Office-Based Point of Care Testing (IgA/IgG-Deamidated Gliadin Peptide) for Celiac Disease

Michelle S. Lau, MBChB[1], Peter D. Mooney, MD[1], William L. White, MBChB[1], Michael A. Rees, BMedSci[1], Simon H. Wong, MBChB[1], Marios Hadjivassiliou, FRCP[2], Peter H. R. Green, MD[3], Benjamin Lebwohl, MD[3] and David S. Sanders, FRCP[1]

OBJECTIVES: **Celiac disease (CD) is common yet under-detected. A point of care test (POCT) may improve CD detection. We aimed to assess the diagnostic performance of an IgA/IgG-deamidated gliadin peptide (DGP)-based POCT for CD detection, patient acceptability, and inter-observer variability of the POCT results.**

METHODS: **From 2013–2017, we prospectively recruited patients referred to secondary care with gastrointestinal symptoms, anemia and/or weight loss (group 1); and patients with self-reported gluten sensitivity with unknown CD status (group 2). All patients had concurrent POCT, IgA-tissue transglutaminase (IgA-TTG), IgA-endomysial antibodies (IgA-EMA), total IgA levels, and duodenal biopsies. Five hundred patients completed acceptability questionnaires, and inter-observer variability of the POCT results was compared among five clinical staff for 400 cases.**

RESULTS: **Group 1: 1000 patients, 58.5% female, age 16–91, median age 57. Forty-one patients (4.1%) were diagnosed with CD. The sensitivities of the POCT, IgA-TTG, and IgA-EMA were 82.9, 78.1, and 70.7%; the specificities were 85.4, 96.3, and 99.8%. Group 2: 61 patients, 83% female; age 17–73, median age 35. The POCT had 100% sensitivity and negative predictive value in detecting CD in group 2. Most patients preferred the POCT to venepuncture (90.4% vs. 2.8%). There was good inter-observer agreement on the POCT results with a Fleiss Kappa coefficient of 0.895.**

CONCLUSIONS: **The POCT had comparable sensitivities to serology, and correctly identified all CD cases in a gluten sensitive cohort. However, its low specificity may increase unnecessary investigations. Despite its advantage of convenience and rapid results, it may not add significant value to case finding in an office-based setting.**

Am J Gastroenterol (2018) 113:1238–1246. https://doi.org/10.1038/s41395-018-0143-3

INTRODUCTION

Celiac disease (CD) is a systemic autoimmune disease associated with gastrointestinal and extra-gastrointestinal symptoms, triggered by gluten in genetically susceptible individuals [1]. It affects 0.3–2.4% of the general population globally [2–9]. CD affects one in 100 in the United Kingdom, but only 24% are detected [10]. Similar observations are also apparent in Europe [3], the United States [11], and worldwide [12]. This is partly because symptoms of CD can be non-specific and difficult for clinicians to recognize. This is further compounded by an emerging clinical entity, non-celiac gluten sensitivity (NCGS), which is clinically indistinguishable from CD [13, 14]. Although the Salerno criteria define NCGS using a double blind placebo controlled challenge [15], self-reported gluten sensitivity describes individuals who complain of gastrointestinal and/or non gastrointestinal symptoms triggered by gluten ingestion and present to physicians accordingly. Exclusion of CD and wheat allergy is fundamental in this group of patients. It is essential to distinguish NCGS from CD, as patients with NCGS do not seem to be at risk of the complications seen in CD, although they derive symptomatic benefit from a gluten free diet [16]. Moreover, any delays in celiac testing before individuals embark on a self-imposed gluten free diet could cause diagnostic challenges.

Early diagnosis of CD is important for the improvement of patients' quality of life and the prevention of complications such

[1]Academic Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, UK. [2]Academic Department of Neurosciences and University of Sheffield, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, UK. [3]Celiac Disease Centre, Columbia University Medical Centre, New York, NY, USA. **Correspondence:** M.S.L. (email: michellelau@doctors.org.uk)
Received 26 January 2018; accepted 4 May 2018; Published online 19 June 2018

as osteoporosis, hip fractures, and lymphoproliferative malignancies. We have previously shown that serological testing in patients with high risk symptoms in a clinic setting yielded 3.3–4.7% CD detection [17]. Similar results were obtained by other groups through case finding [18, 19]. On the other hand, a recent systematic review reported insufficient evidence to support screening for asymptomatic patients at present [13, 20–23]. For these reasons, case finding for CD in at risk individuals has been recommended by international guidelines [24, 25].

Despite guidelines recommending celiac testing in at risk individuals, it has been shown that serological testing for CD is underutilized, where only 30% of patients with suspected CD or anemia had serology performed prior to their endoscopy [26, 27]. This suggests that current case finding strategies with serology may be inadequate. This could be due to a multitude of factors, including a lack of awareness of the guidelines, inconvenience and cost. A finger prick point of care test (POCT) that provides convenience and rapid celiac antibody results may have a role in improving case detection, particularly in an office-based consultation, where the results could provide immediate guidance for the physician on the need for duodenal biopsies. Several POCTs have been developed in the past decade, with the majority detecting IgA-tissue transglutaminase (IgA-TTG). However, these POCTs have not entered widespread clinical use, probably due to their inferior sensitivities compared to conventional serology. A recent head to head POCTs trial comparing Biocard (IgA-TTG), Celiac Quick Test (IgA-TTG), and Simtomax (IgA/IgG-deamidated gliadin peptide (DGP)) revealed that Simtomax significantly outperformed the other two, with sensitivities of 72.2, 77.8, and 94.4%, respectively [28].

Our primary aim was to assess the diagnostic accuracy of the IgA/IgG-DGP-based POCT, Simtomax, in detecting CD in patients presenting to secondary care with gastrointestinal symptoms, anemia and/or weight loss, and those who self-report gluten sensitivity. Our secondary aims were to evaluate patient acceptability of the POCT, and the inter-observer variability of test result interpretation.

METHODS

Study design and patients

The study took place at the Royal Hallamshire Hospital, Sheffield, UK, from March 2013–January 2017. We prospectively recruited patients who were referred to gastroenterology for further evaluation.

Group one consisted of patients presenting to secondary care with gastrointestinal symptoms (abdominal pain, diarrhea and/or dyspepsia), anemia and/or weight loss. Patients with known CD were excluded. Patients who were referred with positive celiac serology by their primary care physicians were excluded from the study so as to avoid tertiary referral bias, thus providing a more accurate assessment of the sensitivities of the POCT that is reflective of clinical practice. All patients who consented to participate in the study were concurrently tested with total immunoglobulin A (IgA) levels, IgA-TTG antibodies, IgA-endomysial antibodies (IgA-EMA) and the DGP-based POCT, Simtomax. An endoscopy with duodenal biopsies was performed in all patients.

Group two consisted of patients presenting to secondary care with self-reported gluten sensitivity, with gastrointestinal and/or extra-gastrointestinal symptoms related to gluten ingestion. The celiac status of these patients was unknown. Patients with known CD were excluded. Those with reduced or no gluten intake were asked to undertake a 6-week gluten challenge of 10 g gluten/day prior to their endoscopy as per guidelines [29, 30]. All patients were concurrently tested with total IgA levels, IgA-TTG, IgA-EMA, and the POCT, and duodenal biopsies were taken in all patients.

Point of care test

The DGP-based POCT for CD, Simtomax, was manufactured by Augurix Diagnostics, Rheinfelden, Switzerland. It detects both IgA/IgG-DGP antibodies, as well as the presence of IgA. The assay is based on lateral flow immunochromatography using colloidal gold antihuman antibodies as a signal detector. A sample of 25 μl of capillary venous blood was obtained through a simple finger prick technique. The blood sample was then applied to the test device, followed by the application of five drops of the provided buffer solution. The result was available after 10 minutes. Positive results were indicated by the presence of a solid red band for IgA/IgG-DGP positivity. A second single red band indicated the presence of IgA. A third inbuilt red control band ensured a correctly functioning test. See Fig. 1 for illustration of the POCT.

Celiac serology

IgA-TTG was assayed using enzyme-linked immunosorbent assay (ELISA) kits (Aesku Diagnostics, Wendelsheim, Germany). IgA-EMA was detected by immunofluorescence on primate esophagus sections (Binding Site, Birmingham, UK). Total IgA was measured on a Behring BN2 nephelometer (Haywards Heath, West Sussex, UK). DGP serology was not available in our laboratory and therefore not tested.

Histological evaluation

In total, at least five biopsies were taken from the duodenum with a single bite per pass technique, including at least one biopsy from the duodenal bulb and four quadrantic biopsies from the second part of the duodenum. Each biopsy was fixed in formalin at the time of the gastroscopy. Specimens were then processed, orientated, and embedded in paraffin wax by the pathology department. Standard 3 μm thick sections at three levels were stained with hematoxylin and eosin, and reported by gastrointestinal histopathologists without knowledge of the POCT or serology results. Villous atrophy was graded according to the modified Marsh criteria [31]. The histological grade recorded was based on the most severe grade detected from the biopsy samples.

Definitions of diagnoses

The definition of CD was based on positive serology (positive TTG and/or EMA) with Marsh 3 villous atrophy.

Seronegative CD was based on Marsh 3 villous atrophy on a normal gluten containing diet, positive human leukocyte antigen (HLA) DQ2 or DQ8, and other supporting information such as family history and response to a gluten free diet. Non-celiac causes

Fig. 1 Three possible outcomes of the point of care test results. Red band A indicates a positive result, red band B indicates the presence of IgA, red band CT is the control line, indicating a correctly functioning test. Left: a solid red band A indicating a positive test; Middle: an absence of a red band A indicating a negative test; Right: a faint pink band A which was classified as a negative test, as none of the patients with a faint band A had celiac disease in our cohort

of seronegative villous atrophy were extensively investigated for, including giardiasis, tuberculosis, whipple's disease, small bowel bacterial overgrowth, helicobacter pylori, human immunodeficiency virus, autoimmune enteropathy and drug related causes. Marsh 3 villous atrophy secondary to CD was the reference standard used in our study for the diagnostic performance evaluation of the POCT and serology.

Potential CD was defined as positive serology with no villous atrophy (Marsh 0–2), with supporting information such as positive HLA DQ2 or DQ8 and family history.

Non-celiac gluten sensitivity was diagnosed in patients self-reporting symptoms related to gluten who had negative serology, absence of villous atrophy, and symptom response to a gluten free diet and gluten challenge. A 6-week gluten challenge of 10 g gluten/day was proposed for group two patients entering the study who had reduced or absent gluten intake prior to their investigations.

Patient acceptability of the POCT

There are no validated patient acceptability questionnaires in the literature for POCTs. Therefore, we devised a questionnaire consisting of five questions regarding the acceptability of the POCT (comfort level, convenience, and satisfaction with result availability) which was filled in by 500 consecutive patients after having had the POCT performed. They were asked to rate on a Likert scale of one to five for each question, with one being a negative experience and five being a positive experience. These 500 patients all had previous experience of a venepuncture. They were also asked to state their preferred mode of testing: POCT, venepuncture, or no preference. A similar acceptability questionnaire for venepuncture was completed by a separate cohort of 63 patients after having had a venepuncture to act as controls. These questionnaires were given out to both groups to fill in independently and anonymously, and the questionnaires were collected by a member of staff on completion.

Inter-observer variability of the POCT results

Inter-observer variability of the POCT results was assessed in 400 consecutive patients in group one. Each observer recorded whether there was a definite red band, a faint red band, or an absence of a red band. There were five observers in total for each case, consisting of one gastroenterologist and four other randomly selected allied health care professionals (for example, nurses). All observers were trained to recognize positive, negative, and indeterminate results. Observation of the results was carried out indoors under fluorescent lighting.

Ethical considerations

The study protocol was approved by the Yorkshire and the Humber Research Ethics committee and registered with the local research and development department of Sheffield Teaching Hospital NHS Foundation Trust under the registration number STH15416. Written consent was obtained from all patients.

Statistical analysis

Data were summarized by descriptive statistics, including counts and percentages for categorical data, and medians and ranges for continuous parameters. The diagnostic accuracies of the POCT, IgA-TTG, and IgA-EMA were presented with sensitivity, specificity, positive (PPV), and negative predictive values (NPV). Clopper–Pearson method was used to calculate the confidence intervals for the sensitivities. Inter-observer variability was presented using Fleiss Kappa coefficient, where 0 indicates no agreement and 1 indicates perfect agreement. Cohen's effect size (r) for patient acceptability between the POCT and venepuncture groups was measured using Mann–Whitney U test, where $r = 0.1$, 0.3, and 0.5 indicates small, medium, and large effect size, respectively. Statistical analysis was performed using IBM SPSS statistics version 24.

RESULTS

Patient demographics and presenting characteristics in group one are illustrated in Table 1. One thousand eligible patients who consented for participation entered group one of the study. There were 585/1000 females (58.5%); age range 16–91, median age 57. Forty-one patients (4.1%) were diagnosed with CD. IgA deficiency detected by total IgA levels from the laboratory assay was found in 29 patients in groups one and two combined (29/1061 = 2.7%). Three IgA deficient patients were diagnosed with CD (3/45 = 6.7% of the total celiac cohort), and all three had a positive POCT. Nine patients (9/41 = 22%) had ultra-short CD with Marsh 3 villous atrophy confined to the duodenal bulb only. The sensitivity of the POCT was comparable to IgA-TTG and IgA-EMA (82.9 vs. 78.1 vs. 70.7%). However, its specificity was significantly lower than IgA-TTG and IgA-EMA (85.9 vs. 96.3 vs. 99.8%). The diagnostic performance of the POCT, IgA-TTG, and IgA-EMA for group one are displayed in Tables 2 and 3. Receiver operating characteristic (ROC) curves for the aforementioned tests for group one are demonstrated in Fig. 2.

In group two, 70 patients self-reported gluten sensitivity. Nine patients who were on a self-imposed gluten free diet and declined a 6-week gluten challenge prior to investigations were excluded from the study. A total of 61 patients consuming gluten entered group two of our study. Twenty-three patients who were previously on a self-imposed gluten free diet underwent a gluten challenge: 16 patients managed a 6-week challenge and seven could only tolerate 4 weeks of gluten challenge at which point the serology and endoscopy were performed due to significant symptoms. The remaining 38 patients were consuming a gluten containing diet and continued to do so at least until the investigations took place. There were 51/61 females (82.9%); age range 17–73, median age 35. Eighteen patients were tested positive for EMA by their general practitioners. The vast majority (57/61) of patients had gastrointestinal symptoms, and ten patients reported extra-gastrointestinal symptoms, predominantly neurological complaints (e.g., headache, paresthesia, foggy mind, ataxia, lethargy, tongue tingling, and arthralgia). Forty-two patients (42/61 = 68.9%) were diagnosed with NCGS, 17/61 (27.9%) with CD, and 2/61 (3.3%) with potential CD. The POCT demonstrated a sensitivity and negative predictive value of 100% (vs. sensitivity 88.2%, 94.1% and negative predictive value 91.8%, 97.77% for IgA-TTG and IgA-EMA, respectively). The diagnostic performance of the POCT, IgA-TTG, and IgA-EMA for group two are displayed in Tables 4 and 5. ROC curves for the aforementioned tests for group two are demonstrated in Fig. 3.

In regards to patient acceptability, the POCT had significantly higher patient satisfaction compared to venepuncture. The difference in the scores between the two groups were statistically significant in all aspects of the acceptability questionnaire, and the effect size difference between the two groups was large ($r = 0.506–0.656$). Table 6 shows the median scores and statistical differences in both groups for each aspect of the tests.

There was a good degree of inter-observer agreement on the POCT result interpretation, with a Fleiss Kappa coefficient of 0.895 overall. Sub-analysis revealed a high level of agreement for definite red bands (Kappa 0.887) and absence of red bands (Kappa 0.956). The level of agreement dropped for faint red bands (Kappa 0.781),

Table 1 Group one patient demographics and presenting characteristics table

	No. of patients	Celiac disease yield
Female	585/1000 (58.5%)	27/585 (4.6%)
Male	415/1000 (41.5%)	14/415 (3.4%)
Diarrhea	75/1000 (7.5%)	8/75 (10.7%)
Abdominal pain	159/1000 (15.9%)	13/159 (8.2%)
Weight loss	104/1000 (10.4%)	6/104 (5.8%)
Anemia	194/1000 (19.4%)	9/194 (4.6%)
Dyspepsia	549/1000 (54.9%)	8/549 (1.5%)

Table 3 Group 1: cross tabulation of the point of care test (POCT) results by the reference standard

	CD	Not CD		CD	Not CD		CD	Not CD
POCT +	34	140	TTG +	32	36	EMA +	29	2
POCT −	7	819	TTG −	9	923	EMA −	12	957

Table 2 The diagnostic accuracy of the point of care test, IgA-tissue transglutaminase antibodies and IgA-endomysial antibodies in detecting celiac disease in symptomatic patients (group one; $n = 1000$, celiac disease prevalence 4.1%)

	Point of care test	IgA-tissue transglutaminase antibodies	IgA-endomysial antibodies
Sensitivity % (95% CI)	82.9 (67.9–92.9)	78.1 (62.4–89.4)	70.7 (54.5–83.9)
Specificity % (95% CI)	85.4 (83.0–87.6)	96.3 (94.8–97.4)	99.8 (99.3–100.0)
Positive predictive value % (95% CI)	19.5 (16.5–23.0)	47.1 (38.3–56.0)	93.6 (78.2–98.3)
Negative predictive value % (95% CI)	99.2 (98.4–99.6)	99.0 (98.3–99.5)	98.8 (98.0–99.2)
Positive likelihood ratio (95% CI)	5.7 (4.6–7.0)	20.8 (14.5–30.0)	339.2 (83.8–1373.2)
Negative likelihood ratio (95% CI)	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.3 (0.2–0.5)
Accuracy % (95% CI)	85.3 (83.0–87.4)	95.5 (94.0–96.7)	98.6 (97.7–99.2)

where there were 31 such cases within the 400 assessed. None of these 31 patients had CD. Only solid red bands were classified as a positive test for the purpose of diagnostic calculations in our study, and faint red bands were interpreted as negative. Figure. 1 illustrates the three possible outcomes of the POCTs results.

DISCUSSION

To our knowledge, this is the largest study to date evaluating the diagnostic accuracy of the DGP-based POCT, Simtomax. This is also the first study to explore the practicalities of this POCT including patient acceptability and inter-observer variability of test result interpretation.

One of the strengths of this study is that all participants had duodenal biopsies taken, irrespective of their celiac antibodies or POCT results. This ensured that no false negative cases of CD would be missed. This methodology contributed to a major difference to most POCT studies for CD, where only patients with positive antibodies (either POCT or serology) were biopsied [32–37]. Additionally, some POCT studies measured the sensitivities against serology rather than duodenal histology as the reference standard [35, 38, 39]. These limitations could lead to a positive ascertainment bias, thereby falsely elevating the reported sensitivities.

Another strength of this study is that our patient cohort had a CD prevalence consistent with real life case finding in patients

Table 5 Group 2: cross tabulation of the point of care test (POCT) results by the reference standard

	CD	Not CD		CD	Not CD		CD	Not CD
POCT +	17	9	TTG +	15	3	EMA +	16	1
POCT −	0	35	TTG −	2	41	EMA −	1	43

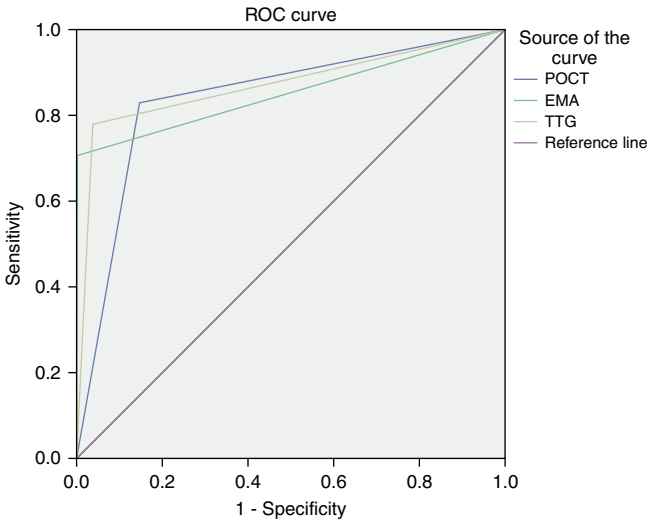

Fig. 2 Group 1 receiver operating characteristic (ROC) curve for the point of care test (POCT), IgA-endomysial antibodies (EMA), and IgA-tissue transglutaminase antibodies (TTG). Area under the curve (AUC) for each test were 0.842 (CI: 0.77-0.9), 0.853 (CI: 0.77-0.94), and 0.871 (CI: 0.8-0.95), respectively. CI = confidence interval

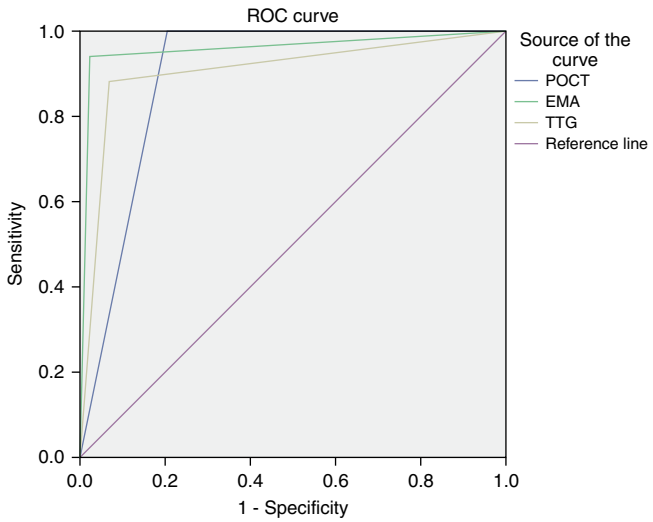

Fig. 3 Group 2 receiver operating characteristic (ROC) curve for the point of care test (POCT), IgA-endomysial antibodies (EMA) and IgA-tissue transglutaminase antibodies (TTG). Area under the curve (AUC) for each test were 0.898 (CI: 0.82–0.98), 0.959 (CI: 0.89–1.0) and 0.907 (CI: 0.81–1.0) respectively. CI = confidence interval

Table 4 The diagnostic accuracy of the point of care test, IgA-tissue transglutaminase antibodies, and IgA-endomysial antibodies in detecting celiac disease in patients who self-reported gluten sensitivity (group two; $n = 61$, celiac disease prevalence 27.9%)

	Point of care test	IgA-tissue transglutaminase antibodies	IgA-endomysial antibodies
Sensitivity % (95% CI)	100 (80.5–100)	88.2 (63.6–98.5)	94.1 (71.3–99.9)
Specificity % (95% CI)	79.6 (64.7–90.2)	93.2 (81.3–98.6)	97.7 (88.0–99.9)
Positive predictive value % (95% CI)	65.4 (51.3–77.2)	83.3 (62.3–93.8)	94.1 (69.6–99.1)
Negative predictive value % (95% CI)	100	91.8 (81.0–97.3)	97.7 (86.5–99.6)
Positive likelihood ratio (95% CI)	4.9 (2.7–8.8)	12.9 (4.3–39.1)	41.4 (5.9–288.5)
Negative likelihood ratio (95% CI)	0	0.1 (0–0.5)	0.06 (0.01–0.4)
Accuracy % (95% CI)	85.3 (73.8–93.0)	91.8 (81.9–97.3)	96.7 (88.7–99.6)

Table 6 Patient acceptability for the point of care test (POCT) and conventional venepuncture. Acceptability was scored with a Likert scale from 1 to 5, with 1 being a negative experience and 5 being a positive experience

	Point of care test (POCT)	Venepuncture	Mann–Whitney *U* test
Blood collection process			
Score for comfort level of the test	4.7	3.3	$U=2988.5$, $Z=12.027$, $p<0.001$, $r=0.506$
Score for speed and ease of the test	4.7	3.3	$U=2182.5$, $Z=13.443$, $p<0.001$, $r=0.566$
Convenience			
Satisfaction score for having the test performed during the consultation (for POCT) vs separately from the consultation by the phlebotomy service	4.8	2.9	$U=1086.5$, $Z=14.675$, $p<0.001$, $r=0.617$
Quality of care			
Satisfaction score for obtaining test results within 10 minutes (for POCT) vs a few days to a week (for serology via venepuncture)	4.8	3.1	$U=583.5$, $Z=15.597$, $p<0.001$, $r=0.656$
Satisfaction score for obtaining and discussing the test results with the clinician within the same consultation (for POCT) vs at a later date (for venepuncture)	4.8	2.9	$U=988.0$, $Z=15.223$, $p<0.001$, $r=0.64$
Preference	**No. of patients**		
Prefers point of care test	452/500 (90.4%)		
Prefers venepuncture	14/500 (2.8%)		
No preference	34/500 (6.8%)		

with high risk symptoms, which have been reported to be 3–4.7% [17, 18]. A much higher CD prevalence is a common limitation in previous POCT studies [34, 40, 41]. This tertiary referral bias restricts the generalizability of their findings. The patient characteristics and pre-test probability of group one allowed a more accurate reflection of the diagnostic performance of these tests in real practice.

There are a few limitations to our study. Ideally, the measurement of laboratory DGP serology would act as a useful comparison of the sensitivities between DGP detection by laboratory assay (serology) and lateral flow immunochromatography (POCT). However, laboratory DGP serology is not widely available in the United Kingdom (UK) and is not available in our center. Therefore, DGP assays were not performed. Another limitation is the evaluation of patient acceptability of the POCT. We devised our own POCT acceptability questionnaire as there were no validated questionnaires in the literature, and the methodology of using a Likert scale provided a quantitative rather than qualitative measure of acceptability. Qualitative interviews would give a more informative representation of patient acceptability. However, patient acceptability was a secondary outcome and not the main focus of this study.

What is noteworthy is the generally lower sensitivities of IgA-TTG and IgA-EMA compared to previous serological studies [42, 43]. There are several potential reasons for this. Although a systematic review in 2006 showed that the pooled sensitivities of IgA-TTG and IgA-EMA from published data were 93% (range 70–100%) and specificities were >98% (range 90–100%) for both, the authors indicated that these figures were likely to be falsely high due to methodological flaws in most studies [42]. Firstly, many studies did not biopsy controls (i.e., take duodenal biopsies in seronegative patients), creating positive ascertainment bias which enhanced the sensitivities of serology. In a subsequent meta-analysis of the diagnostic accuracy of IgA-TTG and IgA-DGP [43], the authors concluded that only two out of 11 studies biopsied controls [44, 45]. In fact, these two studies demonstrated the sensitivities and specificities of IgA-TTG to be 78.3–95% and 97.5–98.4% respectively. Second of all, the results from the aforementioned two studies still may not have reflected their performance in real practice, as it has been demonstrated previously [46], since the CD prevalence was very high at 74% for both studies. This again could have falsely increased the sensitivity and positive predictive value of IgA-TTG. Lastly, the lack of standardization of IgA-TTG laboratory assays could also lead to different IgA-TTG sensitivities. IgA-TTG antibody units and reference ranges are arbitrary and method-specific. Furthermore, over 30 different IgA-TTG assay kits are used in the UK, giving different IgA-TTG titers. A recent study showed that even when the same IgA-TTG ELISA assay kit was used, there was still poor agreement among laboratories as to whether the sample was above or below the defined IgA-TTG level cut off point for Marsh 3 histology using a ROC curve [47]. A recent head to head trial of three different TTG serological kits also found widely variable sensitivities and specificities, ranging from 71.1–95.5% and 82.6–100%, respectively [48]. All these factors explain the huge variability of IgA-TTG sensitivities and why the sensitivities appeared to be lower than average in our study, where we biopsied all patients including controls and the CD prevalence being low in comparison to other studies.

In regards to the prevalence of CD in individuals who self-report gluten sensitivity, there are four studies in the literature which assessed the diagnostic outcomes of this cohort, with sample sizes

ranging from 93 to 238, and the prevalence of CD varying between 2 and 42.4% [49–52]. In our study, the CD prevalence of 27.9% within the self-reported gluten sensitivity cohort lies within the range of the reported data. The wide variation in the reported disease prevalence is likely due to differences in the study population, study design, recruitment methods, and diagnostic criteria. For example, our disease prevalence of 27.9% is higher than the 7% reported by Aziz et al. which derived from a UK population-based questionnaire targeting individuals with gluten related symptoms [51], as opposed to symptomatic individuals actively presenting to primary care who were then referred on to secondary care for further evaluation. Our group 2 patients' gluten-related symptoms may have prompted more proactive celiac screening by their general practitioners, thus possibly explaining the higher prevalence of seropositive patients (18/61), giving a higher disease prevalence. Nevertheless, after excluding the 18 patients who were referred with positive EMA in group 2, the sensitivity and negative predictive value of the POCT remained at 100%, where all four cases of CD were correctly identified.

POCTs for other laboratory measurements, such as human immunodeficiency virus and international normalized ratio have been widely adopted in UK practice in both primary and secondary care settings, owing to their clinical effectiveness and good patient acceptability [53, 54]. We have shown that this POCT had a favorable acceptability to patients compared to venepuncture, with 90.4% patients preferring the POCT. Most patients generally found the POCT to be a simple and quick test to perform (it took on average 1 min to perform the test, and 10 min for the results to become available), and less painful than venepuncture. Table **6** illustrates the satisfaction scores for different aspects of the POCT versus venepuncture.

With regards to the diagnostic performance of the POCT, the sensitivity was comparable to IgA-TTG and IgA-EMA (82.9% vs. 78.1% vs. 70.7%). In our group one cohort, 7.3% (3/41) of the newly diagnosed patients had seronegative CD detected by the POCT alone whilst IgA-TTG was negative. An increase in diagnostic yield with DGP was also demonstrated by Hoerter et al. recently, where the use of IgA-DGP serology resulted in a 15% increase in CD detection where IgA-TTG was negative [55]. However, the specificity and PPV of the POCT were inferior to IgA-TTG and IgA-EMA (specificities 85.4% vs. 96.3% vs. 99.8% and PPVs 19.5% vs. 47.1% vs. 93.6%, respectively), due to a higher rate of false positives. This could potentially lead to unnecessary further investigations. A possible explanation of the low specificity is that approximately half of the group one cohort had dyspepsia, which constituted low risk for CD, and hence may have lowered the pre-test probability of CD and hence the positive predictive value. On the other hand, when the POCT was used in higher risk groups, such as patients who self-reported gluten sensitivity (group two), the positive predictive value increased to 65.4%, with a 100% sensitivity and negative predictive value in detecting CD. Similarly, we have previously shown that the POCT had better diagnostic performance when used in 133 patients with iron deficiency who were referred for an endoscopy (sensitivity, specificity, positive, and negative predictive value of 100, 82.2, 57.8, and 100%, respectively). With the 100% negative predictive value, the POCT could potentially save USD $5141 per 100 endoscopies through duodenal biopsy avoidance (vs. routine duodenal biopsy for anemia) in iron deficient patients with a negative POCT when used in the pre-endoscopy setting, unless the patient has other high-risk malabsorptive symptoms such as weight loss and diarrhea [27].

The advantages of the POCT over conventional serology are favorable patient acceptability and rapidly available results within 10 minutes. Nevertheless, despite there being no significant difference in the overall diagnostic performance between the POCT and serology based on ROC curve analysis, one must consider the clinical impact of the high false positive rates of the POCT. The potential burden of a considerable increase in unnecessary investigations may outweigh the benefits of a sensitive and convenient test. We have previously demonstrated that this POCT could be useful in CD monitoring, as it had a significantly higher sensitivity than IgA-TTG in predicting persistent villous atrophy in known CD patients on a gluten-free diet (67.1% vs. 47.1%, $p = 0.0005$) [56]. Although the sensitivity of the POCT was still suboptimal, it represented a stepwise improvement in current disease monitoring compared to conventional serology. However, as a case finding tool in an office-based setting where the CD prevalence would be expected to be ~4%, as was in our study and other case finding studies based on symptomatic cohorts [17], the POCT may not provide significant added value compared to conventional serology due to its low specificity, albeit its similar sensitivity to IgA-TTG.

CONCLUSION

The DGP-based POCT had comparable sensitivities to IgA-TTG and IgA-EMA in detecting CD in symptomatic patients, and correctly distinguished all cases of CD in a gluten sensitive cohort that was consuming gluten. It also has the advantage of convenience, rapid result availability, and good patient acceptability. However, the POCT is limited by its low specificity which may increase the number of unnecessary investigations. The POCT therefore may not add significant value when used for case finding in a general office-based consultation compared to conventional serology.

CONFLICT OF INTEREST

Guarantor of the article: David Sanders, MBChB, MD, FACG, FRCP.

Specific author contributions: MSL is involved in data collection, analysis and interpretation of the data, statistical analysis, and drafting of the manuscript; PDM is involved in data collection, and analysis and interpretation of the data; WLW, MAR, SHW are responsible for data collection; MH, PHRG, BL are involved in analysis and interpretation of the data, and revision of the manuscript; DSS is responsible for study concept and design, analysis interpretation of the data, revision of the manuscript and study supervision. All authors have approved the manuscript.

Financial support: None.

Potential competing interests: DSS has received educational research grants from Dr Schaer (a gluten-free food manufacturer)

and Tillotts Pharma (distributor of a point of care test for celiac disease) for investigator led studies. Dr Schaer and Tillott's Pharma did not have any input in the study design, access to study data, interpretation of the findings or drafting of the manuscript.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Celiac disease is common but underdetected, partly due to underutilization of serology.
- ✓ Delayed testing could cause diagnostic challenges in individuals who are on a self-imposed gluten-free diet.

WHAT IS NEW HERE

- ✓ The POCT had comparable sensitivities to conventional serology, with the advantage of convenience and rapid results.
- ✓ However, the POCT may have a limited role in general office-based case finding due to its low specificity.

REFERENCES

1. Lebwohl B,Sanders DS,Green PHR, Coeliac disease. Lancet. 2018;391:70–81.
2. Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med. 2003;163:286–92.
3. Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. Ann Med. 2010;42:587–95.
4. Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. Am J Gastroenterol. 2012;107:1538–44. quiz 7, 45
5. Hill I, Fasano A, Schwartz R, Counts D, Glock M, Horvath K. The prevalence of celiac disease in at-risk groups of children in the United States. J Pediatr. 2000;136:86–90.
6. Singh P, Arora S, Singh A, Strand TA, Makharia GK. Prevalence of celiac disease in Asia: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2016;31:1095–101.
7. Mora M, Litwin N, Toca MdC, Azcona MI, Solís Neffa R, Battiston F, et al. Prevalence of celiac disease: multicentric trial among pediatric population from five urban districts in Argentina. Arch Argent De Pedia. 2012;110:490–6.
8. Al Hatlani MM. Prevalence of celiac disease among symptom-free children from the Eastern Province of Saudi Arabia. Saudi J Gastroenterol. 2015;21:367–71.
9. Yap TW, Chan WK, Leow AH, Azmi AN, Loke MF, Vadivelu J, et al. Prevalence of serum celiac antibodies in a multiracial Asian population – a first study in the young Asian adult population of Malaysia. PLOS One. 2015;10:e0121908.
10. West J, Fleming KM, Tata LJ, Card TR, Crooks CJ. Incidence and prevalence of celiac disease and dermatitis herpetiformis in the UK over two decades: population-based study. Am J Gastroenterol. 2014;109:757–68.
11. Rubio–Tapia A, Kyle RA, Kaplan EL, Johnson DR, Page W, Erdtmann F, et al. Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology. 2009;137:88–93.
12. Makharia GK, Mulder CJ, Goh KL, Ahuja V, Bai JC, Catassi C, et al. Issues associated with the emergence of coeliac disease in the Asia-Pacific region: a working party report of the World Gastroenterology Organization and the Asian Pacific Association of Gastroenterology. J Gastroenterol Hepatol. 2014;29:666–77.
13. Talley NJ, Walker MM. Celiac disease and nonceliac gluten or wheat sensitivity: the risks and benefits of diagnosis. JAMA Intern Med. 2017;177:615–6.
14. Leonard MM, Sapone A, Catassi C, Fasano A. Celiac disease and nonceliac gluten sensitivity: a review. JAMA. 2017;318:647–56.
15. Catassi C, Elli L, Bonaz B, Bouma G, Carroccio A, Castillejo G, et al. Diagnosis of non-celiac gluten sensitivity (NCGS): the salerno experts' criteria. Nutrients. 2015;7:4966–77.
16. Aziz I, Hadjivassiliou M, Sanders DS. The spectrum of noncoeliac gluten sensitivity. Nat Rev Gastroenterol Hepatol. 2015;12:516–26.
17. Sanders DS, Patel D, Stephenson TJ, Ward AM, McCloskey EV, Hadjivassiliou M, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. Eur J Gastroenterol Hepatol. 2003;15:407–13.
18. Hin H, Bird G, Fisher P, Mahy N, Jewell D. Coeliac disease in primary care: case finding study. BMJ. 1999;318:164–7.
19. Catassi C, Kryszak D, Louis-Jacques O, Duerksen DR, Hill I, Crowe SE, et al. Detection of Celiac disease in primary care: a multicenter case-finding study in North America. Am J Gastroenterol. 2007;102:1454–60.
20. Chou R, Bougatsos C, Blazina I, Mackey K, Grusing S, Selph S. Screening for celiac disease: evidence report and systematic review for the US preventive services task force. JAMA. 2017;317:1258–68.
21. Jin J. Screening for celiac disease. JAMA. 2017;317:1286.
22. Force USPST, Bibbins-Domingo K, Grossman DC, Curry SJ, Barry MJ, Davidson KW, et al. Screening for celiac disease: US preventive services task force recommendation statement. JAMA. 2017;317:1252–7.
23. Choung RS, Murray JA. The US preventive services task force recommendation on screening for asymptomatic celiac disease: a dearth of evidence. JAMA. 2017;317:1221–3.
24. Ludvigsson JF, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut. 2014;63:1210–28.
25. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA, American College of Gastroenterology ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108:656–76.quiz 77.
26. Wiland HO, Henricks WH, Daly TM. Limited utilization of serologic testing in patients undergoing duodenal biopsy for celiac disease. BMC Gastroenterol. 2013;13:156.
27. Lau MS, Mooney PD, White WL, Appleby V, Moreea S, Haythem I, et al. Erratum to: 'Pre-endoscopy point of care test (Simtomax-IgA/IgG-deamidated gliadin peptide) for coeliac disease in iron deficiency anaemia: diagnostic accuracy and a cost saving economic model'. BMC Gastroenterol. 2016;16:122.
28. Mooney PD, Wong SH, Johnston AJ, Kurien M, Avgerinos A, Sanders DS. Increased detection of celiac disease with measurement of deamidated gliadin peptide antibody before endoscopy. Clin Gastroenterol Hepatol. 2015;13:1278–84.e1.
29. Leffler D, Schuppan D, Pallav K, Najarian R, Goldsmith JD, Hansen J, et al. Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease. Gut. 2013;62:996–1004.
30. Raju SA, Mooney PD, Aziz I, Kurien M, Sanders DS. Letter: gluten challenge in the era of noncoeliac gluten sensitivity – a change in clinical practice? Aliment Pharmacol Ther. 2016;43:656.
31. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: time for a standardized report scheme for pathologists. Eur J Gastroenterol Hepatol. 1999;11:1185–94.
32. Benkebil F, Combescure C, Anghel SI, Besson Duvanel C, Schäppi MG. Diagnostic accuracy of a new point-of-care screening assay for celiac disease. World J Gastroenterol. 2013;19:5111–7.
33. Bienvenu F, Besson Duvanel C, Seignovert C, Rouzaire P, Lachaux A, Bienvenu J. Evaluation of a point-of-care test based on deamidated gliadin peptides for celiac disease screening in a large pediatric population. Eur J Gastroenterol Hepatol. 2012;24:1418–23.
34. Bienvenu F, Anghel SI, Besson Duvanel C, Guillemaud J, Garnier L, Renosi F, et al. Early diagnosis of celiac disease in IgA deficient children: contribution of a point-of-care test. BMC Gastroenterol. 2014;14:186.
35. Raivio T, Kaukinen K, Nemes E, Laurila K, Collin P, Kovács JB, et al. Self transglutaminase-based rapid coeliac disease antibody detection by a lateral flow method. Aliment Pharmacol Ther. 2006;24:147–54.
36. Korponay-Szabó IR, Szabados K, Pusztai J, Uhrin K, Ludmány E, Nemes E, et al. Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study. BMJ. 2007;335:1244–7.
37. Almazán MV, Ortega E, Moreno Torres R, Tovar M, Romero J, López-Casado M, et al. Diagnostic screening for subclinical celiac disease using a rapid test in children aged 2–4. Pediatr Res. 2015;78:280–5.
38. Nemec G, Ventura A, Stefano M, Di Leo G, Baldas V, Tommasini A, et al. Looking for celiac disease: diagnostic accuracy of two rapid commercial assays. Am J Gastroenterol. 2006;101:1597–600.

39. Laadhar L, Kallel-Sellami M, Zitouni M, Mehrezi A, Makni S, Ben Hariz M. Is the rapid whole blood test useful for diagnosis and monitoring celiac disease in children? Tunis Med. 2011;89:16–7.
40. Baviera LC, Aliaga ED, Ortigosa L, Litwin N, Peña-Quintana L, Méndez V, et al. Celiac disease screening by immunochromatographic visual assays: results of a multicenter study. J Pediatr Gastroenterol Nutr. 2007;45:546–50.
41. Singh P, Wadhwa N, Chaturvedi MK, Bhatia V, Saini S, Tandon N, et al. Validation of point-of-care testing for coeliac disease in children in a tertiary hospital in north India. Arch Dis Child. 2014;99:1004–8.
42. Lewis NR, Scott BB. Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests). Aliment Pharmacol Ther. 2006;24: 47–54.
43. Lewis NR, Scott BB. Meta-analysis: deamidated gliadin peptide antibody and tissue transglutaminase antibody compared as screening tests for coeliac disease. Aliment Pharmacol Ther. 2010;31:73–81.
44. Niveloni S, Sugai E, Cabanne A, Vazquez H, Argonz J, Smecuol E, et al. Antibodies against synthetic deamidated gliadin peptides as predictors of celiac disease: prospective assessment in an adult population with a high pretest probability of disease. Clin Chem. 2007;53:2186–92.
45. Rashtak S, Ettore MW, Homburger HA, Murray JA. Comparative usefulness of deamidated gliadin antibodies in the diagnosis of celiac disease. Clin Gastroenterol Hepatol. 2008;6:426–32. quiz 370
46. Abrams JA, Brar P, Diamond B, Rotterdam H, Green PH. Utility in clinical practice of immunoglobulin a anti-tissue transglutaminase antibody for the diagnosis of celiac disease. Clin Gastroenterol Hepatol. 2006;4:726–30.
47. Beltran L, Koenig M, Egner W, Howard M, Butt A, Austin MR, et al. High-titre circulating tissue transglutaminase-2 antibodies predict small bowel villous atrophy, but decision cut-off limits must be locally validated. Clin Exp Immunol. 2014;176:190–8.
48. Venugopal G, Mechenro J, Makharia G, Singh A, Pugazhendhi S, Balamurugan R, et al. Sequential testing with different tissue transglutaminase antibodies, a new approach for diagnosis of celiac disease. Indian J Gastroenterol. 2017;36:481–6.
49. Kaukinen K, Turjanmaa K, Maki M, Partanen J, Venalainen R, Reunala T, et al. Intolerance to cereals is not specific for coeliac disease. Scand J Gastroenterol. 2000;35:942–6.
50. Coburn JA, Vande Voort JL, Lahr BD, Van Dyke CT, Kroning CM, Wu TT, et al. Human leukocyte antigen genetics and clinical features of self-treated patients on a gluten-free diet. J Clin Gastroenterol. 2013; 47:828–33.
51. Aziz I, Lewis NR, Hadjivassiliou M, Winfield SN, Rugg N, Kelsall A, et al. A UK study assessing the population prevalence of self-reported gluten sensitivity and referral characteristics to secondary care. Eur J Gastroenterol Hepatol. 2014;26:33–9.
52. Kabbani TA,Vanga RR,Leffler DA,Villafuerte-Galvez J,Pallav K,Hansen J, et al. Celiac disease or non-celiac gluten sensitivity? An approach to clinical differential diagnosis. Am J Gastroenterol. 2014;109:741–6.
53. Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C, et al. The clinical effectiveness and cost-effectiveness of point-of-care tests (CoaguChek system, INRatio2 PT/INR monitor and ProTime Microcoagulation system) for the self-monitoring of the coagulation status of people receiving long-term vitamin K antagonist therapy, compared with standard UK practice: systematic review and economic evaluation. Health Technol Assess. 2015;19:1–172.
54. Gliddon HD, Peeling RW, Kamb ML, Toskin I, Wi TE, Taylor MM, A systematic review and meta-analysis of studies evaluating the performance and operational characteristics of dual point-of-care tests for HIV and syphilis. Sex Transm Infect. 2017;93:S3–15.
55. Hoerter NA, Shannahan SE, Suarez J, Lewis SK, Green PHR, Leffler DA, et al. Diagnostic yield of isolated deamidated gliadin peptide antibody elevation for celiac disease. Dig Dis Sci. 2017;62:1272–6.
56. Lau MS, Mooney PD, White WL, Rees MA, Wong SH, Kurien M, et al. The role of an IgA/IgG-deamidated gliadin peptide point-of-care test in predicting persistent villous atrophy in patients with celiac disease on a gluten-free diet. Am J Gastroenterol. 2017;112:1859–67.