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Coeliac disease: where are we in 2014?

Background

Coeliac disease (CD) is an autoimmune condition affecting at least 1% of the population, many of whom remain undiagnosed. It is characterised by chronic inflammation of the small-intestinal mucosa and triggered by eating gluten. It is challenging to diagnose because of the many and varied ways in which it may present.

Objective

To present up-to-date information on CD as we now understand it, with recommendations on whom to test and how to test them, and how to manage patients once they are diagnosed.

Discussion

Primary care practitioners have a crucial role in improving rates of CD diagnosis, and in the ongoing care of patients with CD.

A blood test for coeliac-specific antibodies will identify most patients who need to undergo duodenal biopsy to make the diagnosis. Management encompasses supporting patients with adherence to the gluten-free diet and conducting a CD-focused clinical review every 1–2 years.

Keywords

Coeliac disease

CPD

Previously understood to be a disease of the gastrointestinal tract, coeliac disease (CD) is now recognised as the most common of the autoimmune conditions. The target organ is the small intestine and the condition is characterised by chronic inflammation of the intestinal mucosa, leading to a wide range of clinical manifestations. These include malabsorption and abdominal symptoms, and extraintestinal symptoms such as fatigue and skin rashes. CD is unique among the autoimmune conditions because the environmental trigger of the destructive immune response (gluten ingestion) is well known and, for the majority of patients, removal of that trigger by commencing a gluten-free diet (GFD) brings about resolution of the mucosal damage and prevents complications.[1]

Defining coeliac disease

There have been many attempts to define the various patterns of CD over time, but the 2013 Oslo definitions provide the clearest taxonomy of the types of CD to date.[2] A summary of the key definitions is given in *Table 1*.

The role of gluten

Gluten, the principal storage protein in wheat, consists of a number of proline- and glutamine-rich proteins. These amino acids are highly resistant to digestion and in genetically predisposed individuals their contact with the intestinal mucosa triggers the immune response seen in CD.[3] This response to gluten is initiated by tissue transglutaminase (tTG), an enzyme that deamidates gluten peptides present in the small bowel mucosa. The deamidated gliadin peptides (DGPs) are then detected by antigen-presenting cells, which activate and lead to the proliferation of gluten-specific activated cytotoxic T cells.[4] This immune response leads to the mucosal destruction in the small bowel, characteristic of CD. Because of the close similarity of their storage proteins to those in wheat, barley and rye also provoke this response.

Prevalence of coeliac disease

Although CD has been around for centuries, it is only in recent decades that we have begun to appreciate its complexities and impact on our

Table 1. A summary of the Oslo definitions for coeliac disease[2]

Definition*	Features
Classical CD	Dominated by symptoms, signs and sequelae of gastrointestinal malabsorption. Patients have positive coeliac antibodies and villous atrophy on duodenal biopsy.
Non-classical CD	The most commonly presenting variant of CD in which extraintestinal symptoms (such as fatigue) are predominant. There are no overt symptoms of malabsorption. Patients have positive coeliac antibodies and villous atrophy on duodenal biopsy.
Subclinical CD	Patients have no overt symptoms or signs so are below the threshold of clinical detection. They do test positive for coeliac antibodies (usually found on screening at-risk individuals) and evidence of intestinal damage on biopsy.
Potential CD	Previously known as latent CD. The diagnosis in patients with positive coeliac antibodies but no histological evidence of intestinal damage.

*Additional definitions were developed but are beyond the scope of this article. These include a definition for non-coeliac gluten sensitivity (NCGS), which is the Oslo panel's preferred term for conditions labelled as gluten-sensitivity or gluten-intolerance. For a recent discussion that summarises the current understanding of NCGS, refer to work by Biesiekierski et al.[21]

population. Prior to this it was believed that CD was a rare disease, mostly affecting children, particularly those of Celtic or Northern European descent.

It is now clear that CD affects adults and children alike, and its presence has been confirmed in every continent.[5] A population-based study in New Zealand determined a prevalence of biopsy-proven CD of 1.2%.[6] A more recent Australian study estimated a prevalence of CD of 1.2% in men and 1.9% in women.[7] There is also evidence that the prevalence of CD has increased over recent years in some countries.[8–10]

Recognising coeliac disease

CD presents in many different ways, which makes it challenging to recognise. Consequently, the number of people diagnosed remains well short of the number predicted to have CD, including in Australia.[11] In addition to this, the average time to diagnosis can extend to several years.[12,13]

Classical CD is characterised by malabsorption and symptoms or signs associated with the gastrointestinal tract (*Table 1*). The more commonly occurring non-classical CD may manifest in a wide range of complaints. In addition to symptomatic patients, many individuals have subclinical CD. These patients may have underlying conditions associated with increased risk of CD (such as Down syndrome or type 1 diabetes mellitus) or have a first-degree relative with CD. Correct diagnosis of CD in these individuals relies on clinicians recognising their risk of CD and investigating accordingly. The significance of potential CD remains uncertain. A recent study following 175 children with this diagnosis found that 67% continued to have normal duodenal histology after 9 years of follow-up.[14]

The 2009 NICE guidelines, *Recognition and assessment of coeliac disease*,[15] provide recommendations to guide clinicians on when to investigate patients for possible CD, as summarised in *Table 2*.

Table 2. NICE recommendations on who to test for coeliac disease[15]

Offer testing to patients (adults and children) with any of the following:

- Diarrhoea – chronic or intermittent
- Failure to thrive
- Irritable bowel syndrome
- Persistent, recurrent or unexplained nausea, vomiting, abdominal pain or bloating
- Sudden or unexpected weight loss
- Unexplained iron-deficiency (or other) anaemia
- Autoimmune thyroid disease
- Type 1 diabetes
- Dermatitis herpetiformis
- First-degree relative with CD

Consider testing patients with any of the following:

- Addison's disease
- Autoimmune conditions – especially autoimmune liver disease, myocarditis, Sjögren's syndrome, ITP
- Bone disease – osteomalacia, osteopaenia, osteoporosis, rickets, fragility fractures
- Down syndrome
- Gynaecological conditions – amenorrhoea, recurrent miscarriage, unexplained subfertility
- Lymphoma
- Mood disorders – depression or bipolar disease
- Neurological conditions – epilepsy, polyneuropathy
- Oral health problems – recurrent aphthous stomatitis, dental enamel defects
- Other gastrointestinal presentations – persistent or unexplained constipation, microscopic colitis, unexplained elevated liver enzymes
- Sarcoidosis
- Turner syndrome
- Unexplained alopecia

Diagnosing coeliac disease

Testing for CD in older children and adults is usually straightforward, providing the patient is eating a gluten-containing diet, as outlined in *Table 3*. Blood tests can detect the presence of specific IgA antibodies, such as those directed towards tTG and DGP as well as anti-endomysial antibodies (EMA), and can be used to identify individuals with possible CD. In patients with specific IgA-deficiency (2% of patients with CD) these tests will be falsely negative and IgG-based tests are then required. In addition, DGP antibodies have been shown to be more reliable than tTG in younger children (especially those less than 2 years of age).[16]

For patients already on a GFD, the situation is more complicated as the standard antibody tests may be falsely negative. These patients should therefore be advised to undertake a gluten challenge before being tested. The most recent recommendation for an adequate gluten challenge is that patients should consume at least two slices of wheat-bread per day for a minimum of 2 weeks and up to 8 weeks.[17]

Although the antibody tests have high sensitivity and specificity for CD, definitive diagnosis relies on histological examination of biopsies from the duodenum and duodenal cap. Therefore, in the setting of a positive antibody test, or if an individual has significant symptoms and there is high clinical suspicion of CD, referral should be made for endoscopy. The characteristic features of CD (villous atrophy, crypt hyperplasia, intraepithelial lymphocytosis and mucosal inflammation) are seen under light microscopy of mucosal biopsies.[1,16,17]

Genetic testing with the HLA DQ2/DQ8 test can be helpful in certain circumstances. Given that >99% of patients with CD carry one or other of these markers, a **negative** test effectively **excludes** CD. A **positive** test is less helpful and **cannot** be used to diagnose CD because either HLA DQ2 or HLA DQ8 is present in at least 50% of the population,[7] the majority of whom do not have CD. A recent study by Anderson et al[7] suggests that when a patient returns a positive tTG or DGP test, the addition of HLA testing will enable clinicians to identify false-positive antibody tests, leading to a reduction in unnecessary biopsies. However, this approach has yet to be confirmed by other investigators and is not yet endorsed for routine practice.

In addition to the above, other tests are important to assess the impact of CD on intestinal function. These include full blood count, iron studies, vitamin B_{12}, folate, vitamin D and liver chemistry.

Managing coeliac disease

At present the only treatment for CD is a lifelong GFD. The diet should be commenced following confirmation of the diagnosis, with input from a dietitian with expertise in the area. As well as leading to resolution of symptoms and inducing mucosal healing, strict adherence to the GFD also reduces the subsequent risk of the potential sequelae of CD such as osteoporosis, other autoimmune diseases and small bowel lymphoma.[16,17]

Although a GFD has benefits, it can also lead to adverse effects. Patients on a GFD need to ensure that their diet contains enough fibre and the B-goup vitamins normally derived from gluten-containing grains. Constipation and overweight can occur, and the diet can also be high in saturated fats and sugars.[18]

The inclusion of oats in the GFD remains contentious. In the past it was believed that oats were harmful to patients with CD but this may not always be the case. The storage protein in oats is sufficiently different from wheat gluten that for the majority of patients it will not cause harm. However, oats are frequently contaminated with wheat or other cereals, compromising their inclusion in a GFD. The inclusion of uncontaminated oats in an individual's GFD should be considered only after consultation with their gastroenterologist and dietitian, and when a comprehensive plan for follow-up is in place.[16]

Primary care practitioners have important roles to play in the ongoing care of patients with CD, as outlined in *Table 4*. Current guidelines recommend that all patients with CD should have an annual focused review. Primary care would be an appropriate place

Table 3. An approach to testing for coeliac disease

Patient eating gluten? YES ↓	NO → gluten challenge: 2 slices bread/day for 2–8 weeks then coeliac serology If serology negative at 2 weeks then continue with challenge and repeat serology at 8 weeks
Coeliac serology	IgA-tTG +/– IgA-EMA +/– IgA-DGP; total IgA levels
Negative serology	IgA low +/– IgG test if available IgA normal and low index of suspicion → NOT CD IgA normal and high index of suspicion → refer for specialist review Consider HLA DQ2 and DQ8 testing → negative test rules out CD
Positive serology	Refer for duodenal biopsy*

*Duodenal biopsy (with multiple biopsies from the proximal duodenum) is required to confirm the diagnosis of CD. Other conditions that can give an elevated tTG include type 1 diabetes, inflammatory bowel disease, liver disease and other autoimmune diseases

tTG, tissue transglutaminase; EMA, endomysial antibody; DGP, deamidated gliadin peptide; IgA, immunoglobulin A

Table 4. Management of patients with coeliac disease[15,16]	
At diagnosis	• Ensure referral to dietitian with expertise in CD • Investigate for and treat micronutrient deficiencies (eg iron, vitamin B_{12}, folate, vitamin D, calcium) • Review for presence of complications or associated conditions (eg other autoimmune disorders) • Consider evaluating bone mineral density (important for those with delayed diagnosis; past fragility fractures; post-menopausal women; men aged over 55 years) • Review immunisation status • Encourage to join coeliac support group (www.coeliac.org.au)
At 3–6 months	• Assess response to diet: – symptoms: should be resolving/have resolved – antibodies levels (especially tTG) should be falling – micronutrient deficiencies should be resolving/have resolved • Consider specialist dietetic review if recovery inadequate • Recommend screening of first-degree relatives
At 12 months and annually thereafter	• Review symptoms, GFD adherence, complications, associated diseases • Consider specialist gastroenterology review if recovery inadequate or new concerns
CD, coeliac disease; GFD, gluten-free diet; tTG, tissue transglutaminase	

for that to occur.[16,17,19] In addition to enquiring about adherence to the GFD, an evaluation of symptoms should be undertaken (especially new symptoms suggestive of complications), and nutritional state should be assessed (especially in children). Primary care practitioners also have a role in ensuring that individuals with CD are fully vaccinated, including against encapsulated bacteria (eg *Streptococcus pneumoniae*), and receive annual influenza immunisations.[16]

Although not currently relevant to the management of CD, a number of new therapies are undergoing evaluation. They include a therapeutic vaccine targeting T-lymphocyte activation, gluten-specific proteases (derived from bacteria, fungi or cereals) to degrade gluten proteins, probiotics, and immune modulation with hookworm infection.[3,20] These therapies raise the future prospect that not all patients will require a GFD.

Key points

- CD affects at least 1% of the population; evidence suggests its prevalence is increasing.
- The diagnosis of CD depends on primary care practitioners being alert to its myriad presentations and those situations in which patients are at higher risk of the disease.
- Testing for possible CD is simple: a blood test for tTG and/or DGP antibodies. The gold standard for diagnosing coeliac disease remains duodenal biopsy.
- The HLA DQ2/ DQ8 test is useful for excluding CD.
- Treatment is a lifelong, strict GFD but a range of new treatments are under investigation.
- Patients with CD should be reviewed regularly, with attention to symptoms, adherence to the GFD, growth (in children), monitoring for complications and provision of preventive health initiatives.

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Competing interests: Andrew S Day is on the advisory board of Janssen and receives payment for this.

Provenance and peer review: Commissioned, externally peer reviewed.

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