Point-of-care testing for celiac disease has a low sensitivity in endoscopy

Peter D. Mooney, MRCP,[1] Matthew Kurien, MRCP,[1] Kate E. Evans, MRCP,[1] Ioannis Chalkiadakis, MD,[1] Melissa F. Hale, MRCP,[1] Mohamad Z. Kannan, MRCP,[1] Victoria Courtice,[1] Alexander J. Johnston,[1] Andrew J. Irvine,[1] Marios Hadjivassiliou, FRCP,[2] David S. Sanders, FACG[1]

Sheffield, South Yorkshire, United Kingdom

Background: Celiac disease (CD) is a common but underdiagnosed condition. A rapid point-of-care test (POCT) could reduce lead times and missed diagnoses.

Objective: To assess the utility of an immunoglobulin (Ig) A tissue transglutaminase (TTG) antibody POCT in an endoscopic setting.

Design: Prospective observational study.

Setting: A single UK university hospital.

Patients: Patients presenting with suspected CD, known CD, and routine endoscopy for upper GI symptoms.

Interventions: All patients were tested with POCT, serum TTG, endomysial antibody (EMA), and upper GI endoscopy with duodenal biopsies at the same visit.

Main Outcome Measurements: Comparison was made with histology in all cases, with villous atrophy regarded as diagnostic of CD.

Results: A total of 576 patients (63.5% female, mean [± standard deviation] age 49.7 years [± 17.6 years]) were recruited. A total of 523 patients had no prior diagnosis of CD, and 53 patients had known CD coming for reassessment. A total of 117 patients were newly diagnosed with CD, and 82 were positively identified by the POCT. Sensitivity, specificity, positive predictive value, and negative predictive value were 70.1%, 96.6%, 85.4%, and 91.8%, respectively. In comparison, TTG and EMA both performed significantly better than the POCT. Sensitivity and specificity of TTG were 91.0% and 83.5%, respectively, and EMA were 83.8% and 97.5%, respectively. Of patients with known CD coming for reassessment, 26 had villous atrophy, and POCT results were positive in 16 (61.5%). There was poor agreement between POCT and standard serology.

Limitations: High pre-test probability of CD.

Conclusion: The performance of this POCT was disappointing compared with standard serology and cannot at present be recommended within the context of an endoscopy unit. (Gastrointest Endosc 2014;80:456-62.)

(footnotes appear on last page of article)

Adult celiac disease (CD) is the most common chronic inflammatory bowel condition encountered by physicians.[1] Internationally, the prevalence of this condition is estimated to be between 0.2% and 1.0%.[2,3] In the absence of early diagnosis and appropriate management, untreated CD can be associated with significant morbidity and increased mortality.[4,5] We, and others, have reported delays in diagnosis ranging from 4 to 13 years based on United Kingdom and United States cohorts.[6,7] One reason for this may be missed opportunities at endoscopy. A recent U.S. study showed that 5% of patients with newly diagnosed CD had a prior EGD, and in 59% of these patients, a duodenal biopsy specimen was not taken.[8] Similar data have been reported in the United Kingdom.[6] This suggests a failure in case finding for CD at endoscopy.[9-11] One possible explanation for this may be reliance by endoscopists on the presence of endoscopic

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markers of CD to guide biopsy in selected patients. However, endoscopic markers of CD lack the required sensitivity.[12] This has led many centers to advocate routine duodenal biopsies or a very low threshold for biopsy.[8,13] Observational studies suggest that practice is highly variable, with duodenal biopsy rates ranging from 31% to 74%.[13-15] Furthermore, a routine biopsy approach is costly, and for this reason we have previously described a clinical algorithm that combines symptoms and serology.[16] This algorithm advocates biopsy sampling from high-risk individuals with symptoms of diarrhea, weight loss, or anemia and also from patients with positive results for tissue transglutaminase (TTG). By adopting this strategy, our group demonstrated a sensitivity of 100% for detecting patients presenting for endoscopy who had undiagnosed CD and confidently identified those patients who did not require duodenal biopsies. However, the limitation to using this clinical decision tool in practice is that serology results are not always available at the time of the endoscopic procedure. Thus, the use of an accurate point-of-care test (POCT) that can provide a rapid result before EGD in appropriate patient groups could guide biopsy strategies and potentially be cost saving.

There has been limited work undertaken evaluating POCTs in CD and no previous studies within the endoscopy setting. In total, there have been 10 POCT studies (composite n = 6873).[17-26] Of these, 9 of 10 studies were based on Biocard, a whole-blood immunoglobulin (Ig) A transglutaminase–based test (BHR Pharmaceuticals Ltd, Nuneaton, Wawrickshire, UK), and only one other POCT has any published data to evaluate.[26] The reported sensitivity in some data sets was comparable to that of standard serology at >90%; for this reason we chose to use Biocard in the setting of endoscopy. Furthermore, none of the published studies have compared with the criterion standard of small-bowel histology in all tested patients. This study aims to assess the clinical utility of Biocard in a population referred for endoscopy. Comparisons are made against current serology tests and the criterion standard of a duodenal biopsy in all patients.

Take-home Message

- Ideally a rapid point-of-care test used in endoscopy could reduce the numbers of missed diagnoses of celiac disease.
- Based on our study, findings the Biocard point-of-care test cannot be used for case finding or for the reassessment of known celiac disease in an endoscopic setting.

PATIENTS AND METHODS

Patient recruitment

Patients were recruited from a single university hospital in the United Kingdom, which serves an approximate population of 250,000 people. Patients were prospectively recruited into 2 groups from a single, celiac disease–enriched endoscopy list between August 2010 and August 2013. The endoscopy list is open to primary-care and secondary-care referrals for patients with suspected CD or reassessment of known CD but also includes patients who are referred for open access endoscopy from primary care for investigation of other upper GI symptoms such as dyspepsia or GERD. Group 1 comprised 523 patients with no prior diagnosis of CD. Group 2 was a cohort of 53 patients with known CD presenting for reassessment of persistent symptoms. This was to assess the utility of the POCT as a surrogate marker of villous atrophy, which could be used in the assessment of adherence in an office-based setting.

All recruited patients were serologically tested for IgA TTG, endomysial antibody (EMA), and total IgA level and underwent the POCT transglutaminase-based rapid test (Biocard test). Duodenal biopsy was performed as the criterion standard in all cases. Patient consent was obtained before all EGD examinations, with quadrant biopsy specimens taken from the second part of the duodenum in all patients. Patients were excluded from the study if they had coagulopathy (international normalized ratio of >1.3 [normal range, 0.9-1.2] or a platelet count of $<80 \times 10^9$/L [normal range, 140-370 $\times$ 10^9]) or active GI bleeding or if a suspected carcinoma was observed during the examination.

Serology

Total IgA was measured on a Behring BN2 nephelometer (Behring UK, Haywards Heath, West Sussex, UK). IgA TTG antibodies were assayed by using enzyme-linked immunosorbent assay kits (Aesku Diagnostics, Wendelsheim, Germany). A TTG titer of >15 U/mL was regarded as positive. IgA EMA was detected by immunofluorescence on primate esophagus sections (Binding Site, Birmingham, UK).

POCT

In this study we evaluated a single POCT, the Biocard Celiac Test (Kits made by Ani Biotech Oy, Vantaa, Finland. Kits supplied by BHR pharmaceuticals Nuneaton, Wawrickshire, UK). Fresh fingertip whole-blood samples were collected according to the manufacturer's guidance, with samples transferred into a tube containing 0.5 mL of hemolyzing sample buffer by using a glass capillary. Three drops of the hemolyzed sample dilution were then pipetted into the round application field of the Biocard test card, with test results interpreted at 10 minutes. All tests in this study were undertaken by trained endoscopy staff, and findings were interpreted according to the manufacturer's written