

# The investigation of **coeliac disease**: A follow up

Contributed by: Dr Richard Steele, Clinical Immunologist and Immunopathologist, Wellington Hospital and Aotea Pathology.

In **BPJ 9 (October 2007)**, we addressed the topic of managing coeliac disease in primary care. There are a number of tests available for diagnosis and monitoring and there is some confusion over which tests to use and when. We invited Immunologist, Dr Richard Steele who has a special interest in coeliac disease to provide some clarification.

## Key Points

- IgA TTG should be the only test for coeliac disease used in general practice.
- Duodenal biopsy is required to confirm diagnosis.
- There are a number of reasons why IgA TTG tests may be negative in a person with coeliac disease so clinical judgement is important.
- Testing for anti-gliadin antibodies (AGA) is unnecessary for either the diagnosis of coeliac disease or 'gluten sensitivity'.

## Background


Coeliac disease is a common but often unrecognised disorder, affecting about 1% of the population in New Zealand.<sup>1</sup> It is unknown what the identification rate is in New Zealand, but some countries with comprehensive health systems have identification rates of only about 10%.<sup>2</sup> The appropriate use of laboratory tests for coeliac disease in primary care is crucial to increase this number.

Over the years, there have been a significant number of tests used to screen for coeliac disease. The variety of tests reflects the progression in our understanding of coeliac disease over the past three decades.

## **IgA TTG should be the only test used in general practice**

The IgA anti tissue transglutaminase antibodies (IgA TTG) assay has been shown to have a high sensitivity (90-98%) and specificity (90-99%) for coeliac disease and is therefore the only test required in primary practice.<sup>3-5</sup>

In adult patients with a low probability of coeliac disease, the TTG test has high negative predictive value, therefore a negative test result would virtually exclude the condition. Patients with a positive test result require confirmation by endoscopic duodenal biopsy while still on a gluten containing diet.

 **On the laboratory request form, indicate “IgA TTG” rather than ambiguous requests such as “coeliac screen”.**

There are however a number of situations where a negative IgA TTG test does not exclude coeliac disease. In these situations the clinician must have a lower threshold for referral for upper gastrointestinal endoscopy and duodenal biopsy.

### **Why a negative IgA TTG test may not exclude coeliac disease**

**Studies show that up to 10% of people with coeliac disease are antibody negative.**<sup>3</sup> The reasons for this antibody negative status are unknown. If a person has a negative IgA TTG and is still suspected of having coeliac disease, the clinician should assess the likelihood of coeliac disease based on known risk factors, for example, first degree relatives of patients with coeliac disease, presence of gastrointestinal symptoms, iron deficiency anaemia and type I diabetes.<sup>2</sup>

**Antibodies are only present with a normal gluten containing diet,** so IgA TTG testing and duodenal biopsy should not be performed in people on a gluten free diet. The length of time needed to be on a gluten containing diet and the amount of gluten required varies with the individual.<sup>6</sup> A practical approach to this would be to recommend a normal diet (at least four slices of bread per day) until the patient becomes symptomatic and for at least one to two months.<sup>4</sup> Studies have shown that 70-90%<sup>7,8</sup> of patients with a positive IgA TTG test will revert to negative after 12 months on a strict gluten-free diet. The tests can become negative in over 50% of patients after three months.<sup>9</sup>

**IgA deficiency has been reported to be increased in people with coeliac disease.**<sup>10</sup> If a patient is found to be IgA deficient (total IgA less than 0.05g/L), IgA based testing for coeliac disease such as the IgA TTG is usually negative. The frequency of coeliac disease in people with IgA deficiency varies, however in one study, the prevalence of coeliac disease in 126 children with IgA deficiency was found to be 8.7%.<sup>11</sup> If a person is IgA deficient, some experts suggest

IgG based coeliac disease testing, while others suggest going directly to duodenal biopsy, if the clinical suspicion of coeliac disease is high. IgG TTG testing has shown a reasonable sensitivity and specificity in limited case series but further study in this area is needed.<sup>12</sup>

**IgA TTG antibody testing is less reliable in children.** It takes a somewhat more mature immune system to make some of the “anti-self” antibodies, therefore a child may not have detectable IgA TTG levels until several years after the introduction of gluten into the diet. In addition, in one study, about 50% of children who were initially IgA TTG positive became negative later in childhood despite staying on a gluten containing diet.

**People with coeliac disease who are immunosuppressed** are thought to be more likely to have negative coeliac disease tests and also normal duodenal biopsies. There is however little evidence of this at present.

### **Anti-gliadin antibodies and “gluten sensitivity”**

**Anti-gliadin antibody (AGA) testing is now redundant for the diagnosis of coeliac disease.**

AGA testing gained popularity in the 1980s as a test for coeliac disease. It was the first widely available test that could be used for screening. The overall performance of AGA for diagnosing coeliac disease is inferior when compared to IgA TTG.<sup>13-15</sup> There is also significant variation in the performance of the different testing kits available. This test should not be requested in primary care when considering the diagnosis of coeliac disease as it will lead to higher rates of false reassurance or unnecessary duodenal biopsies depending upon the result.

Because of its historical importance and the high rate of false positives, AGA testing has perpetuated and popularised the diagnosis of “gluten sensitivity” (sometimes referred to as “gluten intolerance”). Gluten sensitivity can be termed a syndrome where patients attribute a wide variety of predominantly gastrointestinal, dermatological

and neurological symptoms to the ingestion of gluten containing foods, where the diagnosis of coeliac disease has been reasonably excluded.

Antibodies to gliadin are common, occurring in up to 20% of the population depending upon the assay used and isotypes tested.<sup>16</sup> Studies comparing the frequency of these antibodies in various diseases including psoriasis and multiple sclerosis compared to healthy controls usually show no increase.<sup>17-19</sup>

There are no robust scientific studies to support the testing of AGA in the diagnosis of gluten sensitivity. People who suspect they have gluten sensitivity should be counselled that AGA testing is not reliable in diagnosing this syndrome. For the management of such patients the following steps are suggested:

1. Exclude other diagnoses based on the clinical presentation.
2. Discuss with the patient the pros and cons of the gluten-free diet including the issues of cost and convenience.
3. Referring selected patients to a dietician with clinical expertise in food intolerance can be very helpful. The dietician can assess the nutritional adequacy of the diet and consider food challenges, if appropriate.

In summary, there has been a significant evolution in the serological testing for coeliac disease and further advances are likely to occur in the near future. At present IgA TTG is the recommended test for coeliac disease.

#### References:

1. Cook HB, Burt MJ, Collett JA, Whitehead MR, Frampton CM, Chapman BA. Adult coeliac disease: prevalence and clinical significance. *J Gastroenterol Hepatol* 2000;15(9):1032-6.
2. Fasano A, Catassi C. Current approaches to diagnosis and treatment of coeliac disease: an evolving spectrum. *Gastroenterology* 2001;120(3):636-51.
3. Hopper AD, Cross SS, Hurlstone DP, McAlindon ME, Lobo AJ, Hadjivassiliou M, et al. Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. *BMJ* 2007;334(7596):729.
4. Rostom A, Murray JA, Kagnoff MF. American Gastroenterological Association (AGA) Institute technical review on the diagnosis and management of coeliac disease. *Gastroenterology* 2006;131(6):1981-2002.
5. Wong RC, Wilson RJ, Steele RH, Radford-Smith G, Adelstein S. A comparison of 13 guinea pig and human anti-tissue transglutaminase antibody ELISA kits. *J Clin Pathol* 2002;55(7):488-94.
6. Ansaldi N, Tavassoli K, Fausson D, Forni M, Oderda G. [Clinico-histological behavior of coeliac patients after gluten load following the definitive diagnosis]. *Pediatr Med Chir* 1988;10(1):3-6.
7. Bazzigaluppi E, Roggero P, Parma B, Brambillasca MF, Meroni F, Mora S, et al. Antibodies to recombinant human tissue-transglutaminase in coeliac disease: diagnostic effectiveness and decline pattern after gluten-free diet. *Dig Liver Dis* 2006;38(2):98-102.
8. Raivio T, Korponay-Szabo I, Collin P, Laurila K, Huhtala H, Kaartinen T, et al. Performance of a new rapid whole blood coeliac test in adult patients with low prevalence of endomysial antibodies. *Dig Liver Dis* 2007;39(12):1057-63.
9. Dickey W, Hughes DF, McMillan SA. Disappearance of endomysial antibodies in treated coeliac disease does not indicate histological recovery. *Am J Gastroenterol* 2000;95(3):712-4.
10. Collin P, Maki M, Keyrilainen O, Hallstrom O, Reunala T, Pasternack A. Selective IgA deficiency and coeliac disease. *Scand J Gastroenterol* 1992;27(5):367-71.
11. Lenhardt A, Plebani A, Marchetti F, Gerarduzzi T, Not T, Meini A, et al. Role of human-tissue transglutaminase IgG and anti-gliadin IgG antibodies in the diagnosis of coeliac disease in patients with selective immunoglobulin A deficiency. *Dig Liver Dis* 2004;36(11):730-4.
12. Villalta D, Alessio MG, Tampoia M, Tonutti E, Brusca I, Bagnasco M, et al. Diagnostic accuracy of IgA anti-tissue transglutaminase antibody assays in coeliac disease patients with selective IgA deficiency. *Ann N Y Acad Sci* 2007;1109:212-20.
13. Reeves GE, Squance ML, Duggan AE, Murugasu RR, Wilson RJ, Wong RC, et al. Diagnostic accuracy of coeliac serological tests: a prospective study. *Eur J Gastroenterol Hepatol* 2006;18(5):493-501.
14. Baudon JJ, Johanet C, Absalon YB, Morgant G, Cabrol S, Mougnot JF. Diagnosing coeliac disease: a comparison of human tissue transglutaminase antibodies with antigliadin and antiendomysium antibodies. *Arch Pediatr Adolesc Med* 2004;158(6):584-8.
15. Johnston SD, McMillan SA, Collins JS, Tham TC, McDougall NI, Murphy P. A comparison of antibodies to tissue transglutaminase with conventional serological tests in the diagnosis of coeliac disease. *Eur J Gastroenterol Hepatol* 2003;15(9):1001-4.
16. Catassi C, Fabiani E, Ratsch IM, Coppa GV, Giorgi PL, Pierdomenico R, et al. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatr Suppl* 1996;412:29-35.
17. Borhani Haghighi A, Ansari N, Mokhtari M, Geramizadeh B, Lankarani KB. Multiple sclerosis and gluten sensitivity. *Clin Neurol Neurosurg* 2007;109(8):651-3.
18. Kia KF, Nair RP, Ike RW, Hiremagalore R, Elder JT, Ellis CN. Prevalence of antigliadin antibodies in patients with psoriasis is not elevated compared with controls. *Am J Clin Dermatol* 2007;8(5):301-5.
19. Kermabon C, Ehrhart A, Volant A, Youinou P, Le Goff P. [Antigliadin antibodies in rheumatoid arthritis]. *Rev Rhum Ed Fr* 1993;60(3):189-93.