

ORIGINAL PAPERS

Efficacy of a point-of-care test based on deamidated gliadin peptides for the detection of celiac disease in pediatric patients

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ABSTRACT

Objective: The objective of the study was to assess the effectiveness of a point-of-care test (POCT) based on deamidated gliadin peptides (DGP) compared to the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) criteria diagnosis in the early detection of celiac disease (CD) in pediatric patients.

Methods: One hundred children (≤ 18 years) with suspected CD were selected, including siblings of celiac children that underwent gastroscopy for other gastrointestinal conditions. Patients with severe disease, following a gluten-free diet (GFD), with gastrointestinal bleeding, coagulopathy and infections in the last month were excluded. All children were evaluated with a POCT that detects immunoglobulin A (IgA) and immunoglobulin G (IgG) antibodies to DGP and total IgA. The POCT results were compared to CD diagnosis according to current ESPGHAN criteria. This involved the detection of IgA tissue transglutaminase (tTG) antibodies, the results of an intestinal biopsy and genetic testing.

Results: The prevalence of CD found in the present study was 48% (95% confidence interval in parenthesis 37.9-58.2%). The results of the POCT were concordant with the CD diagnosis made according to ESPGHAN criteria: 95.8% (85.7-99.4%) sensitivity, 98.1% (89.7-99.7%) specificity, 97.9% (88.7-99.6%) positive predictive value and 96.2% (87.0-99.4%) negative predictive value. Positive and negative likelihood ratios were 49.8 (7.2-347.5) and 0.04 (0.01-0.17), respectively. The POCT showed a 100% diagnostic accuracy in children younger than ten years of age. In total, three discordant results were found.

Conclusion: Due to the high diagnostic accuracy in the pediatric population, the POCT can be considered as an effective tool for the early diagnosis of CD, especially in patients younger than ten years of age.

Key words: Celiac disease. Deamidated gliadin peptides. Point-of-care diagnostic test and children.

INTRODUCTION

Recently, celiac disease (CD) has markedly changed due to considerable advances in the knowledge of its patho-

genic and diagnostic characteristics (1-3). CD is now an established immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals. The disease is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes and enteropathy (4,5).

CD is a chronic, multi-organ disease in which small intestinal mucosal damage may lead to malabsorption of nutrients. The only available treatment is a lifelong strict adherence to GFD. The disease may present at any age with a large variety of symptoms and signs (6,7). Problems arising from poor absorption can occur in untreated CD, leading to complications ranging from iron deficiency to osteoporosis, infertility and/or cancer. In this sense, early diagnosis is essential to avoid complications.

The prevalence of CD is 1 to 3% in the general population and approximately 10% among first-degree family members of patients with CD (8). However, only approximately 0.2% is clinically diagnosed (9,10). In Spain, the open access for children to general pediatric care, the wide access of physicians to serologic testing and national-level plans for the early detection of CD (11) are factors that could contribute to the observed increase in CD diagnosis.

Current incidence levels of CD are higher than in previous decades due to advances in the understanding of the disease and an increased use of serological techniques. The techniques of serological markers performed are becoming increasingly sensitive and specific, enabling more a precise diagnosis (2). Although intestinal biopsy is still the diagnostic gold standard, the relevance of serology has recently increased (12). IgA antibodies against tissue transglutaminase (tTG) and endomysium (EmA) are the best markers for CD (4). The current diagnostic algorithm includes initial serological tests, a genetic susceptibility study and an intestinal biopsy. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) periodically updates the recommendations

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and clinical guidelines according to the state of the art technical methods and scientific knowledge. The latest ESPGHAN guidelines published in 2012 state that histological assessment may be omitted in symptomatic patients who have high IgA-tTG levels (more than tenfold above the cut-off, > 10 ULN), verified by EmA positivity, and are HLA-DQ2 and/or HLA-DQ8 heterodimer positive (4). However, in some cases intestinal biopsy is still considered as the gold standard for the diagnosis of CD.

Deamidated gliadin peptides (DGP) are the most recent family of biomarkers used for the diagnosis of CD (13-19). Gliadin is the antigen that triggers the autoimmune reaction of CD and tTG enzymatically deamidates gliadin peptides. This modification of gliadin peptides strengthens the binding to HLA-DQ2/DQ8 receptors and enhances recognition by T lymphocytes derived from the intestine (20). Therefore, DGPs are highly specific to the immune reaction involved in the mechanism of CD (21). In children, the test with anti-DGP antibodies had a greater diagnostic precision than EmA to distinguish CD patients from controls. Moreover, compared with the currently used anti-tTG antibody assays, the DGP-based ELISA test has shown a similar diagnostic precision (22).

The use of POC testing is an alternative to standard laboratory assays and is an approach which offers fast results and is minimally invasive. In children, a DGP-based POCT showed results which were highly concordant with laboratory tTG testing (23,24), including IgA deficient patients (25). In patients with CD-related symptoms of a wide range of ages (1.8-79.2 years old), the POCT accuracy, sensitivity and specificity was high, especially when only considering the patient subgroup where CD was newly diagnosed (26). The same POCT performed marginally better than a laboratory IgA anti-tTG assay in determining compliance to GFD in patients with CD (27). However, not all POCTs are as accurate as conventional laboratory serology, as an IgA tTG-based POCT showed a lower performance than laboratory tTG and EmA tests (28). Therefore, the objective of the present study was to assess the performance of the DGP-based POCT in the early detection of CD in pediatric patients according to the current ESPGHAN criteria.

METHODS

One hundred children under 18 years of age were recruited from the Gastroenterology and Nutrition Department of the Hospital Infantil La Paz in Madrid (Spain). This centre serves a population of approximately 150,000 children/year. Between February 2013 and March 2014, children who presented either with symptoms indicative of CD or with a CD risk factor (siblings diagnosed with CD and/or associated diseases) were invited to participate in the study. Exclusion criteria were: following a GFD, an infection in the last 30 days, coagulopathy (INR > 1.3 or platelets < 80) and/or active gastrointestinal bleeding observed during the examination. None of the patients received a CD diagnosis prior to this study and all were on a gluten-containing diet at the time of the laboratory serology analyses and POC testing.

Serum samples were drawn from all study participants and evaluated in the Immunology Laboratory of the Hospital Universitario La Paz in Madrid. Standard serological testing using IgA anti-tTG ELISA (Celikey; Phadia, anti-gliadin IgG and IgA gliadin (AGA) (EliA Celikey, Phadia) and total serum IgA by nephelometry (BNII system; Siemens) was performed for all participants. IgG anti-tTG immunoassays (Celikey, Phadia) were performed systematically in patients with total IgA deficiency (total IgA levels < 0.07 g/l) and EmA (EmA IgA, detected by indirect immunofluorescence [IFL] on human umbilical cord as substrate) were performed in patients under two years of age. A genetic HLA test was performed for patients who had an IgA anti-tTG ELISA higher than 10 AU/I or a previous diagnosis of CD in parents or relatives. These genetic tests (HLA test kit INNO-LiPA HLA-DQA1 and INNO-LiPA HLA-DQB1, Fujirebio, Europe) were performed by the Institute for Medical and Molecular Genetics (INGEMM) of the Hospital La Paz in Madrid. Patients who did require a biopsy according to current ESPGHAN guidelines underwent gastroscopy. Duodenal biopsies were performed by the pediatric gastroenterologist by upper gastrointestinal endoscopy according to the standard technique (4). Biopsies were taken from the second part of the duodenum in all patients. A minimum of four biopsies was sampled from the bulb up to the distal duodenum. The mucosal biopsy sections were analyzed by an experienced histopathologist to assess the pathologic features of CD. This included villous atrophy, crypt hyperplasia, chronic inflammation in the lamina propria and increased intraepithelial lymphocytes. All biopsies were interpreted following the modified Oberhuber-Marsh classification (29). All duodenal biopsy samples were processed according to the usual practice of the Pediatric Gastroenterology Service and interpreted by the Pathological Anatomy Service.

A point-of-care test (POCT) commercially known as Simtomax[®] (Augurix SA, Monthey, Switzerland) was performed in all patients. Simtomax[®] simultaneously detects both IgA and IgG antibodies against DGP as well as total IgA. In case of IgA deficiency, CD diagnosis can be made based on IgG anti-DGP antibodies using the POCT. For this particular POCT, a small amount (25 µl) of whole blood was taken in parallel with the biopsy sample. This procedure was performed at the time of CD diagnosis in patients that did not require an intestinal biopsy, which was before starting a GFD. POCT was performed following the manufacturer's instructions and results were visually read after ten minutes. Results were interpreted according to the appearance of three lines (A, B and the control line [CT]) (Fig. 1). POCT results were judged to be reliable when the control line was visible. The absence of a B line indicated that the patient was IgA deficient and a CD diagnosis was made when the A line was visually detectable.

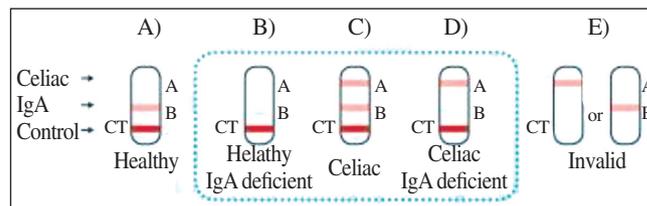


Fig. 1. Result of the interpretation of Simtomax[®]. The possible outcomes for the interpretation of the test were: celiac negative with normal IgA (A); celiac negative with IgA deficiency (B); celiac positive with normal IgA (C); celiac positive with IgA deficiency (D); and invalid test (E).

In this study, CD diagnosis was made following the criteria proposed by the current ESPGHAN guidelines (4), without considering the POCT results. Patients with a confirmed suspicion of CD underwent medical and nutritional monitoring at the Pediatric Gastroenterology Service in the same hospital.

Statistical analyses were performed using the SPSS software version 15.0 (IBM, Armonk, NY). The performance of the POCT Simtomax[®] was evaluated by comparing Simtomax[®] results to CD diagnosis according to ESPGHAN criteria, via the calculation of sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios including 95% confidence intervals. The Biostatistics Unit from the Hospital Universitario La Paz aided in the statistical analyses and the study was approved by the Ethics Committee of the Hospital.

RESULTS

In total, 100 children (49 girls and 51 boys) were included in the study. Age distribution was as follows: 18 were younger than two years of age (16 ± 5 months), 52 were between two and ten years of age (72 ± 27 months), and 30 were older than ten years of age (150 ± 24 months). All patients were referred to the Pediatric Gastroenterology and Nutrition Service due to gastrointestinal symptoms, including diarrhea, nausea and vomiting, poor appetite, cramping, distension and/or abdominal pain. Ten patients had first degree relatives diagnosed with CD and six of them were siblings of celiac patients. Four children presented autoimmune associated diseases (one, type I diabetes; two, thyroiditis; and one, hepatitis). Forty-eight patients were newly diagnosed with CD based on ESPGHAN criteria (4) resulting in a CD prevalence of 48% in the cohort.

Forty-seven patients tested positive for IgA-tTG (> 10 AU/I). All of them were further investigated based on ESPGHAN guidelines. One of the patients (female, ten years of age) with an IgA-tTG value above the cut-off (28 AU/I) showed no villous damage on intestinal biopsy, was CD negative according to the POCT and did not meet ESPGHAN criteria to make a CD diagnosis.

Of the 47 IgA-tTG positive patients, 15 fulfilled the ESPGHAN criteria for biopsy avoidance (4), with high IgA-tTG antibody titers (> 100 AU/I) exceeding ten-times the upper normal limit (> 10 AU/I), genetic results compatible with CD and positive EmA. These 15 patients (eleven younger than two years of age and four between two and ten years of age) with newly diagnosed CD were all correctly identified using the POCT.

One of the IgA-tTG positive patients had a new diagnosis of the CD-associated autoimmune disease diabetes mellitus type 1 at the time when CD was being investigated. The patient was male, seven years old, presented with elevated IgA-tTG levels (71 AU/I), EmA positive, showed villous atrophy as well as genetic compatibility with CD (DQA1*0201, DQB1*0202; DQA1*0501, DQB1*0201) and displayed symptoms indicative of CD. The POCT for this patient was CD positive, compatible with the diagnosis based on ESPGHAN criteria (4).

Fifty-three patients tested negative for IgA-tTG (< 10 AU/I). Two of them were considered to be CD positive according to ESPGHAN criteria (4). One newly diagnosed patient was younger than two years of age (15 months) and had a low IgA-tTG antibody titer (0.3 AU/I) below the cut-off value. He had a normal total IgA value (0.52 g/l), EmA negative and had an IgA anti-gliadin titer of 44 AU/I. In addition, he had a genotype compatible with CD (DRB1*03,DQB*0201; DRB1*03,DQB*0201) and presented with Marsh type 3b on intestinal biopsy. This patient was correctly identified as CD positive by the POCT. The other patient newly diagnosed with CD based on the ESPGHAN criteria had an IgA deficiency (< 0.07 g/l), thus IgA-tTG could not be detected. The IgG-tTG antibody titer was intermediate at 50 AU/I. The genetic results (DQ2/DQ8) together with the presence of villous atrophy (Marsh 3c) further supported the CD diagnosis. This was the only patient in the study cohort presenting with isolated IgA deficiency (< 0.07 g/l). IgA deficiency was correctly identified by POCT testing. However, the POCT was CD negative for this patient and was considered to be a false negative result, as later discussed in the article.

Of the 53 patients who tested negative for IgA-tTG (< 10 AU/I), 28 underwent intestinal endoscopy and a biopsy for other medical reasons (gastrointestinal symptoms compatible with a suspicion of CD or abdominal pain). One patient had villous atrophy (Marsh 3a); however, an immune genotype study ruled out the possibility of CD. The POCT was negative in this patient, in agreement with the clinical diagnosis made. The remaining patients who underwent intestinal endoscopy did not show villous atrophy upon intestinal biopsy and the POCT did correctly identify all of them as CD negative.

In total, 57 patients had a genetic background compatible with CD and the 48 newly diagnosed CD patients presented either with HLA-DQ2 and/or DQ8. Among these 48 patients, 33 underwent intestinal biopsy and lesions were found in all of them according to the Oberhuber-Marsh (29) classification system: type 2 (two cases), type 3a (four cases), type 3b (13 cases) and type 3c (14 cases).

Forty-seven patients were IgA-tTG positive and there was one false positive and two false negatives with IgA-tTG testing. One false negative was IgA deficient and was correctly picked up by IgG-tTG testing. Although no invalid POCT results were reported, six POC tests were repeated for confirmation. The second result confirmed the first in all cases. In total, the POCT Simtomax[®] correctly identified 46 CD patients, including the one patient with newly diagnosed diabetes mellitus type 1. The test also excluded CD correctly in 51 patients, thus achieving a diagnostic accuracy of 97% compared to CD diagnosis based on ESPGHAN criteria (Table 1). In this study, the sensitivity and specificity for the POCT were 95.8% (85.7-99.4%) and 98.1% (89.7-99.7%), respectively. Positive and negative predictive values were 97.9% (88.7-99.6%) and 96.2% (87.0-99.4) respectively. A likelihood ratio (LR)

Table 1. POCT results compared with the diagnosis of CD on the basis of current ESPGHAN criteria

POCT	Diagnosis of CD according to ESPGHAN criteria		
	Positive	Negative	
Positive	46	1	47
Negative	2	51	53
Total	48	52	100

Sensitivity: 95.8% (CI 95%: 85.7-99.4%). Specificity: 98.1% (CI 95%: 89.7-99.7%). PPV: 97.9% (88.7-99.6%). NPV: 96.2% (87.0-99.4%). POCT: Point-of-care test; NPV: Negative predictive values; PPV: Positive predictive value.

was also calculated and a high positive LR of 49.8 (7.2-347.5) and a low negative LR of 0.04 (0.01-0.17) were obtained.

A total of three discordant results were observed using the POCT (Fig. 2). There were two false negative POCT results. One patient was a ten year old girl and the sole case of IgA deficiency in this study with negative IgA-tTG, positive IgG-tTG (50AU/l), negative EmA, HLA-DQ2/DQ8 haplotype and villous atrophy (Marsh 3c). The other false negative POCT result was a male adolescent (15 years old) with a recent history of weight loss as well as previous gastrointestinal symptoms and gastritis and who was previously treated for *Helicobacter pylori* infection. Before study enrolment, a genotype compatible with CD (HLA-DQ2) was identified in this patient and he tested IgA-tTG positive, but had also two negative biopsy results. This

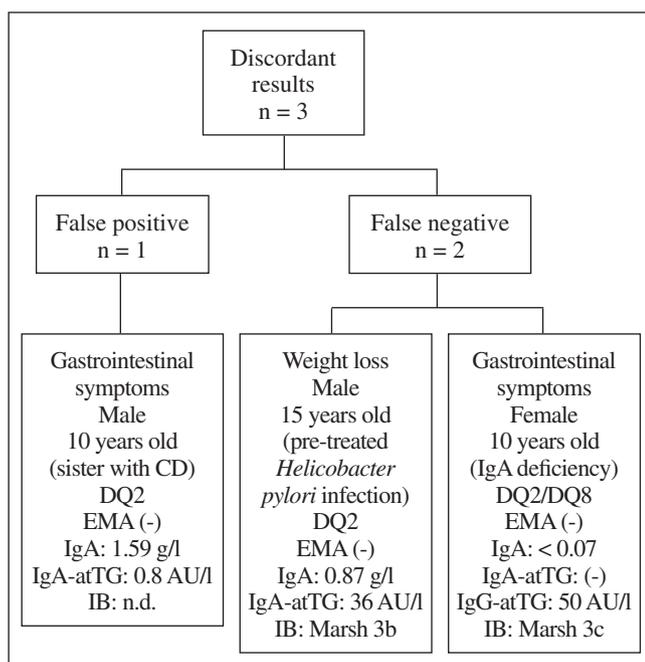


Fig. 2. Clinical symptoms in patients with discordant results between the POCT and CD diagnosis according to ESPGHAN criteria.

patient reported epigastric pain and loss of appetite, tested positive for IgA-tTG (36 AU/l), and a CD diagnosis was confirmed by the presence of villous atrophy (Marsh 3b). The third discordant, false positive result with the POCT was obtained in a male patient (ten years old). This patient displayed gastrointestinal symptoms including nausea and vomiting associated with abdominal pain, had a first degree relative with CD (sister), a CD-compatible genetic background (HLA-DQ2), normal immunoglobulin levels (IgG 10.90 g/l, IgA 1.59 g/l, IgM 1.08 g/l), negative EmA and negative IgA-tTG (0.8 AU/l).

All discordant results were obtained from patients over ten years of age. This prompted us to investigate the performance of the POCT in different age groups. In this cohort, 30 patients were older than ten years of age and the POCT yielded three results in this subpopulation that differed from CD diagnosis based on ESPGHAN criteria. This resulted in a diagnostic accuracy of 90%. However, in the 70 children younger than ten years of age, the POCT had a diagnostic accuracy of 100%. This subgroup included 18 children younger than two years of age and 15 patients that did not require a biopsy according to ESPGHAN criteria.

DISCUSSION

The advantages of POCT include its minimally invasive and rapid nature, which is particularly important for CD diagnosis in children. Thus, we investigated the accuracy of a DGP-based POCT in pediatric patients referred from Primary Care, secondary care or private doctors to a specialized Paediatric Gastroenterology service for CD diagnosis. Moreover, this is the first study that compares the results of a CD POCT with the current criteria for CD diagnosis established by ESPGHAN (4).

The performance of the DGP-based POCT studied here has been previously assessed in paediatric cohorts (23-25), but was compared to conventional tTG lab serology and not to diagnostic ESPGHAN criteria. In a large pediatric population and in a second cohort of IgA deficient children, a high negative predictive value was found of 99% and 100%, respectively. The sensitivity values were 93% and 100%, respectively, indicating that this DGP-based POCT allows for accurate CD screening and is a reliable tool to rule out CD in children. Although we used a different reference for the comparison of the POCT results (ESPGHAN criteria), similar negative predictive (96.2%) and sensitivity values (95.8%) were obtained.

Our data suggest that the POCT may be the most accurate method in children younger than ten years of age. However, no similar observation was reported by Bienvenu et al. (23,25). Moreover, Kurppa et al. (30) found a high sensitivity for IgA/IgG-DGP antibodies in detecting early-stage CD when the villous morphology has not been affected yet. Despite these positive findings in the literature, further data is needed to validate our hypothesis that

the DGP-based POCT is the most suitable for CD diagnosis in children below ten years of age.

In the present study, the use of ESPGHAN criteria to make a CD diagnosis allowed for a biopsy to be avoided in 15 patients with IgA-tTG levels exceeding the upper normal limit by ten times (> 10 ULN). Of these 15 patients, eleven were younger than two years of age and four were between two and ten years old. All 15 patients were newly diagnosed CD cases, thus IgA-tTG testing was perfectly accurate in this patient subset. Similarly, the POCT based on DGPs correctly identified these 15 patients as CD positive.

Despite the association of CD with the autoimmune disease diabetes mellitus type 1 (31), only one insulin dependent patient was found in this study. Interestingly, this patient was diagnosed with type 1 diabetes during the study period. Peretti et al. (32) suggested that CD is most often present before the onset of diabetes. This is consistent with our findings and justifies the importance of monitoring type I diabetes in CD patients.

It is worth mentioning that the CD prevalence in our study cohort (48%) is higher than that reported in different populations at risk of CD (10). This enrichment of CD patients in our study is due to the fact that subjects were selected from a health service specialized in the detection of gastrointestinal diseases, including CD. Thus, the selection of our patients represents the main limiting factor of our study, since the prevalence of CD found in this sample does not represent the prevalence in the general population.

Our results support the use of this DGP-based POCT in specialized pediatric gastroenterology services. In adult patients, this POCT test demonstrated an equivalent sensitivity of serum tTG and an increased accuracy of the diagnosis of CD when used before endoscopy (33). Further studies are needed to clarify whether the POCT could replace conventional laboratory serology for the diagnosis in settings where CD prevalence is lower, as in the general population. In these settings, being the prevalence and, therefore, the risk of suffering the disease, lower than in our cohort, the predictive values would not behave as well as in our sample, especially the positive predictive value. However, the LR obtained, which do not depend on the prevalence of the disease, allow us to suppose that the POCT is a safe way to achieve a rapid, cost-effective and accurate CD diagnosis. Thus, the selection of our patients represents the limiting factor of our study, since the prevalence of CD found in this sample does not represent the prevalence of the general population.

In conclusion, taking into account its high diagnostic accuracy in the pediatric population and its minimal invasiveness, the POCT used in this study should be considered as an effective tool for the early diagnosis of CD, especially in patients younger than ten years of age.

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