Serology and endoscopy in coeliac disease: applications and limitations

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Chapter 11

Summary

Serology and endoscopy in coeliac disease – applications and limitations
Coeliac disease is an extremely common condition, with wide variation in nature and severity of clinical presentation. The non-specific nature of many associated symptoms, both from and outside the gut, means that widespread small bowel biopsy is not possible although it remains mandatory and the gold standard for diagnosis before starting treatment. Much effort has been directed into the development of non-invasive serological tests of sufficient sensitivity and specificity to efficiently select patients for biopsy. To date, the most useful is IgA class endomysial antibody (EmA) although concerns have been expressed about its sensitivity. This thesis assesses firstly the use of EmA for case-finding in two novel situations: primary care and among patients with primary biliary cirrhosis. Then the limitations (false-negatives) of EmA testing are explored, both within and outside the setting of IgA deficiency, and also in patients who have started a gluten-free diet. The possible role of serum antibodies to tissue transglutaminase (anti-tTG) as an additional screening test is assessed, particularly in EmA negative individuals. Coeliac disease may present with dyspeptic symptoms, raising the possibility of diagnosis during routine endoscopy. Two studies assess endoscopic markers of villous atrophy, which may overcome the problem of false negative serology in patients who present with upper gastrointestinal symptoms.

Chapter 1: Summarises current perceptions of the clinical presentations and prevalence of coeliac disease, serological tests, and case-finding, as well as outlining the thesis.

Chapter 2: EmA testing has been available to general practitioners in Northern Ireland for some time, allowing the possibility of coeliac case-finding in primary care. We assessed the use of EmA testing by family doctors in our catchment area. Thirty-one percent of new coeliac patients during the study period had been first identified by primary care EmA testing. General practitioners were aware of presentations other than diarrhoea.

Chapter 3: Anecdotal reports of coeliac disease co-existing with primary biliary cirrhosis (PBC) suggest but do not confirm an association. Using EmA to screen for coeliac disease among patients with PBC, we obtained a minimum (biopsy confirmed, EmA positive) prevalence of 1:14. Screening for coeliac disease is worthwhile as symptoms attributed to PBC may in fact be gluten sensitive and both are potent risk factors for osteoporosis.
Summary: Serology and endoscopy in coeliac disease

Chapter 4. An important cause of false negative EmA testing is IgA deficiency. We assessed the significance of IgA deficiency among patients undergoing diagnostic tests for coeliac disease. Two of five patients with total IgA <0.07 g/l had villous atrophy with negative EmA. Use of undetectable IgA as a selection criterion for small bowel biopsy as well as positive EmA would have improved sensitivity from 87% to 94%, with a fall in positive predictive value from 100% to 91%, but would have maintained high specificity and negative predictive value. Serum IgA was undetectable in 5 (4%) of 117 patients with AGA in the range 0-10 ELISA units (EU) compared with none of 201 with higher AGA. Routine IgA measurement is worthwhile as part of the diagnostic screen for coeliac disease.

Chapter 5. False negative EmA may occur outside the setting of IgA deficiency. We assessed its prevalence in a population of 89 coeliac patients with normal IgA who were selected for biopsy on clinical rather than serological criteria. Sensitivity of EmA for villous atrophy was 78% and was similar for partial (79%) and subtotal/total villous atrophy (77%). Only four of 20 EmA negative patients had raised antigliadin antibody. Reliance on EmA to select patients for biopsy will miss approximately one-fifth of coeliac cases.

Chapter 6. Formation of EmA is thought to require exposure to dietary gluten and may therefore correlate poorly with histology once a gluten-free diet is started. We compared EmA titres with histology in patients having follow-up biopsy after twelve months on a gluten-free diet. Of 77 untreated patients, 62 (81%) had EmA. After treatment, only 5 (15%) of 32 with persisting villous atrophy had EmA: four of these had defects in dietary compliance. EmA may therefore assist in assessment of compliance, but does not predict histological recovery: daily gluten intake before diagnosis may determine whether or not patients are EmA positive.

Chapter 7. Antibodies to tissue transglutaminase (tTG), the recently identified autoantigen of coeliac disease, have been reported to have high sensitivity and specificity for villous atrophy, but appear to correlate with EmA and their performance in EmA negative patients is uncertain. We assess a commercial ELISA kit in 70 coeliac patients. Although anti-tTG offered no advantages in sensitivity or specificity over EmA considered in isolation, 17 patients had only one antibody. A combination protocol would therefore have improved
sensitivity of serology to 93% and may represent an advance over EmA or anti-tTG screening alone.

Chapter 8. Patients with coeliac disease may present with dyspeptic symptoms and undergo upper gastrointestinal endoscopy as first investigation, when endoscopic markers of villous atrophy may allow selection for duodenal biopsy. Of 500 patients having open access endoscopy, ten had abnormalities and 8 proved to have villous atrophy, giving a prevalence of 1:63. Open access endoscopy offers a further opportunity to improve diagnosis rates for coeliac disease.

Chapter 9. In a follow-up study, we compared endoscopic appearances with duodenal histology in 150 patients undergoing routine endoscopy to determine sensitivity as well as specificity. Endoscopic markers had sensitivity of 87.5% and specificity of 100%, with a prevalence of villous atrophy of 1:19. Three of eight patients with villous atrophy were EmA negative.

Chapter 10 shows examples of endoscopic markers of villous atrophy.

Chapter 11 summarises these studies.

Chapter 12 summarises the thesis in Dutch.