# Coeliac Disease

## Current Practice and Future Directions

**Dr Peter Mooney**, MBChB, MRCP, and **Professor David Sanders**, MBChB, MD, FRCP, FACG, Royal Hallamshire Hospital, Sheffield

## Background

Coeliac disease is a common autoimmune condition affecting the small intestine of genetically predisposed individuals. It results from an abnormal immune reaction to the dietary gluten found in wheat, barley and rye, leading to small bowel villous atrophy and impaired small bowel function. Coeliac disease was previously thought to be a rare disease predominantly presenting in childhood, with symptoms of malabsorption and failure to thrive.[1] However, more recent experience, particularly with the advent of widely available serological testing, has shown that coeliac disease is a common condition mainly of adult patients. Many of these patients have minor gastrointestinal symptoms or present with the complications of coeliac disease, such as osteoporosis or iron deficiency anaemia. Contemporary serology studies have shown that adult coeliac disease affects up to one per cent of the Western population.[2, 3] However, many of these patients don't come to diagnosis, with only one in eight patients ever being diagnosed[4] – see **Figure 1**. The mainstays of investigation and treatment of adult coeliac disease remain serology, small bowel biopsy and a lifelong adherence to a strict gluten-free diet. In this article, we will discuss the current approach to the investigation and management of coeliac disease, and highlight some of the areas of research into improving our diagnostic yield and improving treatment for coeliac sufferers.

## Diagnosis

Currently the vast majority of coeliac patients are diagnosed on the basis of positive coeliac serology and a confirmatory duodenal biopsy, taken via endoscopic means, showing the presence of villous atrophy. There is, however, pressure from some quarters to consider removing small bowel biopsy from the diagnostic pathway. Indeed, the 2012 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines include an algorithm for avoiding biopsy in a small proportion of paediatric patients with significant symptoms, very high antibody titres (tTG>10x level of normal and positive EMA) and an appropriate genetic phenotype.[5] Below we will discuss the current serological tests and histology for the diagnosis of coeliac disease.

### Serological tests

Serological testing has been one of the major reasons for the increased awareness and diagnosis of coeliac disease. Serological tests have excellent sensitivity and specificity in appropriate patient groups. Blood tests are inevitably much less invasive than a small bowel biopsy and, as such, have increased the uptake of testing for coeliac disease, greatly improving our selection of appropriate patients for duodenal biopsy.[6, 7]

Endomysial antibody (EMA) testing is highly accurate with a sensitivity and specificity of 95 per cent or more in patients with overt villous atrophy.[8-11] However, it is subjective, labour intensive, and the substrates (monkey oesophagus, umbilicus) are limited.[12] Tissue transglutaminase (tTG) assays are generally cheaper than EMA and more reliable.[8,13] One weakness of the tTG test is that the accuracy of the assay varies between manufacturers.[14] The best assays have a higher sensitivity than EMA and a comparable specificity, both around 98 per cent.[13-18] The cohort studies that comprise the majority of the evidence for the performance of each test are of high quality but too heterogeneous to provide pooled data.[9]

Although EMA and tTG appear to be sensitive and specific, these observations are based on carefully selected high coeliac disease prevalence populations. In the general population, where the prevalence is estimated to be one per cent, the positive predictive value (PPV) of the test falls. When coeliac disease prevalence falls below approximately 35 per cent, the PPV of tTG and EMA falls from 90-100 per cent to 80 per cent or less.[13] In a low prevalence population as seen in screening, the specificity of the test has to be near perfect for the PPV to remain above 90 per cent.[13]

Our group performed serological testing and concurrent duodenal biopsies on 2000 consecutive adults attending for gastroscopy.[19] We identified 77 new cases of coeliac disease (7 antibody negative). In this referral population, tTG had a sensitivity and specificity of 91 per cent, an NPV of 99 per cent but a PPV of just 28 per cent. EMA had a PPV of 71 per cent, and an NPV of 99 per cent. This study highlights the poorer performance of the tests in this heterogeneous group which, perhaps, more accurately reflects typical clinical practice. The sensitivity of the serological tests also falls when histological grades without villous atrophy are considered. In these circumstances the sensitivity falls well below 90 per cent.[16, 19] This is a clinical problem which is difficult to evaluate as most studies have excluded patients without villous atrophy.[12]

As the main EMA and tTG tests are IgA based, they are prone to error in conditions associated with abnormal levels of IgA. For example, IgA deficiency is associated with coeliac disease and is a

cause of false negative serological results.[19] Conversely, false positive tTG may also occur and is associated with conditions of raised IgA such as chronic liver disease and monoclonal gammopathy.[21] One option in the presence of IgA deficiency is to use IgG EMA or IgG tTG antibody tests.[22]

Although gliadin antibodies have largely been superseded by tTG and EMA there has been recent interest in deamidated gliadin peptide antibodies, which are known to play a crucial role in the immunopathogenesis of coeliac disease. A recent meta-analysis, however, has shown that although current assays perform well, tTG is still currently more sensitive and specific and as such remains the screening test of choice.[23]

Point of care testing (finger prick testing) has an apparent advantage as these tests can be applied in the out-patient or endoscopy settings and, potentially, provides clinicians with an immediate result. Results are promising but the reported sensitivities and specificities are still less than conventional serology.[24-26] Public interest in coeliac disease has greatly increased in recent years. As a result many believe a widely available point of care test may increase the numbers of patients tested for coeliac disease and increase our diagnostic rates further. There are, however, legitimate concerns around the potential for public availability of these tests particularly as further work is required in the testing of low risk populations. Furthermore, there is a concern that individuals will place themselves (or be advised to place themselves) on a gluten-free diet without having a biopsy to provide histological confirmation.

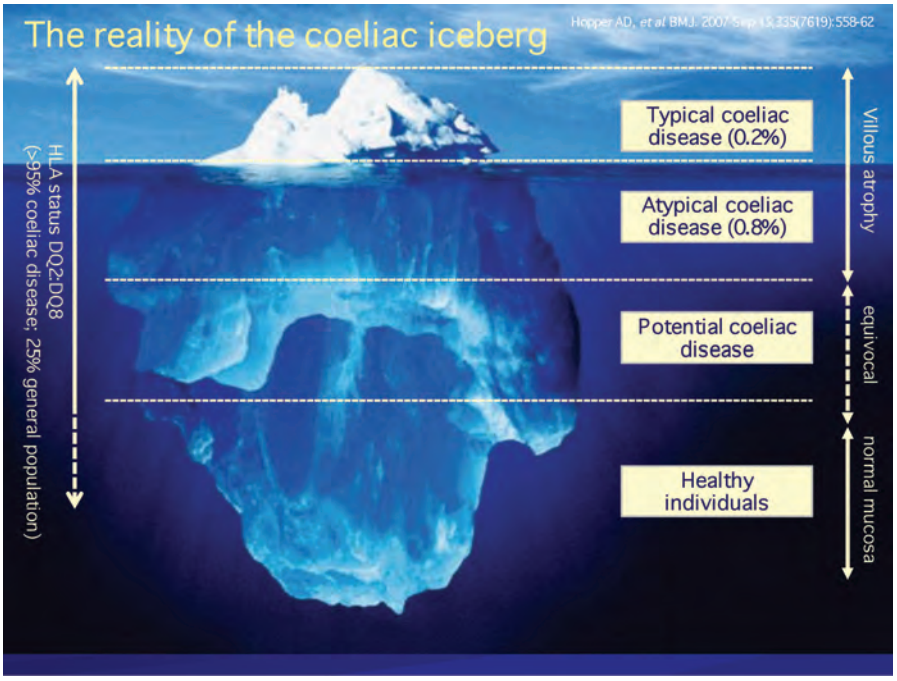
### Duodenal biopsy and histology

As discussed above, serological tests have excellent rates of sensitivity and specificity when used in appropriate populations. However, as more patients undergo the test for increasingly diverse indications the positive predictive value of serology reduces. Although a gluten-free diet is a non-toxic and increasingly available treatment for coeliac disease it can be poorly tolerated and is considerably more expensive than a normal diet. It is imperative, therefore, to be certain of a diagnosis of coeliac disease prior to institution of a strict gluten-free diet. Serological tests alone at present are not able to completely negate the need for duodenal biopsy and, as such, in adult populations this is still mandatory. Histological proof provides a baseline for future assessments of severity or remission. There are also implications for first degree relatives (considering screening) thus a 'cast iron' diagnosis for the index case is imperative. Finally, some primary care practitioners may refuse to provide a gluten-free diet on prescription unless there is histological evidence of coeliac disease.

The histological diagnosis of coeliac disease requires demonstration of villous atrophy, i.e. Marsh 3 changes. Lesser histological lesions, such as Marsh 1 (raised intraepithelial lymphocytes) and Marsh 2 (raised IELs and crypt hyperplasia), are non-specific and only a minority develop overt coeliac disease even after long-term follow up. This was demonstrated by Lahdeaho *et al* who studied adults who had undergone small bowel biopsy due to coeliac suspicion in childhood.[27] Seventy-six subjects with non-diagnostic mucosal changes (Marsh 1 or 2), and 68 with normal mucosa, were screened for coeliac disease 10 to 30 years later. In the intervening years, four patients in the slight mucosal changes group had been diagnosed with coeliac disease on clinical grounds. Of the remaining patients only one new coeliac case was detected in both groups. Our group recently prospectively investigated 100 patients with Type 1 Marsh changes (IEL's only). Usine HLA typing and gluten challenge we were only able to demonstrate coeliac disease in 16 per cent of these adults.[28] As awareness of coeliac disease improves and more people are screened at lower symptom thresholds, then we will inevitably recognise individuals with the borderline position of latent or potential coeliac disease. This was highlighted by a recent study which identified 26/1868 adults with positive coeliac serology.[29] Six of the 26 had villous atrophy on biopsy and were diagnosed with coeliac disease. Of the remaining 20, five refused biopsy and the rest had lesser degrees of enteropathy or normal small bowel. They are now in the unenviable position of having a 'not quite' diagnosis. Should they have repeat biopsy? When should they be retested? Are they at risk of complications and should they follow a gluten-free diet? Do those without overt symptoms follow a more indolent course? We do not have the answers to these questions.

One answer may be to improve our biopsy strategy. Changes of coeliac disease are well recognised to be patchy in some individuals.[30] As a result a multiple biopsy strategy has been advocated for some time. Current recommendations are for four quadrantic biopsies to be taken from the second part of the duodenum.[31] However, a recent review of biopsy practices in the USA has shown that clinicians frequently submit fewer samples than advised, with clinicians taking four or more biopsies in only 35 per cent of cases.[32] When the recommended number of biopsies were received, this more than doubled the rate of diagnosis from 0.7 per cent of cases to 1.8 per cent.

Figure 1: The Coeliac Iceberg




Adapted from Hopper *et al*: BMJ 2007

Traditionally, biopsies have been taken distal to the first part of the duodenum as there were concerns regarding difficulties in analysing histology samples from the duodenal bulb due to the presence of Brunner's glands.[33] There is, however, mounting evidence that changes of coeliac disease can be identified in the first part of the duodenum. As previously mentioned changes of coeliac disease can be patchy, and in 2.4-12.5 per cent of cases the first part of the duodenum may be the only site of positive histology.[34] As a result many centres now recommend a duodenal bulb biopsy in conjunction with biopsies from the second part of the duodenum to improve detection of coeliac disease. See **Figure 2**.

## Existing services, novel therapies and the future

A gluten-free diet is a non-toxic dietary measure that should be a cure for patients with coeliac disease. Although gluten-free foods have greatly improved in recent times, patients still find the diet challenging to completely adhere to. Reported adherence rates vary from 42-91 per cent.[35] The cornerstone of management for patients with coeliac disease is dietetic support. Patients require regular dietetic support with the opportunity or access to a gastroenterologist should further problems arise.[36, 37] Follow-up may be in primary or secondary care as long as the support is adequate. This is what the patients want and may have a positive effect on adherence rates.[35-37] However, there is a significant shortfall in dietetic services throughout the UK. Coeliac UK (National Patient Charity) have estimated that there is only one hour of a dietitians' time per month of 100,000 population in 25 per cent of units currently available to provide this service. There is an urgent need to provide increased funding to dietetic services nationwide in order to ensure that patients with coeliac disease are optimally managed. This approach could also potentially be cost-effective if

the dietetic service were to replace current consultant capacity for the provision of this service.

Up to 30 per cent of patients have persistent symptoms despite apparent adherence to a gluten-free diet, and a significant proportion of these symptoms are related to inadvertent gluten exposure.[39] Some patients are exquisitely sensitive to very small amounts of gluten in their diet and, despite improved labelling and availability of gluten-free foods, it still remains almost impossible to completely avoid some gluten in our modern diet.[40] This has led some researchers to seek out alternative therapies. Gluten is integral to the taste and texture of bread and other gluten containing products. Palatability is one of the main reasons patients struggle to adhere to a gluten-free diet and as such research into genetically modified gluten that doesn't cause the immune reaction in the small bowel is a promising area. Other potential targets aim to ameliorate the immune reaction to gluten, either by direct effects on the mucosa or affecting toxicity of the ingested gluten. The main areas of research are summarised in **Table One**.

## Conclusions

**The diagnosis of coeliac disease has greatly improved over recent years as it has become increasingly recognised as a prevalent condition. However, there is still work to be done to identify patients with this eminently treatable condition. Improvements in serological testing and biopsy strategies will reduce errors in diagnosis, permit earlier diagnosis, and potentially save money.[49]**

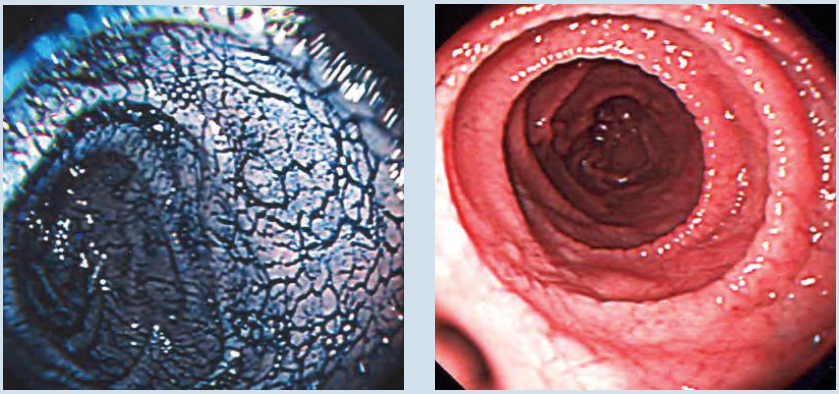
**Many patients find a gluten-free diet difficult to fully adhere to and some patients are very sensitive to small amounts of gluten. This has the potential to cause long-term complications in these individuals. As a result, research into novel therapies as an adjunct or alternative to a gluten-free diet is required. Although research into these areas is at a very early stage, there are several promising avenues for development to improve the lives of coeliac sufferers worldwide.**

### Table One: Areas of Novel Research in Coeliac Disease

| Novel Therapy | Mode of action |
|---|---|
| Genetically modified gluten[41, 42] | Create gluten that doesn't activate abnormal immune reaction |
| Zonulin inhibitors (Larazotide acetate currently in phase IIb trials)[43] | Inhibit intestinal permeability reducing gluten uptake |
| Therapeutic vaccine (Nexvax2 awaiting entry to phase IIa trials)[44] | Induce immune tolerance to gluten |
| Transglutaminase (TG2) inhibitors | Block transamidation of gluten to glutamic acids that increase the immune response |
| Probiotics with enzymes[45, 46] | Detoxify gliadin and promote intestinal healing |
| Hookworms[47] | Helminth infection to suppress immunopathology induced by gluten – no benefit on histology from single study |

Adapted from Bakshi A, *et al*[48]

### Figure 2: Duodenum Demonstrating Scalloping of the Duodenal Folds and Fissuring of the Mucosa Before and After Dye Spraying Consistent with Villous Atrophy in Coeliac Disease



References: **1.** Davidson LS, Fountain JR (1950). Incidence of the sprue syndrome; with some observations on the natural history. BMJ; 1(4663): 1157-1161. **2.** West J, et al (2003). Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. Gut; 52(7): 960-965. **3.** Mustalathi K, et al (2010). The prevalence of celiac disease in Europe: Results of a centralized, international mass screening project. Ann Med.; 42: 587-595. **4.** van Heel DA, West J (2006). Recent advances in coeliac disease. Gut; 55: 1037-1046. **5.** Husby S, et al (2012). European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr.; 54(1): 136-160. **6.** Evans KE, Malloy AR, Gorard DA (2009). Changing patterns of coeliac serology requests. Aliment Pharm Ther.; 29: 1137-1142. **7.** Sinclair D, Duncan H (2004). What happens to patients with positive tissue transglutaminase and endomysium antibody results in general practice? J Clin Pathol.; 57: 943-945. **8.** Leffler DA, Schuppan D (2010). Update on serologic testing in celiac disease. Am J Gastroenterol.; 105(12): 2520-4. **9.** Richey R, et al (2009). Recognition and assessment of coeliac disease in children and adults: summary of NICE guidance. BMJ; 338: b1684. **10.** Toftedal P, et al (2010). Positive predictive value of serological diagnostic measures in celiac disease. Clin Chem Lab Med.; 48(5): 685-91. **11.** James MW, Scott BB (2000). Endomysial antibody in the diagnosis and management of coeliac disease. Postgrad Med J.; 76(898): 466-8. **12.** Lewis NR, Scott BB (2006). 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.; 24(1): 47-54. **13.** Hill ID (2005). What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? Gastroenterology; 128(4 Suppl 1): S25-32. **14.** Naiyer AJ, et al (2009). Comparison of commercially available serologic kits for the detection of celiac disease. J Clin Gastroenterol.; 43(3): 225-32. **15.** Wong RC, et al (2002). A comparison of 13 guinea pig and human anti-tissue transglutaminase antibody ELISA kits. J Clin Pathol.; 55(7): 488-94. **16.** Rostami K, et al (1999). Sensitivity of anti-endomysium and anti-gliadin antibodies in untreated celiac disease: disappointing in clinical practice. Am J Gastroenterol.; 94(4): 888-94. **17.** Rostom A, et al (2005). The diagnostic accuracy of serologic tests for celiac disease: a systematic review. Gastroenterology; 128(4 Suppl 1): S38-46. **18.** Walker MM, et al (2010). Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. Gastroenterology; 139(1): 112-9. **19.** Hopper AD, et al (2007). Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. BMJ; 334(7596): 729. **20.** Latiff AH, Kerr MA (2007). The clinical significance of immunoglobulin A deficiency. Ann Clin Biochem.; 44(Pt 2): 131-9. **21.** McGowan KE, Lyon ME, Butzner JD (2008). Celiac disease and IgA deficiency: complications of serological testing approaches encountered in the clinic. Clin Chem.; 54(7): 1203-9. **22.** Cataldo F, et al (2000). IgG(1) antiendomysium and IgG antitissue transglutaminase (anti-tTG) antibodies in coeliac patients with selective IgA deficiency. Working Groups on Celiac Disease of SIGEP and Club del Tenue. Gut; 47(3): 366-9. **23.** Lewis NR, Scott BB (2010). Meta-analysis: deamidated gliadin peptide antibody and tissues transglutaminase antibody compared as screening tests for coeliac disease. Aliment Pharm Ther.; 31: 73-81.**24.** Korponay-Szabo IR, et al (2007). Population screening for coeliac disease in primary care by district nurses using a rapid antibody test: diagnostic accuracy and feasibility study. BMJ; 335(7632): 1244-7. **25.** Raivio T, et al (2007). Performance of a new rapid whole blood coeliac test in adult patients with low prevalence of endomysial antibodies. Dig Liver Dis.; 39(12): 1057-63. **26.** Raivio T, et al (2008). Comparison of a novel whole blood transglutaminase-based ELISA with a whole blood rapid antibody test and established conventional serological celiac disease assays. J Pediatr Gastroenterol Nutr.; 47(5): 562-7. **27.** Lähdeaho ML, et al (2005). Celiac disease: from inflammation to atrophy: a long-term follow-up study. J Pediatr Gastroenterol Nutr.; 41(1): 44-8. **27.** Aziz I, et al (2010). A prospective study into the aetiology of lymphocytic duodenosis. Aliment Pharm Ther.; 32: 1392-1397. **29.** Mariné M, et al (2009). Impact of mass screening for gluten-sensitive enteropathy in working population. World J Gastroenterol.; 15(11): 1331-8. **30.** Hopper AD, Cross SS, Sanders DS (2007). Patchy villous atrophy in adult patients with suspected gluten-sensitive enteropathy: is a multiple duodenal biopsy strategy appropriate. Endoscopy; 39: 219-224. **31.** Rostom A, Murray JA, Kagnoff MF (2006). American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of celiac disease. Gastroenterology; 131: 1981-2002. **32.** Lebwohl B, et al (2011). Adherence to biopsy guidelines increases celiac disease diagnosis. Gastrointest Endosc.; 74(1): 103-109. **33.** Shidrawi RG, et al (1994). Pitfalls in diagnosing coeliac disease. J Clin Pathol.; 47: 693-694. **34.** Evans KE, et al (2011). A prospective study of duodenal bulb biopsy in newly diagnosed and established adult celiac disease. Am J Gastroent.; 106(10): 1837-1842. **35.** Hall NJ, Rubin G, Charnock A (2009). Systematic review: adherence to gluten-free diet in adult patients with coeliac disease. Aliment Pharm Ther.; 30: 315-330. **36.** Bebb JR, et al (2006). Long-term follow-up of coeliac disease – what do coeliac patients want? Aliment Pharmacol Ther.; 23(6): 827-31. **37.** Herman ML, et al (2012). Patients with celiac disease are not followed up adequately. Clin Gastroenterol Hepatol.; 10(8): 893-99. **38.** Nelson M, Mendoza N, McGough N (2007). A survey of provision of dietetic services for coeliac disease in the UK. J Hum Nutr Diet.; 20(5): 403-11. **39.** Mooney PD, et al (2012). Treatment failure in coeliac disease: a practical guide to investigation and treatment of non-responsive and refractory coeliac disease. J Gastrointestin Liver Dis.; 21(2): 197-203. **40.** Akobeng AK, Thomas AG (2008). Systematic review: tolerable amount of gluten for people with coeliac disease. Aliment Pharmacol Ther.; 27: 1044-1052. **41.** Gianfrani C, et al (2007). Transamidation of wheat flour inhibits the response to gliadin of intestinal T cells in celiac disease. Gastroenterol.; 133: 780-789. **42.** Spaenji-Dekking L, et al (2005). Natural variation intoxicity of wheat: potential for selection of non-toxic varieties for celiac disease patients. Gastroenterol.; 129: 797-806. **43.** Kelly CP, et al (2013). Larazotide acetate in patients with coeliac disease undergoing a gluten challenge: a randomised placebo-controlled study. Aliment Pharmacol Ther.; 37: 252–62. **44.** Brown GJ, et al (2011). A phase I study to determine the safety, tolerability and bioactivity of Nexvax2 in HLA DQ2+ volunteers with celiac disease following a long-term, strict gluten-free diet. Presented at Digestive Disease Week; May 7–10 2011; Chicago, Illinois. Abstract Su1235. **45.** Watson P, et al (2008). Implications of enzymatic detoxification of food gluten in coeliac disease. Gastroenterology.; 134: A213. **46.** Lindfors K, et al (2008). Live probiotic Bifidobacterium lactis bacteria inhibit the toxic effects induced by wheat gliadin in epithelial cell culture. Clin Exp Immunol.; 152: 552-558. **47.** Daveson A, et al (2011). Effect of hookworm infection on wheat challenge in Celiac disease: a randomised double-blinded placebo controlled trial. PLoS One; 6: e17366 **48.** Bakshi A, et al (2012). Emerging therapeutic options for celiac disease: potential alternatives to a gluten free diet. Gastroenterol Hepatol.; 8(9): 582-588. **49.** Voilato M, et al (2012). Resource use and costs associated with coeliac disease before and after diagnosis in 3646 cases: results of a UK primary care database analysis. PLoS One; 7: e41308.