another concern with adopting a non-biopsy strategy is possibly missing another disease that could be discovered only by endoscopy. Several studies have demonstrated that endoscopy

Table 2
Performance (Sensitivity [Sens], Specificity [Spec] and positive predictive value [PPV]) of individual tests and double positive tests by the Aptiva assay for detecting confirmed Marsh 3 damage calculated at different cut-offs (xUNL: times above upper normal limit).

	tTG IgA			DGP IgG			tTG IgA + DGP IgG		
	Sens	Spec	PPV	Sens	Spec	PPV	Sens	Spec	PPV
>1 x UNL	98.5 (96.7–100)	95.7 (92.8–98.7)	98.5 (96.7–100)	93.3 (89.6–96.9)	87.2 (82.4–92.1)	95.4 (92.4–98.5)	92.5 (88.7–96.4)	95.7 (92.8–98.7)	98.4 (96.6–100)
>3 x UNL	94.0 (90.6–97.5)	95.7 (92.8–98.7)	98.4 (96.6–100)	77.6 (71.5–83.7)	95.7 (92.8–98.7)	98.1 (96.1–100)	75.4 (69.1–81.6)	95.7 (92.8–98.7)	98.1 (96.0–100)
>5x UNL	91.0 (86.9–95.2)	95.7 (92.8–98.7)	98.4 (96.5–100)	64.2 (57.2–71.1)	95.7 (92.8–98.7)	97.7 (95.6–99.9)	60.4 (53.3–67.6)	95.7 (92.8–99.7)	97.6 (95.4–99.8)
>10 x UNL	81.3 (75.7–87.0)	97.9 (95.8–100)	99.1 (97.7–100)	48.2 (42.0–56.5)	97.9 (95.8–100)	98.5 (96.7–100)	44.8 (37.5–52.0)	100 (100–100)	100 (100–100)

Table 3
Performance (Sensitivity [Sens], Specificity [Spec] and positive predictive value [PPV]) of double positive tests by the Aptiva assay for detecting confirmed Marsh 3 damage calculated at different cut-offs (xUNL: times above upper normal limit), according to clinical presentation.

	Classical Presentation ($N = 86$)			Non classical Presentation ($N = 78$)			Asymptomatic ($N = 17$)		
	tTG IgA + DGP IgG			tTG IgA + DGP IgG			tTG IgA + DGP IgG		
	Sens	Spec	PPV	Sens	Spec	PPV	Sens	Spec	PPV
>1 x UNL	94.8 (90.1–99.5)	100 (100–100)	100 (100–100)	88.7 (81.7–95.7)	87.5 (80.1–94.8)	96.4 (92.4–100)	100 (100–100)	100 (100–100))	100 (100–100))
>3 x UNL	77.6 (68.8–86.4)	100 (100–100)	100 (100–100)	74.2 (64.5–83.9)	87.5 (80.1–94.8)	95.8 (91.4–100)	71.4 (49.9–92.9)	100 (100–100)	100 (100–100)
>5x UNL	69 (59.2–78.7)	100 (100–100)	100 (100–100)	58.0 (47.1–69.0)	87.5 (80.1–94.8)	94.7 (89.8–99.7)	35.7 (12.9–58.5)	100 (100–100)	100 (100–100)
>10x UNL	47.5 (36.9–58.0)	100 (100–100)	100 (100–100)	48.4 (37.3–59.5)	100 (100–100))	100 (100–100)	21.4 (1.9–40.9)	100 (100–100)	100 (100–100)

findings other than CeD are mostly limited to benign diseases such as gastroesophageal reflux, peptic diseases, lymphocytic and autoimmune gastritis but not serious CeD complications or other possible associated cancers [8-10,22,23]. Recently a real-world Scottish analysis reported that a no-biopsy strategy using a cut-off of TGA-IgA $\geq$10 $\times$ ULN is safe to diagnose CD and that no important pathology would be missed [24].

The present study has several strengths that contribute to the reliability and robustness of the findings. First, the study design was prospective, allowing for data collection in a systematic and controlled manner. This design enhances the quality of the evidence generated and provides a strong basis for drawing conclusive information. Furthermore, the serological results analyzed in the study were obtained from a central laboratory, ensuring standardized and blinded testing procedures. This approach minimizes potential biases and increases the objectivity of the results. A relevant aspect of our study is the observation of different performances when comparing tTG IgA vs. IgG DGP tests, particularly at intermediate cut-off values. It should be noted that the population examined in our study had a high pre-test probability of CeD and all had histological evaluation. The present study's findings align with earlier publications that prospectively assessed the concurrent detection of the same tests in children and adults [25–27]. Moreover, the finding of 100 % PPV at >10xULN found in our study can help overcome the reluctance of some clinicians to abandon the biopsy as the required final step for CeD diagnosis at any patients' age. Infact, the dual target—TTG IgA as an autoantigen against tissue transglutaminase and DGP IgG as an antibody against gluten—would strengthen the dual testing approach. A similar finding was reported by a recently published Italian study, however in this case the authors used the combination of two IgA antibodies [28]. The primary limitation of our prospective study relates to the study design, which focused on patients with a high pre-test probability, collected at tertiary centers specializing in CeD diagnosis. This approach introduces some selection bias into the study cohort. Additionally, our sub-analysis has a limited sample size, and patients with IgA deficiency were excluded. Therefore, we cannot, particularly for this latter point, assess the predictive power of serology alone in IgA-deficient patients. Data from primary care settings are still lacking. However, to our knowledge, both our previous study [10] and the present one are the first prospective multinational studies to evaluate the sensitivity and specificity of TTG IgA and DGP IgG in adult patients with suspected CeD. Future studies should be conducted in primary care settings. Regarding concerns about lower adherence in those diagnosed solely by biopsy, this can only be assessed through a prospective study involving patients diagnosed with CeD based solely on serology. Lastly, the present data are based on tests performed in a central laboratory, so variability across different antibody kits was not an issue. In our previous multinational study, various kits were used, but we demonstrated that this did not affect the significance of the results.

In conclusion, our study demonstrated high sensitivity and specificity of the simultaneous assessment of tTG IgA and IgG DGP in predicting CeD in individuals with a high pre-test probability. We hypothesize that concurrently detecting tTG IgA and DGP IgG may be particularly useful in non-expert settings, where the clinician could rely on the 100 % prediction of Marsh 3 intestinal damage in the presence of dual positivity at >10x ULN.

Contributors

FZ, GLN, JCB and CC equally contributed to the conceptualization of the study, analysis of data, writing the manuscript. All authors critically read and intellectually contributed to the manuscript and approved the submitted version.

Conflict of interest

FZ served as a speaker for Werfen and a consultant for Takeda. CC served as a speaker for Werfen and Takeda. GLN was employee of Werfen at time of study. JCB was consultant for Takeda. All other authors declared no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.10.010.

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