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Article title: 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

Short title: IgA/IgG-DGP in predicting persistent villous atrophy

Authors:

Michelle Shui Yee Lau[1], MBChB, MRCP

Peter D. Mooney[1], MBChB, MRCP, MD

William L. White[1], medical student

Michael A. Rees[1], medical student

Simon H. Wong[1], MBChB

Matthew Kurien[1], MBChB, MRCP, MD

Nick Trott[1], _____

Daniel Leffler[2], MD, MS

Marios Hadjivassiliou[1], MBChB, MRCP, MD, FRCP

David Surendran Sanders[1], MBChB, MRCP, MD, FACG, FRCP

[1]Academic Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Sheffield, United Kingdom.

Celiac Center and Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Corresponding author:

Dr. Michelle Shui Yee Lau

Clinical research fellow in gastroenterology

Department of Gastroenterology, Room P18, Royal Hallamshire Hospital, Sheffield, S10 2JF, United Kingdom.

Email: michellelau@doctors.org.uk

Conflict of interests: Professor Sanders 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. Dr. Daniel Leffler is a Medical Director at Takeda Pharmaceuticals. Takeda Pharmaceuticals did not have any input in the study design, access to study data, interpretation of the findings or drafting of the manuscript. The remaining authors disclose no conflicts of interest.

Abstract

Introduction: Mucosal healing is important in celiac disease (CD) for the prevention of complications. However, obtaining duodenal biopsies is invasive, and there is currently no reliable surrogate marker for histological remission in clinical practice. We aimed to assess the role of a commercially available point of care test (POCT), Simtomax (IgA/IgG-deamidated gliadin peptide, Rheinfelden, Switzerland), in detecting persistent villous atrophy in CD.

Methods: We prospectively recruited patients with CD attending endoscopy for the assessment of histological remission. All patients had IgA-endomysial antibodies (EMA), IgA-tissue transglutaminase antibodies (TTG) and Simtomax performed, and completed a validated gluten free diet (GFD) adherence questionnaire validated by Biagi et al. A gastroscopy was performed in all patients, with four biopsies taken from the second part of the duodenum and one from the duodenal bulb. We compared the diagnostic performance of the surrogate markers against duodenal histology as the reference standard.

Results: A total of 217 patients with CD (70% female, age range 16-83, median age 53) on a GFD (median duration 6 years) were recruited from 2013-2017. Eighty-five (39.2%) patients had persistent villous atrophy. The sensitivities of Simtomax, TTG, EMA and the adherence score in detecting villous atrophy were 67.1%, 44.7%, 37.7% and 24.7% respectively.

Conclusion: The sensitivity of Simtomax was higher than the other surrogate markers in predicting villous atrophy (p=0.0005), although with a lower specificity. In combination with clinical and dietetic assessments, Simtomax could serve as a valuable adjunct to aid decision making on the necessity of repeat biopsies during follow up consultations, with an additional advantage of providing results within 10 minutes.

Introduction

Celiac disease is a systemic autoimmune disease associated with gastrointestinal and extra-gastrointestinal symptoms, triggered by gluten in genetically susceptible individuals affecting approximately 1% of the general population worldwide.(1, 2) A gluten free diet remains the only treatment at present. Strict dietary adherence is often challenging given the ubiquity of gluten in Westernized diets and processed foods, with adherence rates reported to vary between 42% and 91%.(3-5) Dietary transgression is the commonest cause for non responsive celiac disease, (6-8) which can lead to gastrointestinal and extra-gastrointestinal symptoms, persistent villous atrophy, complications such as osteoporosis and malabsorption, and a worse quality of life. Histological remission is not always achieved in adults, with remission rates ranging from 34%-65%.(9-11) This is an important point because persistent villous atrophy increases the risk of lymphoproliferative malignancies (HR 2.26) (12) and hip fractures (HR 1.67).(13) Consequently, the logical approach for disease monitoring would be histological assessment of the duodenum for mucosal healing. However, this method is invasive, costly, and carries risks of complications such as bleeding, perforation and cardiopulmonary complications from sedation. (14, 15) Furthermore, there is little consensus for routine follow up biopsy and the timing of re-biopsy among individual practice and national guidelines.(16-19)

There is certainly an unmet need for a reliable surrogate marker for histological remission in celiac disease. A myriad of novel markers such as serum intestinal fatty acid-binding protein (I-FABP) levels (20), urinary gluten immunogenic peptide,(21) citrulline,(22) fecal fat excretion (23), urinary lactulose-to-mannitol excretion ratios, (24) and the maximum concentration of simvastatin in the small intestine (25) have been studied, but none of them are currently used

in widespread routine clinical practice.

At present, a combination of dietetic evaluation, symptom assessment and serological titers are used during follow up to determine the necessity for a repeat duodenal biopsy. However, these non-invasive surrogate markers have been shown to correlate poorly with persistent villous atrophy. Previous studies have shown a weak association between histological recovery and serology such as tissue transglutaminase antibodies (TTG) and endomysial antibodies (EMA).(10, 26-29) Dietary assessment by a specialist dietitian is currently the optimal method of measuring adherence,(30) although the method of assessment is not standardized. Moreover, there are limited celiac specialist dietitians to provide this service, often with long waiting times for patients.

For all these reasons, a simple and reliable method of assessment to measure dietary adherence is needed. A dietary assessment questionnaire was devised by Biagi and colleagues, which contains 4 simple questions based on the patients' strategy for gluten avoidance rather than assessing the amount of gluten ingested. Biagi et al. reported that the adherence score identified patients in histological remission, with a positive predictive value of 35.7% and negative predictive value of 86.7%.(31) Further studies are required to validate the utility of this questionnaire.

Several point of care tests detecting celiac antibodies have been developed over the past decade. Most of the point of care tests detect TTG using lateral flow immunochromotography, such as Biocard, Celiac Quick Test and Stick CD1 and 2, with the exception of Simtomax which detects deamidated gliadin peptide antibodies (DGP). There is an abundance of studies investigating the performance of point of care tests in the diagnosis of celiac disease, with sensitivities of the aforementioned point of care tests reported to be 58-100%.(32-40) A

recent head to head trial of Simtomax, Biocard and Celiac Quick Test demonstrated that Simtomax outperformed the other two, with sensitivities of 94.4%, 72.2% and 77.8% respectively.(32) On the other hand, there is a paucity of studies examining the role of point of care tests in disease monitoring. Previous studies showed the sensitivities were found to be 78.9% for Simtomax,(36) and 77.8% (using whole blood) and 93.5% (using serum) for Celiac Quick Test in measuring dietary adherence in known celiac disease.(39) However, these results should be interpreted with caution due to study limitations, such as using TTG rather than duodenal histology as the reference standard.We aimed to evaluate the diagnostic performance of Simtomax, a commercially available IgA/IgG-DGP based point of care test, TTG, EMA and the adherence questionnaire devised by Biagi et al. in predicting persistent villous atrophy in patients with celiac disease on a gluten free diet.

Methods

Study design and Patients

The study took place at the Royal Hallamshire Hospital, Sheffield, U.K., from March 2013-January 2017. We prospectively recruited patients with biopsy proven celiac disease on a gluten free diet who were attending for a gastroscopy on a single celiac disease research list for the assessment of histological remission. Written consent for the study was obtained before their blood tests and gastroscopies. All patients were tested with IgA-TTG, IgA-EMA, total IgA levels and the point of care test, Simtomax, at the endoscopy unit. The dietary adherence questionnaire was completed by the patients at the endoscopy unit. A gastroscopy with duodenal biopsies was then performed in all patients.

Point of care test, Simtomax

Simtomax is a point of care test for celiac disease manufactured by Augurix Diagnostics, Rheinfelden, Switzerland. It detects both IgA-DGP and IgG-DGP, 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 5 drops of the provided buffer solution. The result was available after 10 minutes. Positive results were indicated by the presence of a solid red test line for IgA and/or IgG-DGP positivity. A second single red line indicated the presence of IgA. An in-built red control line ensured a correctly functioning test.

Celiac serology

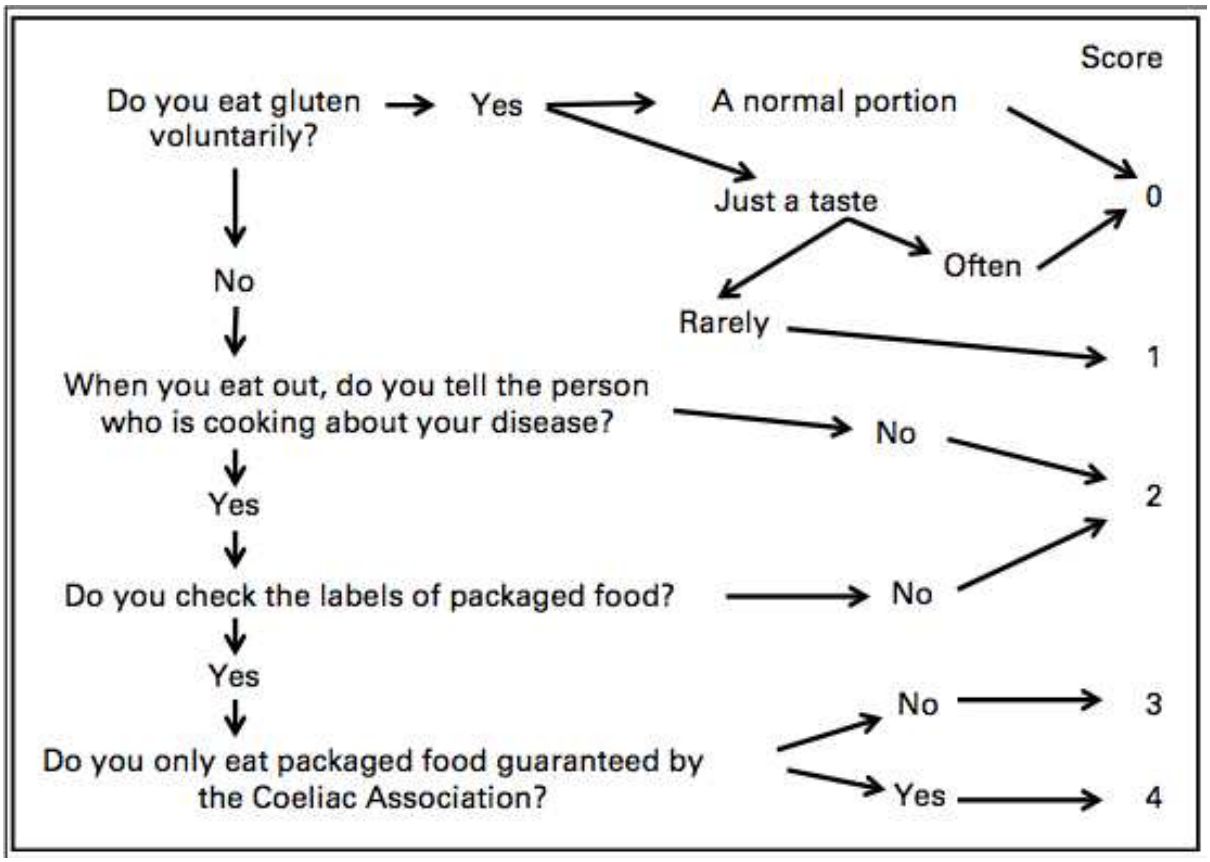
TTG antibodies were assayed using enzyme-linked immunosorbent assay (ELISA) kits (Aesku Diagnostics, Wendelsheim, Germany). A TTG titer of > 15 U/ml before 20/5/2014, a new cut off level of >9 U/ml from 20/5-11/12/2014, and then >7 U/ml from 12/12/ 2014 onwards, were regarded as positive as per the manufacturer's guidance. 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).

Dietary adherence questionnaire

The validated dietary adherence questionnaire devised by Biagi et al consisted of 4 simple questions. It gave a 5 point score (0-4), with scores 3-4 indicating strict dietary adherence, and scores 0-2 indicating non-adherence. This questionnaire was administered to the patients at the endoscopy unit before their gastroscopy. Please refer to figure 1 for the questionnaire.

Figure 1: Questionnaire and scoring system devised by Biagi et al. to assess compliance with a gluten-free diet in coeliac patients. 'Often': the patient consumes gluten so often that

he/she cannot remember when and how many times that has happened. 'Rarely': the patient consumes gluten only occasionally. She/he can remember when and how many times that has happened.



Histological evaluation

In total, at least 5 biopsies were taken from the duodenum with a single bite per pass technique, including at least 1 biopsy from the duodenal bulb and 4 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 3 levels were stained with haematoxylin and eosin, and reported by gastrointestinal histopathologists without knowledge of the Simtomax or serology results. Villous atrophy was graded according to the modified Marsh criteria. Patients with March 0-2 histology without villous atrophy were considered to be in histological remission for the purpose of diagnostic accuracy calculations.

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 accuracy of TTG, EMA, Simtomax and the adherence questionnaire in detecting ongoing villous atrophy was presented with sensitivity, specificity, positive (PPV) and negative predictive values, measuring against duodenal histology as the reference standard. Clopper-Pearson method was used to calculate the confidence intervals for the diagnostic test sensitivities.

Results

A total of 217 patients with biopsy proven celiac disease on a gluten free diet were recruited from 2013-2017 (70% female, age range 16-83, median age 53). The median duration of a gluten free diet was 6 years (76.5 months; range: 6-900 months). Eighty-five (39.2%) patients had persistent villous atrophy as defined by Marsh grade 3 histology. Sixty-eight (80.0%) patients had Marsh 3 villous atrophy in both the duodenal bulb and second part of the duodenum, 10 (11.8%) patients had villous atrophy isolated to the duodenal bulb, and 6 (7.1%) patients had villous atrophy only in the second part of the duodenum. One patient with Marsh 3 villous atrophy in the second part of the duodenum could not be graded in the duodenal bulb. There were no invalid or uninterpretable Simtomax results.

Amongst patients with persistent villous atrophy, 8 had type 1 refractory celiac disease (age range 44-71; median age 51.0; 6 females [75%]), and 4 had type 2 refractory disease (age range 57-65; median age 60.0; 1 female [25%]).

Table 1: the number of patients for each Marsh grade, and the number and proportion of patients whose surrogate markers correctly identified the presence (Marsh 3a-c histology) or absence (Marsh 0-2 histology) of persistent villous atrophy.

	Marsh 0	**Marsh 1**	**Marsh 2**	**Marsh 0-2**	**Marsh 3a**	**Marsh 3b**	**Marsh 3c**	**Marsh 3a-c**
No. of patients	78	37	17	132	38	24	23	85
Simtomax	48 (61.5%)	23 (62.2%)	7 (41.2%)	78 (59.1%)	21 (55.3%)	21 (87.5%)	15 (65.2%)	57 (67.1%)
TTG	73 (93.6%)	30 (81.1%)	15 (88.2%)	118 (89.4%)	9 (23.7%)	12 (50.0%)	11 (47.8%)	32 (37.6%)
EMA	70 (89.8%)	30 (81.1%)	14 (82.4%)	114 (86.5%)	9 (23.7%)	16 (66.7%)	13 (56.5%)	38 (44.7%)
Adherence score	69 (88.5%)	31 (83.8%)	14 (82.4%)	114 (86.4%)	4 (10.5%)	9 (37.5%)	8 (34.8%)	21 (24.7%)
	Surrogate markers correctly testing negative for villous atrophy.				Surrogate markers correctly testing positive for villous atrophy.			

Table 2: The diagnostic performance of Simtomax, TTG, EMA and the adherence score in detecting persistent villous atrophy measuring against duodenal histology.

	Sensitivity (%)	**Specificity (%)**	**Positive predictive value (%)**	**Negative predictive value (%)**
Simtomax	67.1 (56.0-76.9)	59.1 (50.2-67.6)	51.4 (45.0-57.6)	73.6 (66.6-79.6)
TTG	44.7 (33.9-55.9)	86.4 (79.3-91.7)	67.9 (56.4-77.5)	70.8 (66.5-74.8)
EMA	37.7 (27.4-48.8)	89.4 (82.9-94.1)	69.6 (56.5-80.1)	69.0 (65.1-72.6)
Adherence score	24.7 (16.0-35.3)	86.4 (79.3-91.7)	53.9 (39.8-67.3)	64.0 (60.8-67.2)

Discussion

This is the largest study that evaluates the point of care test, Simtomax, in disease monitoring. One of the strengths of this study is that duodenal biopsies were taken from all patients irrespective of their celiac antibody or adherence score results, ensuring that false negative cases would be taken into account when calculating the sensitivities and specificities of the surrogate markers. The only other published study investigating the role of Simtomax in disease monitoring was performed by Benkebil et al. (36) The authors tested Simtomax and TTG in 46 patients with known celiac disease, but only those with a positive TTG serology had duodenal biopsies taken. The sensitivity and specificity of Simtomax was reported to be 78.9% and 95.7% respectively. These results are unlikely to reflect the true performance of Simtomax in disease monitoring, as only patients with a positive TTG were biopsied, which means false negative cases would be missed.

Deamidated gliadin peptide (DGP) serology has been shown in several studies to be useful for disease monitoring in celiac disease, and appeared to be superior to TTG in this respect. (41-44) Spatola et al. showed that IgG-DGP was an effective surrogate marker for histological recovery, with a sensitivity and specificity of 87% and 89% (at a positive threshold of 12U/ml), versus 33% and 100% for TTG (at a positive threshold of 5U/ml) when tested on 60 patients with known celiac disease who were strictly adherent, of which 15 (20%) had persistent villous atrophy. ROC curve analysis showed that IgG-DGP substantially outperformed IgA-TTG with a receiver operator curve (ROC) area under the curve (AUC) of 0.94 versus 0.61.(42) Similar results were replicated by de Chaisemartin's group subsequently, with a ROC analysis demonstrating AUC 0.817 for IgG-DGP in detecting ongoing villous atrophy.(44)

Although the sensitivity of Simtomax was significantly higher than TTG in our study (p=0.0005), Simtomax alone is still inadequate as a surrogate marker for ongoing villous atrophy. It is not clear why there is such marked difference between the performance of Simtomax and IgG-DGP serology as previously reported.(42, 44) It is conceivable that the serological cut off value for untreated celiac disease is not appropriate for disease monitoring purposes, and the threshold for the generation of a positive result in Simtomax cannot be adjusted like laboratory serological titers to identify the optimal cut off numerical value.

Table 1 shows the performance of the surrogate markers across the range of Marsh grades, demonstrating where the true positives/negatives and false positives/negatives lie within the Marsh grade spectrum. TTG, EMA and the adherence score generally faired better in correctly identifying patients in histological remission (Marsh 0-2), but missed a relatively large proportion of patients with villous atrophy (higher rates of false negatives). Conversely, Simtomax performed better in detecting patients with villous atrophy than correctly identifying those in remission (higher rates of false positives). For a disease monitoring surrogate marker, it is more important to have a high sensitivity than a high specificity, as the priority is to identify patients with ongoing villous atrophy which can lead to serious complications, whilst accepting a certain degree of false positives as a drawback.

Although Simtomax outperformed the other surrogate markers, it is not sensitive enough to be used in isolation during follow up. However, we believe that by combining dietetic evaluation and symptom assessment, Simtomax could serve as a useful adjunct to provide instant DGP results during a follow up consultation, not only for the benefit of the clinicians,

but also immediate feedback for the patients which they highly value. Currently, patients have their celiac serology taken on the day of their follow up consultation, and the results usually takes 3-5 days or more to turn around. This adds to the clinician's administrative burden to communicate the results with the patients retrospectively, and it also often causes delays in clinical decision making regarding the management plan. With the use of a point of care test during a clinic consultation, a face to face discussion between the clinician and the patient making a joint decision regarding the need for re-biopsy or a dietetic review is made possible.

The low sensitivity of 44.7% for IgA-TTG in detecting persistent villous atrophy in our study is in line with what has been reported in the literature. For instance, Kaukinen et al. reported the IgA-TTG sensitivity to be 41%,(26) and more recently 43.6% by Sharkey's group.(10) The even lower sensitivity of 37.7% for IgA-EMA also mirrors the 26% sensitivity reported by Kaukinen et al. (26)

The dietary adherence questionnaire was quick and simple to administer, although its performance in identifying patients with ongoing villous atrophy was disappointing in our study. A recent study by Bannister et al. evaluated this adherence questionnaire and found that the adherence score had a similarly low correlation to villous atrophy, with a sensitivity, specificity, positive and negative predictive values of 33%, 89%, 13% and 97% respectively.(45) The sensitivity and specificity of the adherence score were consistent with our results of 24.7% and 86.4%, however the positive and negative predictive values were strikingly different from our findings. This could be due to the significantly lower prevalence of persistent villous atrophy in Bannister's pediatric cohort (5.3%) compared to our adult cohort (39.2%), where a low prevalence population could lead to a high negative predictive value for

a diagnostic test. Indeed, previous follow up studies have demonstrated a slower and more incomplete mucosal healing in adults with celiac disease treated with a gluten free diet. (11, 46-48) Potential reasons for the low sensitivity of the adherence questionnaire include reliance on the patient understanding of what foods contain gluten and their forthcomingness.

To conclude, this study showed for the first time that the commercially available DGP based point of care test, Simtomax, had a superior sensitivity in detecting persistent villous atrophy in patients with known celiac disease, compared to the adherence score and conventional celiac serology (TTG and EMA) which are routinely used for disease monitoring at the present time. Simtomax could help streamline the follow up process by providing DGP results during the consultation, and facilitate the decision making between the clinician and the patient regarding the onward management plan such as the necessity of follow up duodenal biopsy.

WHAT IS CURRENT KNOWLEDGE

- Persistent villous atrophy in celiac disease increases the risk of complications in celiac disease.
- There are currently no reliable surrogate markers for persistent villous atrophy.

WHAT IS NEW HERE

- Simtomax has significantly higher sensitivity than conventional serology in detecting persistent villous atrophy.
- Simtomax could provide instant DGP results during follow up consultations to facilitate onward management.

- The validated dietary adherence questionnaire was inferior to Simtomax and serology in identifying ongoing villous atrophy.

References

1. 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(3):286-92.
2. West J, Logan RF, Hill PG, Lloyd A, Lewis S, Hubbard R, et al. Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. Gut. 2003;52(7):960-5.
3. Silvester JA, Weiten D, Graff LA, Walker JR, Duerksen DR. Living gluten-free: adherence, knowledge, lifestyle adaptations and feelings towards a gluten-free diet. J Hum Nutr Diet. 2016;29(3):374-82.
4. Hall NJ, Rubin GP, Charnock A. Intentional and inadvertent non-adherence in adult coeliac disease. A cross-sectional survey. Appetite. 2013;68:56-62.
5. Hall NJ, Rubin G, Charnock A. Systematic review: adherence to a gluten-free diet in adult patients with coeliac disease. Aliment Pharmacol Ther. 2009;30(4):315-30.
6. Leffler DA, Dennis M, Hyett B, Kelly E, Schuppan D, Kelly CP. Etiologies and predictors of diagnosis in nonresponsive celiac disease. Clin Gastroenterol Hepatol. 2007;5(4):445-50.
7. Abdulkarim AS, Burgart LJ, See J, Murray JA. Etiology of nonresponsive celiac disease: results of a systematic approach. Am J Gastroenterol. 2002;97(8):2016-21.
8. Dewar DH, Donnelly SC, McLaughlin SD, Johnson MW, Ellis HJ, Ciclitira PJ. Celiac disease: management of persistent symptoms in patients on a gluten-free diet. World J Gastroenterol. 2012;18(12):1348-56.
9. Rubio-Tapia A, Rahim MW, See JA, Lahr BD, Wu TT, Murray JA. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. Am J Gastroenterol. 2010;105(6):1412-20.
10. Sharkey LM, Corbett G, Currie E, Lee J, Sweeney N, Woodward JM. Optimising delivery of care in coeliac disease - comparison of the benefits of repeat biopsy and serological follow-up. Aliment Pharmacol Ther. 2013;38(10):1278-91.
11. Wahab PJ, Meijer JW, Mulder CJ. Histologic follow-up of people with celiac disease on a gluten-free diet: slow and incomplete recovery. Am J Clin Pathol. 2002;118(3):459-63.
12. Lebwohl B, Granath F, Ekbom A, Smedby KE, Murray JA, Neugut AI, et al. Mucosal healing and risk for lymphoproliferative malignancy in celiac disease: a population-based cohort study. Annals of internal medicine. 2013;159(3):169.
13. Lebwohl B, Michaelsson K, Green PH, Ludvigsson JF. Persistent mucosal damage and risk of fracture in celiac disease. J Clin Endocrinol Metab. 2014;99(2):609-16.
14. Kavic SM, Basson MD. Complications of endoscopy. Am J Surg. 2001;181(4):319-32.
15. Committee ASoP, Ben-Menachem T, Decker GA, Early DS, Evans J, Fanelli RD, et al. Adverse events of upper GI endoscopy. Gastrointest Endosc. 2012;76(4):707-18.
16. 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(8):1210-28.

17. Bai JC, Fried M, Corazza GR, Schuppan D, Farthing M, Catassi C, et al. World Gastroenterology Organisation global guidelines on celiac disease. J Clin Gastroenterol. 2013;47(2):121-6.
18. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology. 2006;131(6):1981-2002.
19. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA, American College of G. ACG clinical guidelines: diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108(5):656-76; quiz 77.
20. Marlou PMA, Daniel AL, Ciaran PK, Detlef S, Robert MN, Jeffrey DG, et al. Serum I-FABP Detects Gluten Responsiveness in Adult Celiac Disease Patients on a Short-Term Gluten Challenge. The American Journal of Gastroenterology. 2016.
21. Moreno ML, Cebolla A, Munoz-Suano A, Carrillo-Carrion C, Comino I, Pizarro A, et al. Detection of gluten immunogenic peptides in the urine of patients with coeliac disease reveals transgressions in the gluten-free diet and incomplete mucosal healing. Gut. 2017;66(2):250-7.
22. Adriaanse M, Leffler DA. Serum markers in the clinical management of celiac disease. Dig Dis. 2015;33(2):236-43.
23. Pyle GG, Paaso B, Anderson BE, Allen D, Marti T, Khosla C, et al. Low-dose gluten challenge in celiac sprue: malabsorptive and antibody responses. Clin Gastroenterol Hepatol. 2005;3(7):679-86.
24. Vilela EG, de Abreu Ferrari Mde L, de Gama Torres HO, Martins FP, Goulart EM, Lima AS, et al. Intestinal permeability and antigliadin antibody test for monitoring adult patients with celiac disease. Dig Dis Sci. 2007;52(5):1304-9.
25. Moron B, Verma AK, Das P, Taavela J, Dafik L, Diraimondo TR, et al. CYP3A4-catalyzed simvastatin metabolism as a non-invasive marker of small intestinal health in celiac disease. Am J Gastroenterol. 2013;108(8):1344-51.
26. Kaukinen K, Sulkanen S, Maki M, Collin P. IgA-class transglutaminase antibodies in evaluating the efficacy of gluten-free diet in coeliac disease. Eur J Gastroenterol Hepatol. 2002;14(3):311-5.
27. Dickey W, Hughes DF, McMillan SA. Disappearance of endomysial antibodies in treated celiac disease does not indicate histological recovery. Am J Gastroenterol. 2000;95(3):712-4.
28. Hopper AD, Hadjivassiliou M, Hurlstone DP, Lobo AJ, McAlindon ME, Egner W, et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. Clin Gastroenterol Hepatol. 2008;6(3):314-20.
29. Tursi A, Brandimarte G, Giorgetti GM. Lack of usefulness of anti-transglutaminase antibodies in assessing histologic recovery after gluten-free diet in celiac disease. J Clin Gastroenterol. 2003;37(5):387-91.
30. Leffler DA, Edwards George JB, Dennis M, Cook EF, Schuppan D, Kelly CP. A prospective comparative study of five measures of gluten-free diet adherence in adults with coeliac disease. Aliment Pharmacol Ther. 2007;26(9):1227-35.
31. Biagi F, Bianchi PI, Marchese A, Trotta L, Vattiato C, Balduzzi D, et al. A score that verifies adherence to a gluten-free diet: a cross-sectional, multicentre validation in real clinical life. Br J Nutr. 2012;108(10):1884-8.

32. 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(7):1278-84.e1.
33. Mooney PD, Kurien M, Evans KE, Chalkiadakis I, Hale MF, Kannan MZ, et al. Point-of-care testing for celiac disease has a low sensitivity in endoscopy. Gastrointest Endosc. 2014;80(3):456-62.
34. 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(1):147-54.
35. 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.
36. 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(31):5111-7.
37. 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(7632):1244-7.
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(7):1597-600.
39. George DA, Hui LL, Rattehalli D, Lovatt T, Perry I, Green M, et al. The role of near-patient coeliac serology testing in the follow- up of patients with coeliac disease. Frontline Gastroenterol. 2014;5(1):20.
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(5):546-50.
41. Volta U, Granito A, Fiorini E, Parisi C, Piscaglia M, Pappas G, et al. Usefulness of antibodies to deamidated gliadin peptides in celiac disease diagnosis and follow-up. Dig Dis Sci. 2008;53(6):1582-8.
42. Spatola BN, Kaukinen K, Collin P, Maki M, Kagnoff MF, Daugherty PS. Persistence of elevated deamidated gliadin peptide antibodies on a gluten-free diet indicates nonresponsive coeliac disease. Aliment Pharmacol Ther. 2014;39(4):407-17.
43. Monzani A, Rapa A, Fonio P, Tognato E, Panigati L, Oderda G. Use of deamidated gliadin peptide antibodies to monitor diet compliance in childhood celiac disease. J Pediatr Gastroenterol Nutr. 2011;53(1):55-60.
44. de Chaisemartin L, Meatchi T, Malamut G, Fernani-Oukil F, Hosking F, Rault D, et al. Application of Deamidated Gliadin Antibodies in the Follow-Up of Treated Celiac Disease. PLoS One. 2015;10(8):e0136745.
45. Bannister EG, Cameron DJ, Ng J, Chow CW, Oliver MR, Alex G, et al. Can celiac serology alone be used as a marker of duodenal mucosal recovery in children with celiac disease on a gluten-free diet? Am J Gastroenterol. 2014;109(9):1478-83.
46. Kaukinen K, Peraaho M, Lindfors K, Partanen J, Woolley N, Pikkarainen P, et al. Persistent small bowel mucosal villous atrophy without symptoms in coeliac disease. Aliment Pharmacol Ther. 2007;25(10):1237-45.
47. Bardella MT, Velio P, Cesana BM, Prampolini L, Casella G, Di Bella C, et al. Coeliac disease: a histological follow-up study. Histopathology. 2007;50(4):465-71.

48. Lanzini A, Lanzarotto F, Villanacci V, Mora A, Bertolazzi S, Turini D, et al. Complete recovery of intestinal mucosa occurs very rarely in adult coeliac patients despite adherence to gluten-free diet. Aliment Pharmacol Ther. 2009;29(12):1299-308.

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

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