Current status and management of coeliac disease

Coeliac disease nowadays generally presents with milder, more nonspecific symptoms than 20 or so years ago, providing a diagnostic challenge. It is readily treatable with a gluten-free diet and regular monitoring of health and nutritional status.

DHF WRITING GROUP ON COELIAC DISEASE

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Coeliac disease, or gluten-sensitive enteropathy, is a lifelong intolerance of the small intestine mucosa to dietary gluten that results in malabsorption and nutritional deficiencies. It is caused by an abnormal immune response to gliadin, a wheat prolamine protein that is a subfraction of gluten. Prolamines similar to gliadin are found in barley (hordein), rye (secalin) and, possibly, oats (avenin), and cause the same immune response. The affected mucosa becomes inflamed, with infiltration of lymphocytes into the epithelium and loss of the normal villous architecture (called villous atrophy) giving rise to the characteristic 'flat' histological appearance of untreated coeliac disease (Figure 1).

Prevalence

Coeliac disease has been considered a disease predominantly of Caucasians, but is now known to also occur in Indians and Arabs. It is, however, very uncommon in Africans, Chinese and Japanese. The clinical prevalence ranges from one in 300 to one in 2000, although a prevalence as high as one in 100 in Northern Ireland has been suggested.[1] There are many people with silent coeliac disease in the community. Coeliac disease is seen in about 10% of first-degree relatives and there is a 70% concordance in identical twins, a reflection of the strong HLA association seen in the condition (see the box on page 31).

Presentation

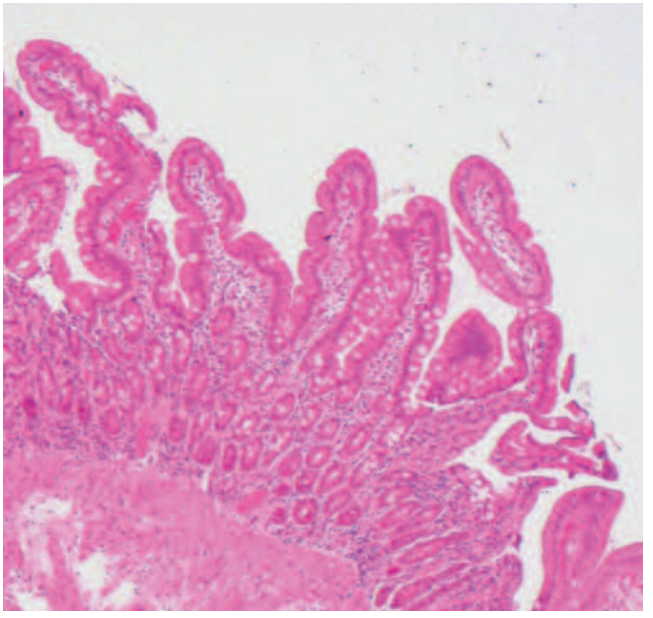
The presentation of coeliac disease varies widely, providing a diagnostic challenge. A delay in diagnosis can occur because of the subtlety of symptoms. Previous expectations that it is a disease of childhood or always presents with diarrhoea, are no longer true: onset is often in adulthood and symptoms may be very mild or absent. Anaemia is often the only manifestation.

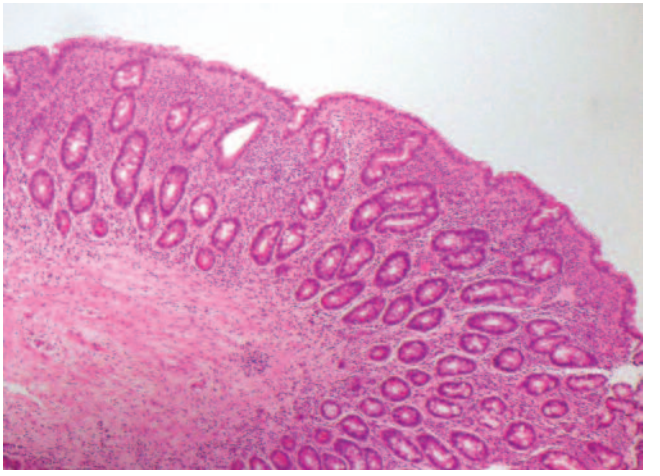
Clinical features in adults

The classic presentation of coeliac disease – features of malabsorption and malnutrition, such

IN SUMMARY

- **Coeliac disease is an important and readily treatable cause of malabsorption and nutritional deficiency.**
- **The prevalence of coeliac disease in Australia is not known but is almost certainly higher than previously suspected.**
- **Coeliac disease can commonly present without gastrointestinal symptoms.**
- **Coeliac disease should always be considered in patients with unexplained iron and/or folate deficiency.**
- **Antibody testing alone cannot substitute for histological diagnosis.**
- **Coeliac disease is treated by lifelong withdrawal of gluten-containing foods from the diet.**
- **There is no role for a trial of gluten-free diet without a preceeding biopsy.**





Figures 1a and b. Small bowel biopsy. a (left). normal histology. b (above). Coeliac disease. Note the characteristic 'flat' histological appearance of untreated coeliac disease.

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as steatorrhoea, weight loss, weakness and bruising – is now relatively uncommon. There has been a shift towards milder, more nonspecific symptoms, such as diarrhoea, flatulence, bloating or fatigue, which are often attributed to irritable bowel syndrome. There may be no gastrointestinal symptoms and the disease may present with otherwise unexplained iron and/or folate deficiency. Women may have a history of delayed menarche or recurrent miscarriages, and infertility may occur in either gender. Recurrent oral aphthous ulceration can also be a manifestation of coeliac disease, as can enamel defects of permanent teeth.

Many patients have reduced bone mineral density at the time of diagnosis. As a corollary of this, approximately 5% of patients who present with osteoporosis will have underlying coeliac disease as its cause.

Pathogenesis of coeliac disease

Coeliac disease is associated with HLA class II alleles DR3 and DQ2. Considerable advances have recently been made in the understanding of the way ingested gluten induces the disease – in particular, the discovery of tissue transglutaminase (tTG), which is a component of lamina propria reticulin and now recognised as the auto-antigen of coeliac disease. In susceptible individuals gluten forms complexes with tTG, thus making it antigenic. In the lamina propria, DR3 and DQ2 antigen-presenting cells deliver the antigenic tTG to the local T-cell population, thereby initiating a local immune response. Large quantities of tTG are found in monkey oesophagus endomysium and human umbilical cord, and monkey oesophagus endomysium forms the basis of the anti-endomysial antibody test.

A much larger number of individuals with the same HLA haplotype do not develop coeliac disease than do, suggesting that other factors are probably also involved in susceptibility to the condition.

Clinical features in childhood and adolescence

As in adults, the presentation of coeliac disease in children has changed over the last 20 years. The classic picture of an infant or young child with failure to thrive, abdominal distension, muscle wasting and diarrhoea is now less common than other presentations.

Coeliac disease may present in any age group, with any combination of loose stools, poor weight gain, vomiting, apparent food intolerances, other gastrointestinal symptoms, apparent recurrent giardiasis, growth or pubertal failure, iron and/or folate deficiency, signs of other specific nutritional deficiencies, mood disturbance, general malaise and suboptimal school performance. Constipation does not exclude coeliac disease. Some children or adolescents may be truly asymptomatic or their symptoms so subtle that coeliac disease might not be considered.

Table 1. Conditions that are associated with coeliac disease

Strongly associated conditions

Dermatitis herpetiformis
Type 1 diabetes

Other associated conditions

Autoimmune disorders – e.g. thyroid disease, IgA deficiency, pernicious anaemia
Down syndrome
Unexplained female infertility
Primary biliary cirrhosis
Hyposplenism
Osteoporosis
Alopecia
Epilepsy with cerebral calcifications
Unexplained ataxia
Other unexplained idiopathic neurological conditions

Associated disorders

An increasing number of non-gastrointestinal disorders are being associated with coeliac disease (Table 1). Dermatitis herpetiformis, an intensely itchy rash on the buttocks and extensor surfaces, is associated with villous atrophy in 75% of patients; dermatitis herpetiformis and coeliac disease share the HLA–DQ2 haplotype. Some autoimmune disorders that have the HLA–DR3 or HLA–DQ2 haplotype, such as type 1 diabetes, autoimmune thyroid disease, pernicious anaemia and IgA deficiency, have an increased incidence of coeliac disease. For example, about 5% of patients with type 1 diabetes also have coeliac disease.

There is also an association with Down syndrome, with villous atrophy found in up to 5% of patients. Alopecia is another unusual presentation. Primary biliary cirrhosis and hyposplenism have also been found to be associated with coeliac disease more frequently than expected.

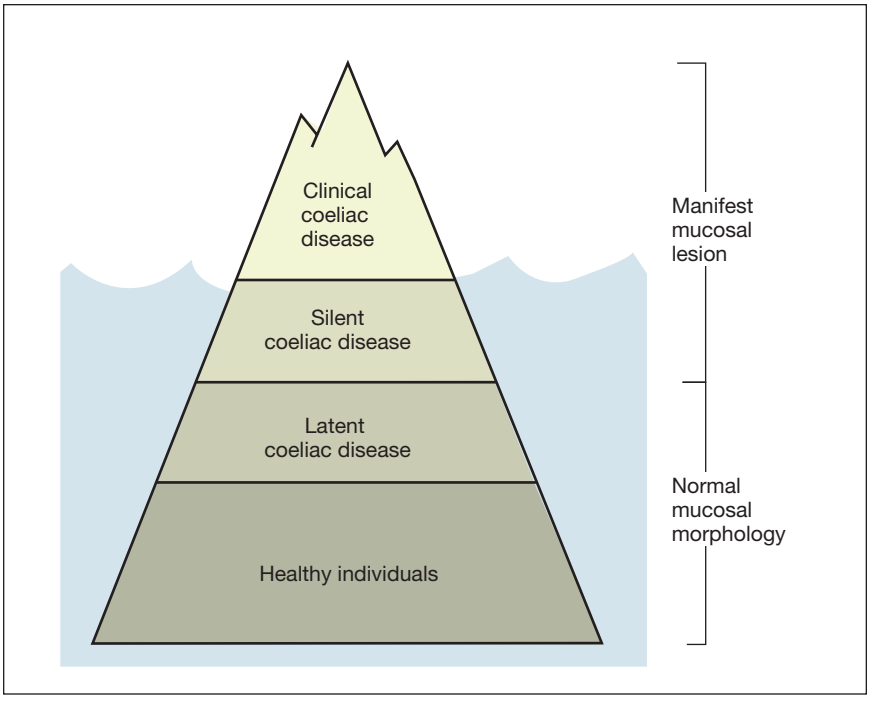

Figure 2. The coeliac disease iceberg for genetically susceptible patients. (Adapted from: Maki M, Collin P. Coeliac disease. *Lancet* 1997; 349: 1755-1759.)

A rare but interesting possible association with villous atrophy is that with cryptogenic neurological illnesses such as ataxia, peripheral neuropathy, myopathy and epilepsy with cerebral calcifications. The term 'gluten ataxia' is used to describe the association with cerebellar dysfunction.

Spectrum of coeliac disease

Not all patients with underlying villous atrophy will develop clinical manifestations, leading to the concept of 'silent' coeliac disease. This can be seen in high-risk groups such as some first-degree relatives of those with coeliac disease or some people with type 1 diabetes, when screening for coeliac disease shows villous atrophy but the patients have no symptoms. Some of these people may have unrecognised nutritional deficiencies or mild symptoms, but many are asymptomatic. The significance of these abnormalities is yet to be determined.

'Latent' coeliac disease is the term used when patients with or without symptoms have strongly positive antibodies for coeliac disease but essentially normal small bowel biopsy. Some, but not all, of these patients will eventually develop villous atrophy .

The concept of the coeliac disease 'iceberg' describes the spectrum of gluten sensitivity in people with genetic susceptibility to the disorder (Figure 2).

Diagnosis

The diagnosis of coeliac disease requires typical mucosal changes on duodenal biopsies, usually taken endoscopically. Multiple biopsies must be taken, as the changes may be variable. A biopsy should be performed whenever coeliac disease is suspected on the basis of clinical symptoms or blood tests, including serological tests. Serological tests alone are insufficient for the diagnosis. Differential diagnoses are listed in Table 2.

Serological tests available for coeliac disease screen for IgA and IgG antigliadin

antibodies, IgA antiendomysial and IgA tissue transglutaminase antibodies. Although the tests for the latter two antibodies have the greater specificity for coeliac disease, any of the IgA antibody tests may be falsely negative in up to 3 to 5% of coeliac patients, mainly in those with associated IgA deficiency. Currently recommended tests are total IgA level, IgA and IgG antigliadin antibodies and either IgA antiendomysial or tissue transglutaminase antibodies.

Bloating and diarrhoea due to fermentation of wheat starches may be experienced by noncoeliac patients and improve on a gluten-free diet, raising the clinical suspicion of coeliac disease. It is important that these patients are not started on a gluten-free or a wheat-free diet before the diagnosis of coeliac disease can be confirmed or excluded by biopsy. This is because a gluten-free diet in patients with coeliac disease is lifelong and once the small bowel mucosa has recovered, coeliac disease can only be diagnosed after gluten challenge. The same applies to patients with positive antibody tests.

Mixed results from the serological tests may make it unclear as to whether to proceed to small bowel biopsy. This should be assessed on an individual basis, taking into account clinical presentation, how strongly positive the screening tests were, and the presence or absence of nutrient deficiencies. Referral to a gastroenterologist for an opinion on whether to proceed to biopsy may be indicated.

The meaning of a negative small bowel biopsy in a patient with positive antibodies with or without symptoms of coeliac disease is unclear. Adequacy of gluten exposure prior to the biopsy needs to be checked, and if the patient was already on a gluten-free diet, a repeat biopsy following three months of adequate gluten intake may be considered. If gluten intake was adequate, such a finding may represent latent coeliac disease, the significance of which is uncertain. These patients should be followed up with repeat serology every one to two years, and re-biopsy considered.

Special considerations in children

The serological tests currently recommended for children are those mentioned above. However, there is a high incidence of transient IgA deficiency in children under 5 tears of age so tests relying on IgA antibody production may be unreliable in this age group.

As histological and serological changes may not occur until children have been on a gluten-containing diet for two years, negative investigations before that time do not exclude coeliac disease. Information about the duration and amount of gluten exposure should be sought. (Adequate gluten for a child would be provided by a typical unrestricted diet – for example, one containing a minimum of 30 g wheat-based cereal and two slices of wheat bread daily.) Some children may already have a low gluten intake because of self-selection or as part of a restricted diet.

While many children acquire a label of multiple food intolerance as a cause for their symptoms, children with genuine food intolerances may also develop coeliac disease. Additionally, some infants have transient wheat allergy, a quite separate condition that resolves. When in doubt, listen to the parents and screen and refer early, as unresolved perceived ill health can have negative consequences for both the child and the family.

The gluten-free diet

The treatment of coeliac disease is a lifelong, strict gluten-free diet, and usually no ongoing medications are required. Adherence to the diet is essential, even in the absence of symptoms. The diet prevents further damage to the intestinal villi, and allows the mucosa to return to normal so that nutrients can be properly absorbed. Once the diagnosis has been made, referral to a dietitian experienced in coeliac disease is important for nutritional education. The Dietitians Association of Australia and the State Coeliac Societies can provide details of experienced dietitians.

Prolamines that trigger coeliac disease are found in wheat, rye, triticale (a hybrid of wheat and rye), barley and possibly oats. The gluten-free diet involves more than just avoiding these grains themselves – gluten is present in small amounts in many ingredients, such as wheatstarch and malt, that are processed from these grains for use in manufactured foods. The current food standard of the Food Standards Australia New Zealand (FSANZ, formerly the Australia New Zealand Food Authority) does not allow a food product to be labelled as 'gluten-free' if it contains detectable gluten (the prescribed method for detecting gluten, an ELISA test, is sensitive to 0.003% gluten – i.e. 30 parts per million). Any food labelled 'gluten-free' is required by FSANZ to indicate on its nutrition information panel the result of the test for the presence of gluten.

The standard of treatment for coeliac disease advised by dietitians in Australia is a gluten-free diet devoid of detectable

Table 2. Major differential diagnoses of coeliac disease

In adults	In children
Irritable bowel syndrome	Toddler diarrhoea
Chronic giardiasis	Chronic giardiasis
Crohn's disease	Post-gastroenteritis disaccharidase deficiency
Bacterial overgrowth	Cystic fibrosis
Intestinal lymphoma	Milk protein intolerance

gluten, i.e. wheatstarch and malt cannot be included in gluten-free foods. This differs from the gluten-free food labelling standards in a number of other countries, including the United Kingdom, where wheatstarch and malt are permitted in the gluten-free foods sold there. There is now some published data showing that while a proportion of people with coeliac disease are symptomatic when eating wheatstarch and/or malt, a number are not. To date it is unclear if these ingredients have any significant effect of the small bowel mucosa.

The key elements in the education of a coeliac patient about the gluten-free diet are:

- understanding the reasons for following a gluten-free diet for life
- understanding where and why both large and trace amounts of gluten can be found in foods, including knowledge of food manufacturing and processing practices
- developing skills in reading and interpreting food labels.

Problems and challenges associated with the gluten-free diet are important to note, as quality of life may not improve markedly for all patients. These include:

- higher cost of some gluten-free foods
- limited availability of convenience foods that are gluten-free
- dining out with confidence and safety
- palatability of some gluten-free foods
- difficulties with adherence given peer group issues (particularly in adolescence)
- lack of motivation for adherence in asymptomatic patients
- issues such as weight gain in some patients
- constipation, because the diet can be low in fibre if not well-planned.

Although patients may find the diet overwhelming at first, with education, support and practical advice from dietitians, the Coeliac Society and medical practitioners, many of the issues can be overcome or managed satisfactorily. Sources of information are given in the box on page 39.

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Figure 3. Gluten-free foods that are readily available: (centre) rice noodles, corn spaghetti and corn and vegetable pasta, and (clockwise from upper left) rice cereal, soya bean flakes, millet seeds, brown rice flakes, buckwheat flakes, fruit and carob biscuits, plain biscuits, soya flour, potato flour and maize meal.

Availability of gluten-free foods

There are many gluten-free foods available, and many specialty gluten-free foods make a 'gluten-free' claim on the food label. Gluten-free breads are available in supermarkets or health foods stores, both ready-made and in bread mixes for home baking, and there is an increasing variety of gluten-free pastas, baking mixes, crispbreads, biscuits and snack foods (Figure 3).

All patients should be encouraged to contact their State Coeliac Society. These societies are valuable sources of support and information about new food product information, and membership includes a handbook on coeliac disease, an ingredient list booklet and a quarterly magazine. Some societies offer functions such as cooking demonstrations, children's camps, social evenings and dietitian-led group information sessions.

Oats

Recent studies in Europe have indicated that oats may be suitable for inclusion in the gluten-free diet. There is not, however, a supply of oats for consumption in Australia that is known to be free from wheat contamination. Therefore, until the studies are conclusive and a pure, uncontaminated source of oats is available, oats should continue to be omitted from the gluten-free diet.

Treatment issues in children and adolescents

Management of the gluten-free diet for coeliac disease in children may present additional challenges because of the psychological and educational implications. It is helpful to make sure the child's school and classmates are actively informed, and that the family is involved with the Coeliac Society. Educational and management issues to be addressed include:

- ongoing education of the child and parents about coeliac disease and the diet
- adherence issues such as school

lunch-swapping, parties, school camps and increasing independence throughout adolescence
- the nutritional adequacy of the diet for the requirements of growth and development, including catch-up growth if applicable.

Psychological adjustment and coping with the gluten-free diet

The reactions of patients and their families to the diagnosis of coeliac disease can vary widely – from relief at being diagnosed with a treatable condition that requires no long-term medication, to disbelief, anger or denial, which may be experienced by patients with mild or no symptoms at diagnosis.

Reassurance of an expected improvement in health is important, as is encouragement to accept the diagnosis and explanation of the rationale for following a strict, lifelong diet. It is also helpful to acknowledge that the gluten-free diet can be challenging and difficult, especially for the first few months after diagnosis, but that it progressively becomes easier as familiarity with the diet and available foods increases and health improves.

Dietitians and the coeliac societies provide valuable support. Occasionally, counselling may be required.

Additional investigations and therapy

Once the diagnosis of coeliac disease has been made, the following tests are recommended if not previously undertaken:
- full blood examination
- iron studies
- folate and vitamin B_{12} studies
- calcium and vitamin D levels
- albumin
- bone mineral density (in selected cases).

Any nutritional deficiencies should be corrected with oral supplementation, or parenterally if they are severe. Long term supplementation is not usually required if the diet is adequate and mucosal healing has taken place.

If osteopenia is present and is associated with calcium and/or vitamin D deficiency, the deficiency should be corrected. Bone mineral density will improve on the gluten-free diet in most patients. Medication aimed at improving bone mineral density and a referral to an endocrinologist may be required.

Diarrhoea may initially continue despite gluten withdrawal. This may be due to secondary lactase deficiency, which will require a lactose-free diet until there is substantial histological improvement. Lactose can usually be re-introduced later into the diet

Follow up

A clinical response to the gluten-free diet may be seen within several weeks.

However, histological improvement and resolution takes longer, with the most proximal small intestine being the last to recover.

Follow up should target each patient's specific symptoms and deficiencies found on presentation, as well the development of possible complications.

Repeating the duodenal biopsy after six to 12 months on the diet provides objective evidence of recovery and confirms the diagnosis, thereby ruling out other conditions that can mimic coeliac disease on initial biopsy. It also encourages patient adherence to the diet.

Vitamin and nutritional supplements that may have been required initially are generally not necessary in the long term. Iron and vitamin B_{12} supplementation may, however, be needed indefinitely, despite strict adherence to the diet and histological improvement.

Failure to respond to the diet or a recurrence of problems is more likely to be due to inadvertent gluten ingestion than a complication of coeliac disease. Although some patients in apparent remission can tolerate dietary gluten without symptoms, particularly those with few complaints before diagnosis, gluten should be avoided because of the risks of malignancy (see the section on 'Complications'), subclinical bone disease such as osteopenia, and occult malabsorption. Gradual dietary nonadherence is common, with some patients slipping into unrecognised ill health. It is suggested that all patients be reviewed annually (full blood examination, red cell and serum folate, iron studies and albumin estimations, and an assessment of weight and growth velocity in children).

Dietary review with a dietitian should emphasise adequacy of nutrient intake, as well as avoidance of gluten ingestion. A bone mineral density scan should be repeated every three to four years if the initial assessment was abnormal, particularly in postmenopausal women. Bone mineral density measurement should also be considered in the early adolescence age group, as this is the most important period for bone mineral acquisition.

There are no satisfactory serological tests to monitor progress on the gluten-free diet. Antiendomysial antibody levels return to normal in most patients on a gluten-free diet and may be an indicator of long term adherence to the diet, but not of transient exposure to gluten.

Complications

The vast majority of patients with coeliac disease have an excellent prognosis if they adhere to the gluten-free diet. Treated patients have a normal life expectancy. Patients whose coeliac disease is untreated or suboptimally treated have an increased risk of oropharyngeal, oesophageal and

intestinal cancers as well as extra-intestinal lymphomas and possibly breast cancer. However, with continuous adherence to a gluten-free diet for five years or longer, this risk becomes no different from the general population.

The form of lymphoma seen in coeliac disease is the rare enteropathy-associated T-cell lymphoma. It is most common between the ages of 40 and 60 years and mostly presents with pain, refractory malabsorption (despite adherence to a gluten-free diet) and small bowel obstruction or perforation.

Other rarer complications include collagenous sprue, ulcerative jejunoileitis and refractory sprue, all of which present with severe malabsorption. These conditions respond poorly to a strict gluten-free diet, and corticosteroids or other immunosuppressants are often used, although with limited success.

Screening

Adult or child first-degree relatives (over the age of 2 years) of patients diagnosed with coeliac disease and those with associated conditions are at higher risk of coeliac disease than the general population, and should be considered for serological screening (see Table 1). Anyone in whom all the screening tests are positive should undergo a duodenal biopsy to confirm the diagnosis of coeliac disease. Patients with suspicious symptoms who have negative serological testing should also undergo duodenal biopsy because the tests can have false negative results.

Conclusion

Coeliac disease is probably more common in Australia than has been previously thought, and it is now recognised that the spectrum of its presentation is changing. Increased awareness of this can lead to earlier diagnosis, resulting in improved health and quality of life for many coeliac patients. The condition is readily treatable with a gluten-free diet and regular monitoring of health and nutritional status. Only those with biopsy-proven coeliac disease should be placed on a gluten-free diet. MT

Coeliac disease information sources

Leaflets for patients

Patient information leaflets on coeliac disease are available from the Digestive Health Foundation, 145 Macquarie Street, Sydney, NSW, 2000.
Telephone (02) 9256 5455; facsimile (02) 9241 4586.
Website www.gesa.org.au

State coeliac societies

NSW/ACT
First Floor, 306 Victoria Avenue,
Chatswood, NSW 2057.
Telephone (02) 9411 4100;
facsimile (02) 9413 1296.

QLD
PO Box 2110,
Fortitude Valley ,Qld 4006.
Level 1, 25 Evelyn Street,
Newstead, Qld 4006.
Telephone (07) 3854 0123;
facsimile (07) 3854 0121.

SA/NT
Unit 5, 88 Glynburn Road,
Hectorville,SA 5073.
Telephone (08) 8365 1488;
facsimile (08) 8365 1265.

TAS
PO Box 159, Launceston, Tas 7250.
Telephone (03) 6427 2844;
facsimile (03) 6344 4284.

VIC
11 Barlyn Road,
Mount Waverley, Vic 3149.
PO Box 89, Holmesglen, Vic 3148.
Telephone (03) 9808 5566;
facsimile (03) 9808 9922.

WA
38 Kalgoorlie Street,
Mount Hawthorn, WA 6915.
PO Box 245,
Mount Hawthorn, WA 6915.
Telephone (08) 9444 9200;
facsimile (08) 9444 9255.

Internet resources

Many internet sites include information relating to the scientific, medical, food science, food product and nutritional aspects of coeliac disease. It is important to be aware that overseas websites may include information relating to gluten-free food standards or food processing and manufacturing procedures that are different from those in Australia.
Recommended sites are:

Gastroenterological Society of Australia	www.gesa.org.au
Coeliac Society of Australia	www.coeliac.org.au
Gastronet (an Australian gastroenterology site)	www.gastro.net.au
UK Coeliac Society	www.coeliac.co.uk
Celiac.com (an American coeliac disease site)	www.celiac.com

Reference

1. McMillan SA, Watson RP, McCrum EE, Evans AE. Factors associated with serum antibodies to reticulin, endomysium, and gliadin in an adult population. Gut 1996; 39: 43-47.