

## Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool

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### ABSTRACT

**Objective** To determine an effective diagnostic method of detecting all cases of coeliac disease in patients referred for gastroscopy without performing routine duodenal biopsy.

**Design** An initial retrospective cohort of patients attending for gastroscopy was analysed to derive a clinical decision tool that could increase the detection of coeliac disease without performing routine duodenal biopsy. The tool incorporated serology (measuring antibodies to tissue transglutaminase) and stratifying patients according to their referral symptoms (patients were classified as having a “high risk” or “low risk” of coeliac disease). The decision tool was then tested on a second cohort of patients attending for gastroscopy. In the second cohort all patients had a routine duodenal biopsy and serology performed.

**Setting** Teaching hospital in Sheffield.

**Participants** 2000 consecutive adult patients referred for gastroscopy recruited prospectively.

**Main outcome measure** Evaluation of a clinical decision tool using patients’ referral symptoms, tissue transglutaminase antibody results, and duodenal biopsy results.

**Results** No cases of coeliac disease were missed by the pre-endoscopy testing algorithm. The prevalence of coeliac disease in patients attending for endoscopy was 3.9% (77/2000, 95% confidence interval 3.1% to 4.8%). The prevalence in the high risk and low risk groups was 9.6% (71/739, 7.7% to 12.0%) and 0.5% (6/1261, 0.2% to 1.0%). The prevalence of coeliac disease in patients who were negative for tissue transglutaminase antibody was 0.4% (7/2000). The sensitivity, specificity, positive predictive value, and negative predictive value for a positive antibody result to diagnose coeliac disease was 90.9%, 90.9%, 28.6%, and 99.6%, respectively. Evaluation of the clinical decision tool gave a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 60.8%, 9.3%, and 100%, respectively.

**Conclusions** Pre-endoscopy serological testing in combination with biopsy of high risk cases detected all cases of coeliac disease. The use of this decision tool may enable the endoscopist to target patients who need a duodenal biopsy.

### INTRODUCTION

Adults with the classic (typical) form of coeliac disease usually present with diarrhoea, weight loss, or symptoms that suggest malabsorption or anaemia. Patients can also have the silent or atypical form, with non-specific abdominal pain, oesophageal reflux, osteoporosis, cryptogenic hypertransaminasaemia, insulin dependent diabetes mellitus, or neurological symptoms. A recent meta-analysis indicated that the ratio of known to undiagnosed cases of coeliac disease was 1:7.<sup>1</sup> The median delay in diagnosis ranges from 4.9 to 11 years.<sup>2-4</sup>

Serological markers are a cheap non-invasive method to identify patients with coeliac disease. The positive and negative predictive value of combining the measurement of IgA antibodies to tissue transglutaminase and IgA endomysial antibodies has been reported to be greater than 96%.<sup>5</sup> However, the internationally accepted “gold standard” diagnostic test is the demonstration of villous atrophy on a duodenal biopsy.<sup>6,7</sup> The presence of villous atrophy together with a positive antibody profile is currently internationally accepted as coeliac disease, although antibody negative coeliac disease does exist and is reported to account for 6.4% (8 of 126) of all cases.<sup>8</sup> See [bmj.com](http://bmj.com).

Endoscopic features for recognising coeliac disease are only 50.0-87.5% sensitive.<sup>9</sup> Higher levels of detection are thought to correlate with endoscopic experience and the severity of villous atrophy. In addition, inter-rater reliability is poor.<sup>9</sup>

Because of the limitations of endoscopy, antibody negative coeliac disease, and delays in diagnosis, many centres around the world recommend routine duodenal biopsy. In practice this policy varies greatly, and reported rates of duodenal biopsy range from 30.9% to 74.0%. The reported prevalence of coeliac disease when taking a routine duodenal biopsy ranges from 1.0% to 5.2%. However, prevalence depends on the population studied.

We devised and evaluated a clinical decision tool that used a combination of pre-endoscopy serological testing (for tissue transglutaminase antibodies) and assessment of symptoms to identify patients with coeliac disease. This decision tool might help increase the detection of coeliac disease in patients attending for

gastroscopy without the need to perform routine duodenal biopsy.

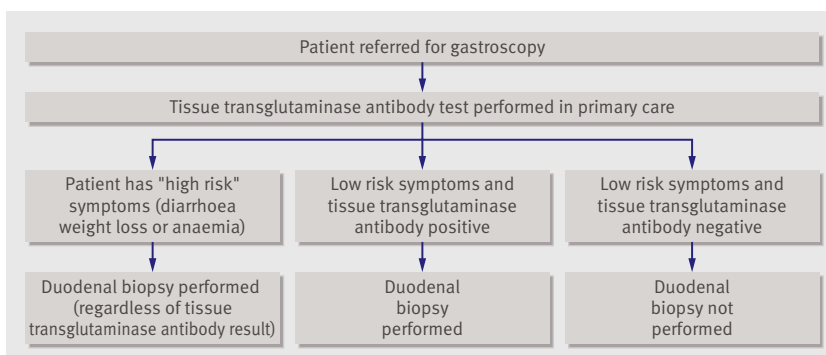
## METHODS

### Retrospective analysis and creation of a clinical decision tool

From January 2003 to January 2004 our centre performed 5979 gastroscopies. We analysed the data from 1464 unselected patients who had both a gastroscopy and duodenal biopsy. On the basis of this retrospective data, the prevalence of new cases of coeliac disease identified in patients referred for endoscopy was 4.2% (61 of 1464).

We assessed the indications for referral in these unselected patients and whether the biopsy findings indicated coeliac disease. We categorised patients with indications of weight loss, anaemia, or diarrhoea as having a "high risk" for coeliac disease. In routine clinical practice, such patients should have a duodenal biopsy taken.<sup>10,11</sup> The remaining patients were categorised as having a "low risk." Of the 1464 patients analysed who had gastroscopy and a duodenal biopsy, 1085 (74.1%) were high risk and 379 (25.9%) were low risk.

Tissue transglutaminase antibody titre was part of the antibody profile performed in 109 patients. Eighty nine (81.7%) were at high risk and 20 (18.3%) were at low risk of coeliac disease. Eighteen of the 109 patients (16.5%) had coeliac disease, two of whom were negative for tissue transglutaminase antibodies. Nineteen of the 109 patients were positive for tissue transglutaminase antibodies—16 had coeliac disease but three had a normal duodenal biopsy. The sensitivity, specificity, positive predictive value, and negative predictive value for tissue transglutaminase antibodies in the detection of coeliac disease were 94.1%, 96.7%, 84.2%, and 97.8%. The two antibody negative patients with coeliac disease both had high risk referral symptoms. When we combined the referral indication of high risk with positive tissue transglutaminase antibody results the sensitivity for diagnosing coeliac disease was 100% (95% confidence interval 82.4% to 100%).



**Fig 1** | Suggested clinical decision tool of pre-endoscopy serological testing and identification of high risk patients to target patients who need a duodenal biopsy

On the basis of these data, we devised a clinical decision tool that might obviate the need to perform routine duodenal biopsy but still detect unrecognised coeliac disease in patients referred for gastroscopy. We proposed that combining pre-endoscopy serological testing (using tissue transglutaminase antibodies) with identification of high risk patients would allow us to target patients who need a duodenal biopsy (fig 1).

### Prospective evaluation of clinical decision tool

We recruited patients from a single endoscopy department serving a population of around 250 000 and carrying out 5000-6000 gastroscopies annually. The patients had been referred by their general practitioner for either gastroscopy or a consultation and gastroscopy. A single endoscopist recruited participants between January 2004 and April 2006. We classified all patients according to the referral information into high risk and low risk groups. Quadrantic biopsies were taken from the second part of the duodenum in all patients. We also took a blood sample which was analysed for IgA tissue transglutaminase antibodies. We excluded patients if they had a known diagnosis of coeliac disease, coagulopathy or active gastrointestinal bleeding, or if a suspected carcinoma was identified (n=220).

We classed patients with villous atrophy and a negative antibody profile as having antibody negative coeliac disease only if they fulfilled previously described criteria<sup>6,7,12,13</sup> and we had excluded alternative causes of villous atrophy. All cases of coeliac disease and any equivocal cases were reviewed by a gastrointestinal histopathologist who independently assessed the consistency of sampling and reporting.

### Data analysis

For our prospective study to give a sensitivity of 100% (like our retrospective data), but with a narrower confidence width, our sample size needed to be 2000. This would give a 95% confidence interval of 98.8% to 100% (a width of 1.2%).

## RESULTS

We recruited 2000 patients (1167 (58.3%) women, mean age 55.8, range 16-94). We categorised 739 patients into the high risk group and 1261 into the low risk group according to their referral indications (fig 2). In total, 77 patients were newly diagnosed with coeliac disease. The independent gastrointestinal histopathology review confirmed consistency in both sampling and reporting of duodenal biopsies. No diagnoses were changed as a result of this review.

The prevalence of coeliac disease in all patients attending for gastroscopy was 3.9% (77/2000, 95% confidence interval 3.1% to 4.8%). In the high risk group prevalence was 9.6% (71/739, 7.7% to 12.0%).

The prevalence of tissue transglutaminase antibody negative coeliac disease was 0.4% (7/2000, 0.2% to 0.7%). All cases of antibody negative coeliac disease

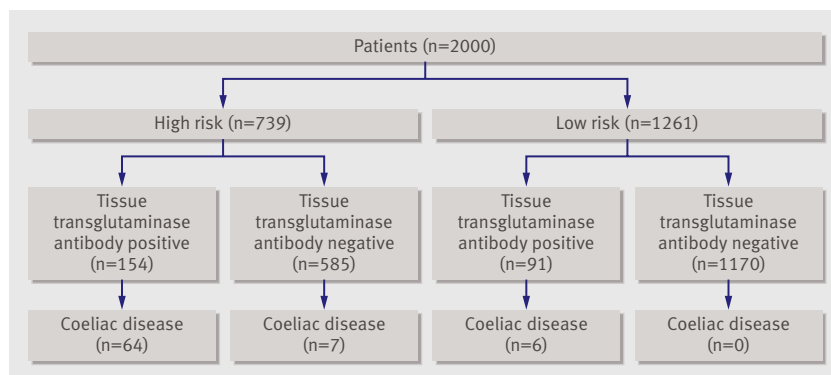


Fig 2 | Patients' serological and histopathology results according to high and low risk of coeliac disease

occurred in the high risk group (fig 2). Only one of these seven antibody negative patients had selective IgA deficiency. Antibody negative coeliac disease accounted for 9.1% (7/77, 4.5% to 17.6%) of cases within this cohort.

The prevalence of coeliac disease in the low risk group was 0.5% (6/1261, 0.2% to 1.0%). Symptoms (abdominal pain, reflux, and irritable bowel syndrome) improved in these six patients when they ate a gluten-free diet (duration of follow-up three to 18 months).

Using the tissue transglutaminase antibody test alone to diagnose coeliac disease gave a sensitivity, specificity, positive predictive value, and negative predictive value of 90.9%, 90.9%, 28.6%, and 99.6%.

#### Evaluating the clinical decision tool

Combining biopsy of the high risk group and those patients with a positive antibody result gave a sensitivity of 100% (77/77, 95.2% to 100%). The specificity was 60.8% (1170/1923, 58.6% to 63.0%), positive predictive value was 9.3% (77/830, 7.5% to 11.4%), and negative predictive value was 100% (1170/1170, 99.7% to 100%) (fig 2). The prevalence of coeliac disease in patients undergoing biopsy as a result of the decision tool was 9.3%.

#### DISCUSSION

We devised and evaluated a strategy of pre-endoscopy serological testing for coeliac disease combined with

#### WHAT IS ALREADY KNOWN ON THIS TOPIC

The symptoms of coeliac disease may be insidious so delays in diagnosis are common

Routine duodenal biopsy has been suggested as a way to ensure that no cases are missed at gastroscopy

#### WHAT THIS STUDY ADDS

Pre-endoscopy serological testing and biopsy of "high risk" cases has a 100% sensitivity

All patients referred for gastroscopy with high risk symptoms should be biopsied irrespective of their antibody profile

biopsy of high risk cases. The clinical decision tool had a sensitivity of 100% (95.2% to 100%) in our cohort of patients and no cases of coeliac disease were missed. Although the decision tool was accurate, the confidence interval was around 5%, so this tool may not necessarily detect all cases when applied to other groups.

#### Limitations

We performed the serological testing in secondary care on patients from primary care. We did not test the implementation of this decision tool in primary care. The prevalence of coeliac disease is lower in primary care (0.5-1.0%) than in the endoscopy unit (1.0-5.2%), and this might affect the performance of the decision tool.

#### Implications

By using our clinical decision tool instead of routine duodenal biopsy, 58.5% (1170/2000) of patients would have avoided a duodenal biopsy yet the same number of cases of coeliac disease would have been detected.

Our data support the need for duodenal biopsy in high risk patients even if they are antibody negative.<sup>10,11</sup> One option would be to serologically test the low risk group only, but we think the most pragmatic approach would be serological testing for all patients referred for gastroscopy.

The exact antibody test needed is debateable. Many centres recommend a two step approach (tissue transglutaminase antibodies first, followed by endomysial antibodies in patients with positive results).<sup>14</sup> However, the complete antibody profile may not be available by the time the patient arrives for gastroscopy. We found that using tissue transglutaminase antibodies alone was adequate and cheap and that no cases of coeliac disease were overlooked.

#### Cost effectiveness

We anticipate that our decision tool will be cost effective; in our study, it reduced the workload associated with processing and reporting duodenal biopsies to 41.5% of that of the routine biopsy method. Earlier diagnosis might result in fewer consultations in primary care and possibly fewer referrals to secondary care, which would also reduce healthcare costs. In addition, a prompt diagnosis would potentially save money by delaying onset of the complications of coeliac disease.

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- 1 Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001;120:636-51.
- 2 Sanders DS, Hurlstone DP, Stokes RO, Rashid F, Milford-Ward A, Hadjivassiliou M, et al. Changing face of adult coeliac disease: experience of a single university hospital in South Yorkshire. *Postgrad Med J* 2002;78:31-3.

- 3 Green PHR, Stavropoulos SN, Panagi SG, Goldstein SL, McMahon DJ, Absan H, et al. Characteristics of adult celiac disease in the USA: results of a national survey. *Am J Gastroenterol* 2001;96:126-31.
- 4 Lankisch PG, Martinez Schramm A, Petersen F, Droge M, Lehnick D, Lembcke B. Diagnostic intervals for recognizing celiac disease. *Z Gastroenterol* 1996;34:473-7.
- 5 Hill ID. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? *Gastroenterology* 2005;128(4 suppl 1):S25-32.
- 6 Revised criteria for diagnosis of coeliac disease. Report of working group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child* 1990;65:909-11.
- 7 National Institutes of Health Consensus Development Conference Statement on Celiac Disease, June 28-30, 2004. *Gastroenterology* 2005;128(4 suppl 1):S1-9.
- 8 Collin P, Kaukinen K, Vogelsang H, Korponay-Szabo I, Sommer R, Schreier E, et al. Antiendomysial and antihuman recombinant tissue transglutaminase antibodies in the diagnosis of coeliac disease: a biopsy-proven European multicentre study. *Eur J Gastroenterol Hepatol* 2005;17:85-91.
- 9 Olds G, McLoughlin R, O'Morian C, Sivak MV Jr. Celiac disease for the endoscopist. *Gastrointest Endosc* 2002;56:407-15.
- 10 Goddard AF, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. British Society of Gastroenterology. *Gut* 2000;46(suppl 3-4):IV1-5.
- 11 Thomas PD, Forbes A, Green J, Howdle P, Long R, Playford R, et al. Guidelines for the investigation of chronic diarrhoea, 2nd edition. *Gut* 2003;52(suppl 5):v1-15.
- 12 Feighery C, Weir DG, Whelan A, Willoughby R, Youngprapakorn S, Lynch S, et al. Diagnosis of gluten-sensitive enteropathy: is exclusive reliance on histology appropriate? *Eur J Gastroenterol Hepatol* 1998;10:919-25.
- 13 Shidrawi RG, Przemioslo R, Davies DR, Tighe MR, Ciclitira PJ. Pitfalls in diagnosing coeliac disease. *J Clin Pathol* 1994;47:693-4.
- 14 Hill PG, McMillan SA. Anti-tissue transglutaminase antibodies and their role in the investigation of coeliac disease. *Ann Clin Biochem* 2006;43:105-17.

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## Commentary: Reaching a milestone in diagnosing coeliac disease

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Clinical prediction rules for diagnosis seek to optimise the sensitivity and specificity of our diagnostic approach to a given problem. In this issue of the *BMJ*, Hopper and colleagues report a rare accomplishment in this regard—a decision rule that achieved 100% sensitivity in disease detection, in this case for coeliac disease.<sup>1</sup> The rule is simple—a positive serological test for IgA antibody to tissue transglutaminase combined with being at “high risk” (having weight loss, diarrhoea, or anaemia). The rule identified every patient with the disease in a cohort of 2000 patients, all of whom underwent intestinal biopsy as the gold standard and the final diagnostic step. This is a welcome advance. As the authors emphasise, coeliac disease may affect up to one in a 100 people, only one case in seven is ever diagnosed, and an appreciable diagnostic delay of many years often occurs.<sup>2,3</sup>

This result will probably not change clinical practice, however, as current algorithms for coeliac disease already incorporate these factors. Rather, this study strongly validates this approach and allows us to estimate with some confidence the probabilities of success or failure at each step of the process. The results support the current practice of forgoing endoscopic biopsy in low risk patients with negative serology, as none of the 1170 patients meeting these criteria was found to have coeliac disease on biopsy. The study confirms that biopsy has an important role in high risk patients with positive serology. It has been suggested that this combination provides adequate evidence to diagnose coeliac disease without the need for biopsy, and a substantial proportion of patients given the diagnosis (up to 25% in one survey) have never been biopsied.<sup>3</sup> However, 40% of high risk patients with positive serology in Hopper and colleagues' study did not have coeliac disease when biopsied. Even acknowledging the possibility that coeliac disease can be missed on

biopsy, we agree with the authors that biopsy is essential in this cohort, given the daunting prospect of lifelong adherence to a gluten-free diet.

The wisdom of biopsy in high risk patients who are tissue transglutaminase antibody negative is debatable. Although Hopper and colleagues recommend biopsy in this group, this approach identified only seven additional cases out of the 585 patients biopsied, and at least some of these cases could be predicted by testing for IgA deficiency.

This decision rule now needs to be tested in other settings,<sup>4</sup> and the rule may fare less well because:

- The population studied was a referral cohort; the base rate of disease will probably be lower in primary care cohorts
- Variability in assigning patients at high risk will increase if subsequent clinicians use their own definitions of weight loss, diarrhoea, or anaemia
- The results of tissue transglutaminase antibody testing will vary more as many different laboratories will be used
- The interpretation of biopsies will be less uniform, given the inherent variability between pathologists and differences in the quality of biopsy samples, which will come from multiple endoscopists.

The decision rule might be improved by incorporating a panel of serological markers. In particular, almost all patients with coeliac disease carry the HLA markers DQ2 or sometimes DQ8. The absence of DQ2 and DQ8 would therefore be reassuring in patients who are at high risk but are tissue transglutaminase antibody negative. Until a better rule is developed and validated, the decision rule of Hopper and colleagues seems to be the most cost effective and efficient way to assess coeliac disease.