Coeliac disease
a practical overview

There is an increasing awareness of coeliac disease but the majority of patients remain undiagnosed – this is the so-called coeliac iceberg.

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Coeliac disease is a common and often unrecognised disorder that reportedly occurs in up to one in 100 individuals. It affects a large number of ethnic groups but mostly people of European origin, including those living in North America and Australia. Given the diverse population of Australia, it is important to recognise that coeliac disease does occur in non-Caucasians, including individuals from the Indian subcontinent. It has been reported in Arabs, Hispanics, Israeli Jews and Sudanese but is rare in individuals from pure Afro-Caribbean, Chinese or Japanese backgrounds. First-degree relatives of individuals with coeliac disease have an up to 10% greater risk of having the condition compared with non-relatives, and hence should be screened.

Pathogenesis and genetics

Coeliac disease results from both cell-mediated and humoral responses to ingested gluten, a mixture of proteins found in wheat, barley and rye, in a genetically susceptible person. Certain HLA haplotypes are necessary for coeliac disease to develop: HLA-DQ2 is found in up to 95% of patients with coeliac while nearly all the remainder have HLA-DQ8. About 30% of the general population possess HLA-DQ2 or HLA-DQ8, although only a small proportion of these individuals have coeliac disease. Conversely, coeliac disease is extremely unlikely in the absence of these haplotypes.

Although not recommended as a primary screening test for coeliac disease, HLA testing is useful in either confirming or ruling out the diagnosis in individuals who, for example, have positive serology and a normal small bowel biopsy.

Categories and clinical presentation

The classification of coeliac disease has evolved in recent years, as more serological, genetic and

IN SUMMARY

- **The prevalence of coeliac disease is reportedly as high as one in 100. Both Caucasians and non-Caucasians are affected, but it is extremely rare in Chinese, Japanese and Afro-Caribbean people.**
- **In contrast to its classic presentation with malabsorption, there is increasing recognition of more subtle presentations, including fatigue from anaemia secondary to iron and/or folate deficiency, osteoporosis and nonspecific gastrointestinal symptoms.**
- **Coeliac disease should be considered in patients with symptoms suggestive of irritable bowel syndrome as well as in those with type 1 diabetes or osteoporosis.**
- **Relatives of people with coeliac disease are at an increased risk of the condition and should be screened.**
- **Serology is useful for screening, but histology is the gold standard for diagnosis.**
- **Assessment for all nutritional consequences, including bone disease, is vital.**
- **Lifelong adherence to a gluten-free diet is important to reduce symptoms and prevent complications. Noncompliance is the most common cause for nonresponse.**

histological data have become available. Symptomatic individuals diagnosed as having coeliac disease represent the 'tip of the iceberg' as the vast majority of patients remain undiagnosed, being hidden 'under the waterline'. Silent coeliac disease is referred to when there are no symptoms despite the presence of the characteristic intestinal morphology. In addition, there is a group of patients who have positive coeliac serology in the absence of any histological changes in the small bowel mucosa; some of these patients will eventually develop overt coeliac disease.

The clinical manifestations of coeliac disease are variable and hence it has been referred to as the great imitator of our times. The classic presentation in infants (diarrhoea, steatorrhoea, failure to thrive, weight loss and abdominal distension) is rarely seen now. This is partly due to the longer length of time infants are breastfed and the later introduction of gluten in the infant diet nowadays. In recent times, there has been an increasing awareness of more subtle presentations in adults, including:

- fatigue resulting from anaemia secondary to iron and/or folate deficiency
- osteopenic bone disease
- nonspecific gastrointestinal symptoms often mimicking irritable bowel syndrome (bloating, abdominal pain and bowel irregularity).

Age at presentation is usually between 10 and 40 years, but coeliac disease can occur at any age, at times being incidentally detected in elderly individuals following evaluation for osteoporosis or iron deficiency. Individuals with the nonspecific gastrointestinal symptoms are often labelled as having irritable bowel syndrome (IBS) when they may, in fact, be suffering from coeliac disease.

The nongastrointestinal manifestations of coeliac disease are wide ranging and it is important to consider coeliac disease when determining the causes of these symptoms (Figure 1). Neurological problems as varied as epilepsy, encephalopathy, cerebellar dysfunction, myelopathy, peripheral neuropathy or combinations of these may also be indicators of underlying coeliac disease. Psychological disturbances, including depression and schizophrenia, have also been described. Peripheral as well as axial arthritis may be a feature in some individuals. Menstrual abnormalities include late menarche, early menopause and reduced fertility. Pregnant women with undiagnosed coeliac disease, especially those who had symptoms before becoming pregnant, are at increased risk for recurrent miscarriage, stillbirth, perinatal deaths and intrauterine growth retardation. In men, abnormalities in sperm motility and morphology can result in infertility. Hyposplenism may occur; the presence of Howell Jolly bodies in the peripheral blood smear may be a clue to this, and administration of pneumococcal vaccine to these individuals is reasonable.

There is an increased frequency in individuals with coeliac disease of various autoimmune conditions, including type 1 diabetes mellitus, autoimmune thyroid disease, primary biliary cirrhosis and Sjögren's syndrome. In addition, asymptomatic

When to consider coeliac disease

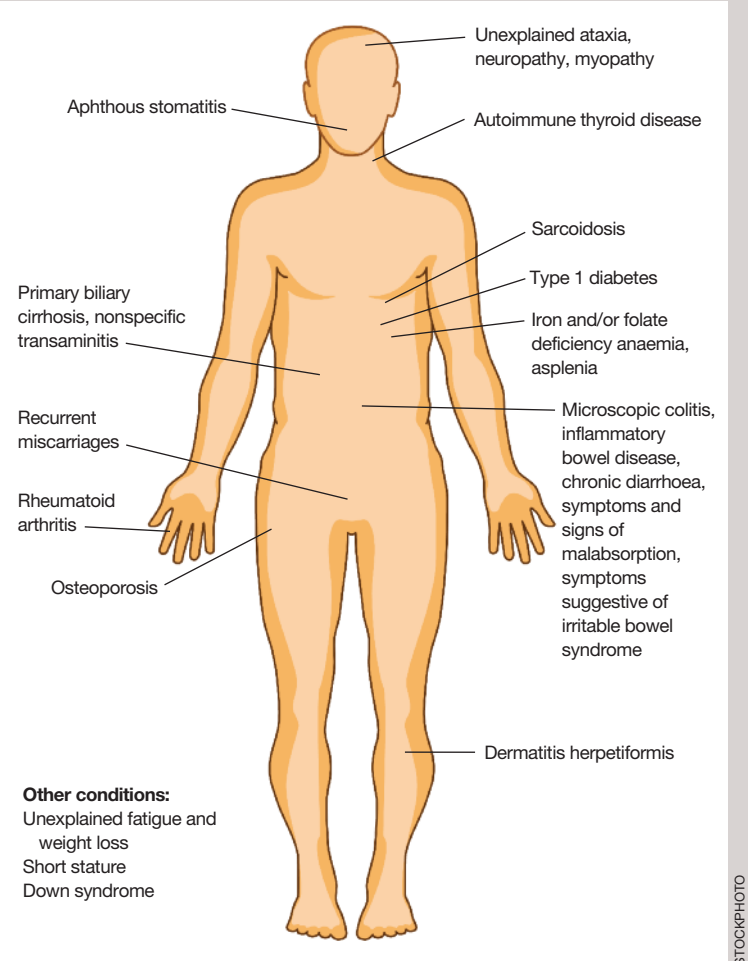

Figure 1. Conditions prompting investigation for coeliac disease.

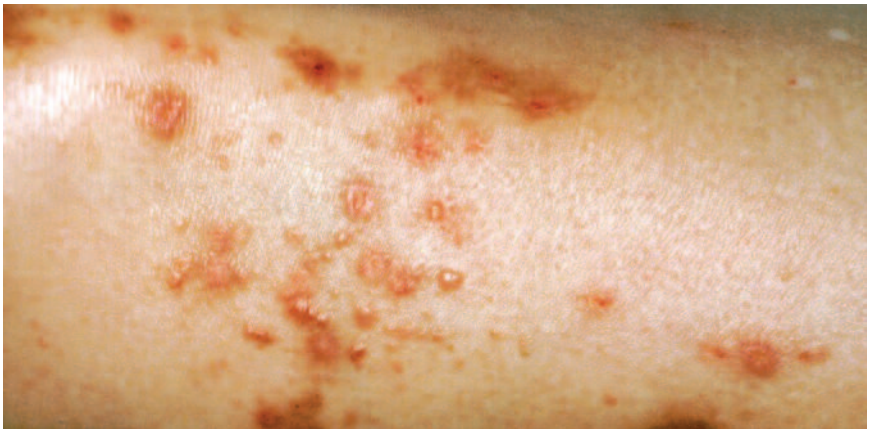

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Figure 2. Dermatitis herpetiformis on a limb. About 80% of patients with this skin disorder have coeliac disease.

liver function test (LFT) abnormalities, predominantly elevated transaminases, are found in about 40% of patients.

Dermatitis herpetiformis

The skin disorder dermatitis herpetiformis is associated with coeliac disease and is characterised by an itchy papular vesicular eruption, usually symmetrically distributed on the elbows, knees, buttocks, face, neck and trunk (Figure 2). Approximately 80% of patients with dermatitis herpetiformis have coeliac disease, whereas less than 10% of patients with coeliac disease develop this skin condition. A strict gluten-free diet usually reverses both the intestinal symptoms and the skin lesions.

Several other cutaneous disorders have reportedly been associated with coeliac disease, including psoriasis, eczema, oral ulcers and cutaneous vasculitis. The mechanism is thought to be due to increased intestinal permeability to exogenous antigens and the induction of hypersensitivity reactions or the formation of immune complexes. Nutritional deficiencies related to malabsorption may also play a part. The frequency of association of some of these cutaneous conditions needs to be determined but serological testing for coeliac disease appears justified when lesions are recurrent or persistent.

Malignancy risk

Malignancy has always been the dreaded complication of untreated coeliac disease, with the disorder posing an increased risk for lymphomas and gastrointestinal malignancies, in particular squamous cell carcinomas of the oesophagus, mouth and pharynx as well as adenocarcinoma of the small intestine. The good news is that the risk is much less than previously thought. The current considerations of only modest increased risk for cancer and about sixfold increased risk for malignant lymphoma are in sharp contrast to the 40-fold increased incidence reported in earlier studies.

Also, evidence suggests that strict adherence to a gluten-free diet protects against malignancies and lymphoma.

Diagnosing coeliac disease

Before labelling an individual as having coeliac disease and subjecting him or her to a gluten-free diet for life, it is important to confirm the diagnosis. There is a growing role for serological tests in the screening for coeliac disease, but the gold standard for diagnosis remains small bowel biopsy.

Serological testing

The main role of serological tests is to screen patients who have nonspecific symptoms, metabolic sequelae or one of the conditions associated with coeliac disease. Serology is also useful for screening first-degree relatives of patients with coeliac disease (first-degree relatives have an up to 10% higher prevalence of the condition, and second-degree relatives have an up to 2% higher prevalence). Four serological tests are commonly available:

- IgA tissue transglutaminase antibody (IgA tTGA)
- IgA endomysial antibody (IgA EMA)
- IgA antigliadin antibody (IgA AGA)
- IgG antigliadin antibody (IgG AGA).

The IgA tTGA test is both sensitive and specific for coeliac disease and supplants the use of gliadin antibody testing as the preferred means of serological screening. However, it is important to remember that the test will be negative in patients with IgA deficiency.

When interpreting coeliac serological results there are several points that should be considered, including the following:

- the sensitivity of assays in certain commercial laboratories may not be as high as those published from research centres
- the IgA tTGA test has a sensitivity greater than 95% and a specificity in the range of 90 to 96%
- the antigliadin antibody tests have lower diagnostic accuracy than the IgA tTGA and endomysial antibody tests and hence are not recommended
- as 2 to 3% of individuals with coeliac disease have selective IgA deficiency, IgA levels should be measured to avoid false negatives
- antibody tests are useful in monitoring compliance as antibody levels will decrease on a gluten-free diet and increase after the ingestion of gluten
- measurement of antibodies has a role in screening individuals at high risk for coeliac disease, including relatives of coeliac patients, people with type 1 diabetes and those with symptoms suggestive of irritable bowel syndrome
- small intestinal biopsy specimens should be obtained in all individuals with elevated EMA or tTGA antibodies

with the exception of those unable or unwilling to undergo endoscopy.

Gastroscopy and biopsy

The definitive diagnosis of coeliac disease requires a characteristic appearance on histology, and at least three biopsies should be taken from the second or third part of the duodenum as the changes due to coeliac disease may be patchy. Small bowel biopsies should also be taken routinely in patients undergoing gastroscopy for investigation of iron deficiency anaemia and in those who have one of the conditions associated with coeliac disease and are undergoing gastroscopy for any reason.

Endoscopic findings include scalloping, absence of duodenal folds and a mosaic pattern (Figure 3). However, these findings are both insensitive and nonspecific for coeliac disease. Histological features of coeliac disease include varying degrees of villous atrophy, a change in the normal columnar appearance of the absorptive epithelium with crypt hyperplasia and an increased number of intraepithelial lymphocytes and mononuclear cells in the lamina propria (Figure 4).

Histological differential diagnosis

The histological pattern seen in coeliac disease is not unique and can be seen in several other clinical situations including:

- giardiasis
- viral gastroenteritis
- intestinal lymphoma
- Crohn's disease
- eosinophilic gastroenteritis
- HIV enteropathy
- tropical sprue.

Establishing the diagnosis

Small bowel biopsy is required to establish the diagnosis of coeliac disease – a diagnosis should not be based purely on serological testing or even clinical presentation. A gluten-free diet is not only expensive but also often tedious and hence a high price to pay for a person who does not suffer from the condition. A subjective feeling of wellbeing on a gluten-free diet should not be equated to a diagnosis of coeliac disease as some patients suffering from irritable bowel syndrome claim improvement with such a diet. Patients on self-imposed gluten-free diets should be challenged with a diet containing at least 10 g of gluten per day (equivalent to four slices of bread) for one to two weeks and then be re-evaluated with serology and histology.

Genetic testing (HLA-DQ2 or HLA-DQ8) may be useful in certain individuals, such as patients with negative serology but positive histology in the absence of other causes of mucosal changes (Table 1). In the absence of HLA-DQ2 or HLA-DQ8, coeliac disease is unlikely.

Ancillary laboratory tests

Once coeliac disease is diagnosed in a patient, metabolic consequences should be looked for if these are not already apparent. Baseline investigations include:

- full blood count
- iron, folate and vitamin B_{12} levels
- calcium, phosphorus and vitamin D levels
- bone mineral density
- LFTs
- thyroid function tests
- blood glucose level.

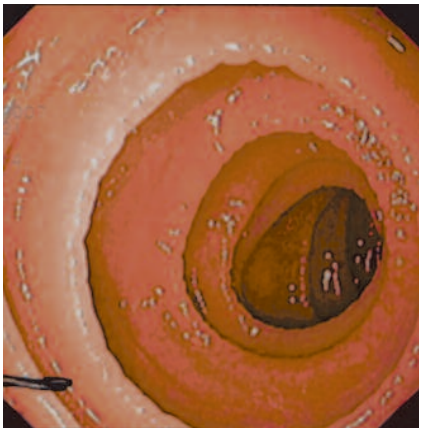
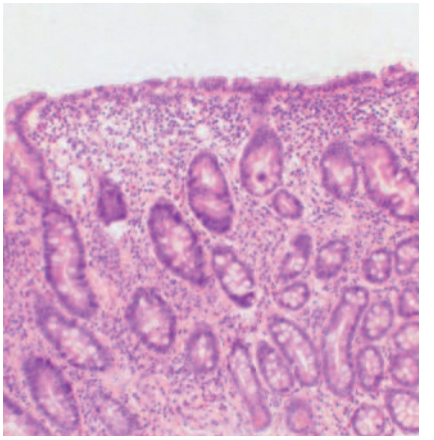


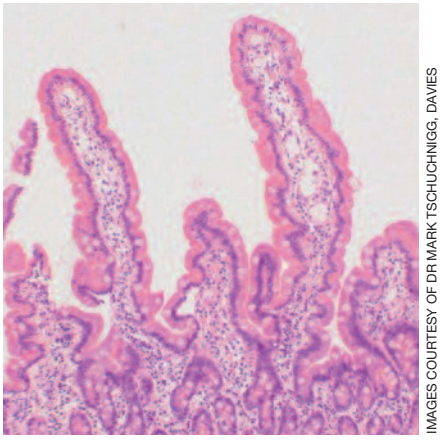
Figure 3. Endoscopic image of a patient with coeliac disease demonstrating scalloping.

Treatment

The seven key elements in the management of patients with coeliac disease are:

- involvement of a skilled dietitian
- nutritional assessment for all deficiencies
- encouragement to join a regional coeliac society
- education about the disease
- reinforcement that a gluten-free diet is for life
- identification of all associated disorders





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Figures 4a and b. a (left). Small bowel biopsy in a patient with coeliac disease, showing loss of normal villous architecture, with crypt hyperplasia and increased intraepithelial lymphocytes and mononuclear cells in the lamina propria. b (right). Normal small bowel biopsy, showing normal large finger-like villi.

Table 1. Diagnosing coeliac disease

Serology	Histology	Comment
Positive	Positive	Coeliac disease confirmed
Negative	Negative	Coeliac disease excluded
Positive	Negative	Follow up patient
Negative	Positive	Exclude other causes. Check HLA status (if HLA-DQ2 or HLA-DQ8 negative then coeliac disease is unlikely)

- regular follow up for compliance, complications and associated disorders.

General dietary rules

Gluten-free diet

Lifelong adherence to a gluten-free diet is essential. Gluten is present in wheat, barley and rye and hence individuals with coeliac disease should avoid these grains and all foods derived from them. Oats may become contaminated with these grains and so should also be avoided.

The Australia and New Zealand Food Standards Code requires that foods labelled as gluten-free must contain no detectable gluten as well as no oats or malted gluten-containing cereals or their products. However, manufacturing standards are not the same on a global basis and gluten-free products may be manufactured with the same machines that are used for gluten-rich products, and consequently may become contaminated. Patients who travel must be aware of this fact. Patients also need to be aware of the risk of contamination when sharing cooking utensils with family members. A dietitian's advice is very useful in this regard and a dietitian should be an integral member of the team managing the coeliac patient. Patients and healthcare providers should also be linked to regional coeliac societies. These societies are good ongoing resource bases and can provide much needed support so that patients can learn to live with the disease. Some useful internet resources are listed in the box on this page.

Determining which foods are completely free of gluten can be difficult. The term 'glutinous', for example, refers to the stickiness of the product and not its gluten content and hence products such as 'glutinous rice' are safe for patients with coeliac disease. Many foods are naturally gluten-free but processed and manufactured food products based on them often contain small amounts of gluten-containing ingredients (Tables 2 and 3). An example of this is the wheat-based thickeners used in ice cream, cheese spreads, salad dressings, soups, sauces and seasonings. Food labels must, therefore, be carefully examined for ingredients derived from gluten-containing grains. A wide range of gluten-free breads, biscuits, cereals, pastas and other foods are available from supermarkets and health food stores.

Traditional beers must be avoided as barley malt is used in their production. However, there are a few gluten-free beers available in Australia; these are based on sorghum instead of barley.

Other dietary considerations

Gluten is present in some oral medicines and supplements and also in some lipsticks and lip balms, and ingredient labels for

Coeliac disease: internet resources

Coeliac Society of Australia
www.coeliac.org.au

Coeliac UK
www.coeliac.co.uk

Gastroenterological Society of Australia
www.gesa.org.au

Table 2. Some gluten-free foods*

- Fruit, vegetables, nuts and pulses – without sauces
- Meat, poultry, fish – without crumbs, batters or sauces
- Eggs, milk, cheeses, natural yoghurt
- Rice, corn (maize), cornmeal, tapioca, buckwheat, quinoa, millet
- Butter, margarine, cooking oils

*Input from an experienced dietitian is vital. Check internet resources for exhaustive lists.

Table 3. Frequently overlooked products that may contain gluten*

Foods

- Broths, soup bases, sauces, gravies, salad dressing and meat stuffings
- Cornflour (some types)
- Icing sugar mixtures
- Sweets including licorice, some chocolates and ice creams
- Imitation bacon and self-basting poultry
- Imitation seafoods
- Communion wafers
- Processed luncheon meats
- Soy sauce

Other products

- Some nutritional, herbal, vitamin and mineral supplements
- Some drugs (pills and capsules) including over-the-counter medications
- Some lipsticks and lip balms
- Playdough

* Check all labels and ask manufacturer if in doubt.

these products should be read carefully.

Lactose intolerance may coexist initially due to mucosal injury, and hence a diet free of both gluten and lactose may be required. Also, a gluten-free diet is low in fibre, so patients should ensure an adequate intake of gluten-free wholegrains (e.g. brown rice, maize and cornmeal [polenta]) and high fibre vegetables and legumes. In addition, documented nutritional deficiencies (e.g. vitamins, iron, folate and calcium) should be corrected with supplements.

Monitoring response

It is imperative that patients on a gluten-free diet are followed up to monitor response and continually reinforce the importance of dietary compliance. There are several salient points that need to be considered when monitoring individuals:

- the rapidity of response is variable but 70% of patients with coeliac disease have clinical improvement in two weeks
- histological recovery lags behind clinical recovery – it can take months for the small bowel changes to return to normal
- serological response can be used to monitor recovery and compliance – it can take up to a year for antibody levels to be undetectable
- the need for routine follow up biopsy is debatable.

Nonresponders

Most patients with coeliac disease respond to a gluten-free diet. The reasons for nonresponse include:

- noncompliance, deliberate or unintentional – this is by far the most common cause of nonresponse
- the presence of other disorders, including concomitant or secondary lactose intolerance, irritable bowel syndrome, small intestinal bacterial overgrowth, coexisting pancreatic insufficiency and intestinal lymphoma
- refractory coeliac disease.

It is important to note that not all clinical features respond at the same rate, and bone disease and secondary hyperparathyroidism as well as peripheral neuropathy may only improve partially.

Refractory coeliac disease

Patients who fail to respond or develop refractory disease after an initial period of response despite a strict gluten-free diet are considered to have refractory coeliac disease. This can be severe and may be associated with progressive malabsorption and death. The exact cause is unknown and treatment has focused on immunosuppression.

Conclusion

Every clinician must be alert not only to the prevalence of coeliac disease but also to the fact that individuals are now more likely to present with fatigue, iron and/or folate deficiency anaemia, bone disease and nonspecific gastrointestinal symptoms often wrongly attributed to irritable bowel syndrome than with its classic presentation of malabsorption.

First-degree relatives of patients with coeliac disease and individuals with disorders known to be associated with coeliac disease, including type 1 diabetes and osteoporosis, should be screened for the disorder. Serology has a role in screening but histological confirmation is necessary before subjecting an individual to a lifelong gluten-free diet.

Dietary adherence is mandatory for affected individuals, with noncompliance being the most common cause for lack of response. MT

Further reading

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