# An Update on Coeliac Serology

**Introduction:** Coeliac disease is a common disorder affecting the gastrointestinal tract, secondary to an immunologic reaction to gluten. At present it can only be managed by lifelong avoidance of gluten, and thus presents a challenge for patients and their health care professionals.

While accounts of coeliac sprue date back to the first century AD, the link with gluten was first characterised in the late 1940s. The wartime shortage of wheat, and adoption of a surrogate gluten-free diet, allowed children with diarrhoea and failure to thrive to improve, only to worsen again when the cereal supplies were restored.

Initially thought to be a rare disease of children, we now recognise it to be more prevalent in adults, including the elderly. Data from the UK reveal that the most common age group diagnosed is between 30 and 45, with more people over 60 than those under 16 years.

The illness occurs in people of European, Turkish, Middle Eastern, Egyptian and Indian backgrounds. It appears to be rare in sub-Saharan Africa and South-East Asia. There is debate over mass screening in Caucasian populations where the disease incidence approaches 1%. The Gastroenterological Society of Australia (GESA) currently recommends screening in persons with Type 1 diabetes mellitus, Down syndrome, Turner syndrome, immunoglobulin A (IgA) deficiency, or a family history of coeliac disease, where the condition may be as common as 1 in 10.

### Table 1

| Clinical features of Coeliac Disease |
|---|
| • Chronic diarrhoea or alternating bowel habit |
| • Unexplained weight loss |
| • Abdominal distension, unexplained abdominal discomfort |
| • Apthous ulceration |
| • Steatorrhoea |
| • Prolonged, unexplained fatigue |
| • Arthralgia |
| • Iron or folate deficiency |
| • Unexplained abnormal liver function tests (elevated transaminases) |
| • Idiopathic osteoporosis |
| • Short stature / failure to thrive/ delayed puberty in children |
| **Possible clinical features:** |
| • Polyneuropathy/ataxia |
| • Infertility/recurrent abortions |

### Table 2

| Clinical associations with coeliac disease |
|---|
| • **IgA deficiency** |
| • **Other autoimmune disease:** |
| Sjogrens Syndrome |
| Type I diabetes mellitus |
| Autoimmune thyroiditis |
| Autoimmune liver diseases |
| Alopecia |
| Addisons Disease |
| Myaesthenia Gravis |
| Rheumatoid Arthritis |
| • **Downs Syndrome** |
| • **Turner Syndrome** |
| • **Williams Syndrome** |
| • **Congenital heart defects** |

## What is coeliac disease?

Coeliac disease occurs in genetically predisposed individuals upon exposure to gluten containing food. It is primarily a small bowel disorder characterised by mucosal inflammation, villous atrophy and crypt hyperplasia.

## How do patients with coeliac disease present?

Coeliac disease most commonly manifests with diarrhoea, flatulence and weight loss. Some patients are mistakenly diagnosed with irritable bowel syndrome due to abdominal discomfort and bloating, or chronic fatigue syndrome due to general malaise and tiredness. Approximately half of adult patients do not have gastrointestinal symptoms at diagnosis; they may be largely asymptomatic or have manifestations of malabsorption, such as iron deficiency anaemia, folate deficiency or even osteoporosis. Many other symptoms have been linked with coeliac disease and, more commonly, gliadin antibodies. These include inflammatory arthritis, various neurological symptoms (such as peripheral neuropathy or ataxia) and infertility (including miscarriages). The evidence behind these associations is often weak. Infertility remains an area of uncertainty, though GESA suggest testing may be appropriate.

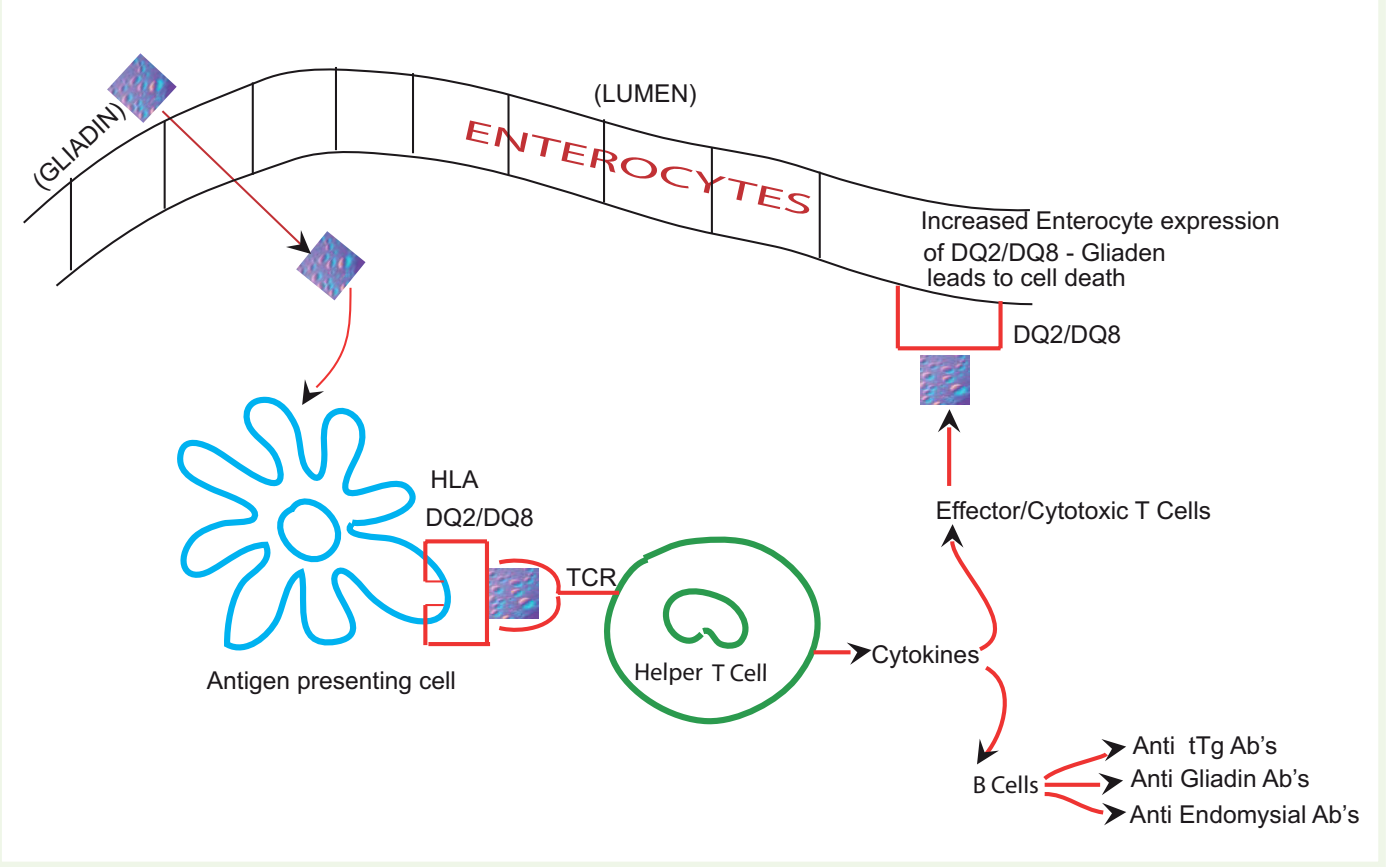


*Figure 1. Immunopathology of Coeliac Disease*

**Dermatitis herpetiformis** is the cutaneous manifestation of coeliac disease. The rash is vesicular and intensely pruritic, occurring over the extensor surfaces of the limbs, buttocks, trunk and scalp. It can be diagnosed by immunofluorescence of a normal area of skin, which will show granular IgA deposits in the dermis. The rash responds to a gluten free diet.

There is a strong association between coeliac disease and other organ specific autoimmune diseases particularly Type I diabetes and autoimmune thyroiditis. IgA deficiency is also ten times more common in these patients. See Table 2 for a list of common disease associations.

## Immunopathology

The aetiology of coeliac disease has advanced considerably over the past 10 years, although our understanding is still incomplete.

Predisposed individuals express the HLA DQ2 or DQ8 molecules. Their antigen presenting cells take up the gluten peptides in the gut mucosa, and present them to T cells. The combination of the processed gluten peptide and these particular HLA molecules potently activates T cells. This leads to intense inflammation, antibody formation and particular attack on the enterocytes which also express these HLA molecules. (See Figure 1)

The antibodies form to gliadin and also to an enzyme, tissue transglutaminase. This enzyme modifies the gluten peptides and exposes epitopes which increase their immunostimulatory potential. It is not yet known whether these antibodies are bystanders, or whether they have a pathological role.

There are still a lot of unknowns in the pathogenesis. In particular, it is important to emphasise that many people have this HLA DQ2 or DQ8 haplotype, but do not develop coeliac disease.

## What Testing Should be Done?

Serological testing for coeliac disease has undergone refinement in the past decade. In most situations, antibody testing to gliadin has now been superseded by the more accurate tests – anti-endomyseal and anti-tissue transglutaminase antibodies.

**Endomyseal antibodies** recognise tissue transglutaminase. The test is done by immunofluorescence, and while it has excellent diagnostic utility in coeliac disease, it requires substrates which can be difficult to obtain, is labour intensive and operator dependent. Endomyseal antibodies are of limited use in monitoring coeliac patients as they take 12-18 months to become negative.

# An Update on Coeliac Serology continued

For these reasons, an ELISA test for antibodies to **tissue transglutaminase** (tTG antibodies) has been established. This provides a standardised and quantitative method for the diagnosis and monitoring of coeliac disease. Clinipath Pathology has recently changed from a combined (IgA+IgG) tTG assay to an IgA tTG assay. The IgA tTG has a sensitivity around 95%, and is thus a good screening test. It has a specificity of approximately 90%. It is suspected that there will be less false positive results with this assay compared with the previous combined assay. Small bowel biopsy remains the gold standard for diagnosis, however, and it is recommended that all patients with positive serology go on to have an endoscopy and biopsy.It is important to note that the tTG antibodies become negative approximately 3-9 months after the introduction of a gluten-free diet. This may be a useful monitoring tool, but must also be considered in interpreting negative results. Patients don't always tell their doctors that they have been avoiding gluten prior to diagnostic testing being performed!

While we do not routinely test for endomyseal antibodies, they may be useful in patients where there is discordance between their tTG antibody and biopsy results. Please contact Dr Tiffany Hughes for further discussion if required.

- *A positive tTG antibody test indicates that CD is likely, and this should then be confirmed with a small bowel biopsy.*
- *A negative tTG antibody test virtually excludes CD. However, in patients with a high clinical suspicion of coeliac disease, further tests should be done.*
- *Further testing may include:*

  *Coeliac Disease HLA Typing*

  *A small bowel biopsy*

## Coeliac Disease HLA Typing

More than 99% of patients with coeliac disease possess the HLA-DQ2 or HLA-DQ8 allele. It is therefore a good test for excluding coeliac disease – a patient is highly unlikely to have coeliac disease if s/he does not have these alleles.

However, a large proportion of the healthy population also have these alleles, so if it is positive, it does not contribute to the diagnostic decision making.

- *HLA-DQ2/DQ 8 positive –*
  *Coeliac Disease is not excluded.*
- *HLA-DQ2/DQ8 negative –*
  *Coeliac Disease is excluded.*

## IgA Deficiency

IgA deficiency is defined as 'undetectable or barely detectable' serum IgA. In IgA-deficient patients IgA tTG, IgA endomyseal and IgA antigliadin antibodies are not produced. We routinely report total IgA levels with the IgA tTG so that these patients are identified.

In these patients, IgG antigliadin or anti IgG tTG antibodies can be tested. Referral to a gastroenterologist is advised for patients with IgA deficiency in whom coeliac disease is suspected regardless of the biopsy result. A small biopsy may be necessary, for the diagnosis of coeliac disease, but also to exclude other diseases associated with IgA deficiency, such as chronic Giardia and autoimmune enteritis.

## Infants and Coeliac Disease

In children less than 2 years of age, antibody production is not mature and may result in false negative tTG antibodies. This is especially true for those less than one year of age. Please contact Dr Tiffany Hughes for advice in these age groups.

## Is it important to diagnose?

In addition to the complications of chronic malabsorption, there is an increased risk of malignancy in patients with coeliac disease. Strict adherence to diet is seen to reduce this risk.

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## References

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