

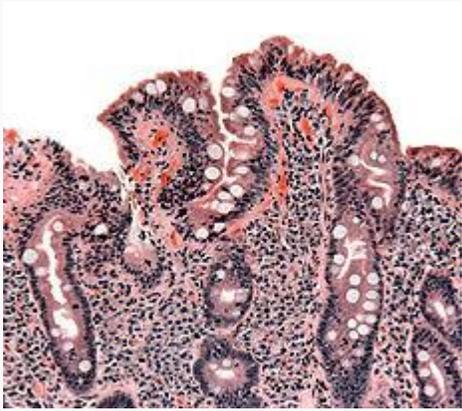
Coeliac disease

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Jump to: [navigation](#), [search](#)

Coeliac disease

Classification and external resources



Biopsy of [small bowel](#) showing coeliac disease manifested by blunting of [villi](#), crypt hyperplasia, and [lymphocyte](#) infiltration of crypts

[ICD-10](#)

[K90.0](#)

[ICD-9](#)

[579.0](#)

[OMIM](#)

[212750](#)

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[2922](#)

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[MeSH](#)

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[Celiac Disease](#)

Coeliac disease (ⓘ[ⓘ] /ˈsiːliːæk/; spelled **celiac disease** in North America^[1] and often **celiac sprue**) is an [autoimmune](#) disorder of the [small intestine](#) that occurs in [genetically predisposed](#) people of all ages from middle infancy onward. Symptoms include chronic [diarrhoea](#), [failure to thrive](#) (in children), and [fatigue](#), but these may be absent, and symptoms in other [organ systems](#) have been described.

Increasingly, diagnoses are being made in [asymptomatic](#) persons as a result of increased [screening](#),^[2] the condition is thought to affect between 1 in 1,750 and 1 in 105 people in the United States.^[3] Coeliac disease is caused by a reaction to [gliadin](#), a [prolamin](#) ([gluten](#) protein) found in wheat, and similar proteins found in the crops of the [tribe Triticeae](#) (which includes other common grains such as [barley](#) and rye).^[4]

Upon exposure to gliadin, and specifically to three peptides found in prolamins, the enzyme [tissue transglutaminase](#) modifies the protein, and the [immune system](#) cross-reacts with the small-bowel tissue, causing an [inflammatory reaction](#). That leads to a truncating of the villi lining the small intestine (called villous atrophy). This [interferes with the absorption](#) of nutrients, because the [intestinal villi](#) are responsible for absorption. The only known effective treatment is a lifelong [gluten-free diet](#).^[4] While the disease is caused by a reaction to wheat proteins, it is not the same as [wheat allergy](#).

- This condition has several other names, including: *cœliac disease* (with [œ ligature](#)), c(o)eliac sprue, non-tropical sprue, endemic sprue, gluten enteropathy or gluten-sensitive enteropathy, and gluten intolerance. The term *coeliac* derived from the Greek *κοιλιακός* (*koiliakós*, "abdominal"), and was introduced in the 19th century in a translation of what is generally regarded as an ancient Greek description of the disease by [Aretaeus of Cappadocia](#).^{[5][6]}

[edit] Signs and symptoms

Severe coeliac disease leads to the characteristic symptoms of pale, loose and greasy stool ([steatorrhoea](#)), and weight loss or failure to gain weight (in young children). People with milder coeliac disease may have symptoms that are much more subtle and occur in other organs rather than the bowel itself. It is also possible to have coeliac disease without any symptoms whatsoever.^[4] Many adults with subtle disease only have fatigue or [anaemia](#).^[2]

[edit] Gastrointestinal

The diarrhoea that is characteristic of coeliac disease is (chronic) [pale](#), voluminous and malodorous. [Abdominal pain](#) and cramping, bloatedness with [abdominal distension](#) (thought to be due to fermentative production of bowel gas) and [mouth ulcers](#)^[7] may be present. As the bowel becomes more damaged, a degree of [lactose intolerance](#) may develop.^[4] Frequently, the symptoms are ascribed to [irritable bowel syndrome](#) (IBS), only later to be recognised as coeliac disease; a small proportion of patients with symptoms of IBS have underlying coeliac disease, and screening for coeliac disease is recommended for those with IBS symptoms.^[8]

Coeliac disease leads to an increased risk of both [adenocarcinoma](#) ([small intestine cancer](#)) and [lymphoma](#) of the small bowel ([enteropathy-associated T-cell lymphoma](#) or EATL). This risk returns to baseline with diet. Longstanding and untreated disease may lead to other complications, such as ulcerative jejunitis (ulcer formation of the small bowel) and stricturing (narrowing as a result of scarring with obstruction of the bowel).^[9]

[edit] Malabsorption-related

The changes in the bowel make it less able to absorb nutrients, minerals and the [fat-soluble](#) vitamins A, D, E, and K.^{[4][10]}

- The inability to absorb carbohydrates and fats may cause [weight loss](#) (or [failure to thrive](#)/stunted growth in children) and [fatigue](#) or lack of energy.

- [Anaemia](#) may develop in several ways: iron malabsorption may cause [iron deficiency anaemia](#), and [folic acid](#) and [vitamin B₁₂](#) malabsorption may give rise to [megaloblastic anaemia](#).
- [Calcium](#) and [vitamin D](#) malabsorption (and compensatory secondary [hyperparathyroidism](#)) may cause [osteopenia](#) (decreased mineral content of the bone) or [osteoporosis](#) (bone weakening and risk of fragility fractures).
- A small proportion have abnormal [coagulation](#) due to [vitamin K deficiency](#) and are slightly at risk for abnormal bleeding.
- Coeliac disease is also associated with [bacterial overgrowth](#) of the [small intestine](#), which can worsen malabsorption or cause malabsorption despite adherence to treatment.^[11]

[\[edit\]](#) Miscellaneous

Coeliac disease has been linked with a number of conditions. In many cases, it is unclear whether the gluten-induced bowel disease is a causative factor or whether these conditions share a common predisposition.

- [IgA deficiency](#) is present in 2.3% of patients with coeliac disease, and in turn, this condition features a tenfold increased risk of coeliac disease. Other features of this condition are an increased risk of infections and [autoimmune disease](#).^[12]
- [Dermatitis herpetiformis](#); this itchy cutaneous condition has been linked to a transglutaminase enzyme in the skin, features small-bowel changes identical to those in coeliac disease, and may respond to gluten withdrawal even if there are no gastrointestinal symptoms.^{[13][14]}
- [Growth failure](#) and/or [pubertal delay](#) in later childhood can occur even without obvious bowel symptoms or severe [malnutrition](#). Evaluation of growth failure often includes coeliac screening.^[4]
- [Recurrent miscarriage](#) and [unexplained infertility](#).^[4]
- [Hyposplenism](#) (a small and underactive [spleen](#));^[15] this occurs in about a third of cases and may predispose to infection given the role of the spleen in protecting against bacteria.^[4]
- Abnormal [liver function tests](#) (randomly detected on blood tests).^[4]

Coeliac disease is associated with a number of other medical conditions, many of which are [autoimmune disorders](#): [diabetes mellitus type 1](#), [autoimmune thyroiditis](#),^[16] [primary biliary cirrhosis](#), and [microscopic colitis](#).^[17]

A more controversial area is a group of diseases in which anti-gliadin antibodies (an older and non-specific test for coeliac disease) are sometimes detected, but no small bowel disease can be demonstrated. Sometimes, these conditions improve by removing gluten from the diet. This includes [cerebellar ataxia](#), [peripheral neuropathy](#), [schizophrenia](#) and [autism](#).^[18]

[\[edit\]](#) Other grains

Wheat subspecies (such as [spelt](#), [semolina](#) and [durum](#)) and related species such as [barley](#), [rye](#), [triticale](#) and [Kamut](#) also induce symptoms of coeliac disease.^[19] A small minority of coeliac patients also react to [oats](#).^[4] It is most probable that oats produce symptoms due to cross contamination with other grains in the fields or in the distribution channels. Generally, oats are therefore not recommended. However, many companies assure the 'purity' of oats, and are therefore still able to be consumed through these sources.^[19]

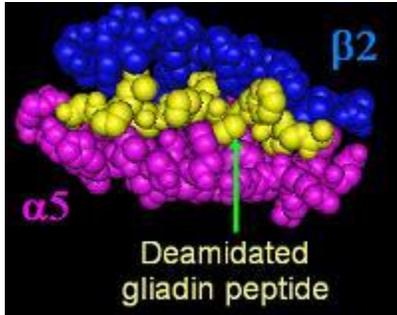
Other cereals such as maize (corn), [millet](#), [sorghum](#), [teff](#), rice, and [wild rice](#) are safe for patients to consume, as well as non cereals such as [amaranth](#), [quinoa](#) or [buckwheat](#).^{[19][20]} Non-cereal carbohydrate-rich foods such as potatoes and bananas do not contain gluten and do not trigger symptoms.^[19]

[\[edit\]](#) Pathophysiology

Coeliac disease appears to be polyfactorial, both in that more than one genetic factor can cause the disease and that more than one factor is necessary for the disease to manifest in a patient.

Almost all people with coeliac disease have either the variant [HLA-DQ2 allele](#) or (less commonly) the [HLA-DQ8 allele](#).^[21] However, about 20–30% of people without coeliac disease have also inherited either of these alleles.^[21] This suggests additional factors are needed for coeliac disease to develop – that is, the predisposing HLA risk allele is necessary but not sufficient to develop coeliac disease. Furthermore, around 5% of those people who do develop coeliac disease do not have typical HLA-DQ2 or HLA-DQ8 alleles (see below).^[21]

[\[edit\]](#) Genetics



🔍 DQ α^5 - β^2 -binding cleft with a deamidated gliadin peptide (yellow), modified from [PDB 1S9V](#)^[22]

The vast majority of coeliac patients have one of two types of the [HLA-DQ](#) protein.^[21] HLA-DQ is part of the [MHC class II antigen-presenting receptor](#) (also called the [human leukocyte antigen](#)) system and distinguishes cells between self and non-self for the purposes of the [immune system](#). The two subunits of the HLA-DQ protein are encoded by the HLA-DQA1 and HLA-DQB1 genes, located on the short arm of the [sixth chromosome](#).

There are seven [HLA-DQ](#) variants (DQ2 and DQ4–DQ9). Over 95% of coeliac patients have the isoform of DQ2 or DQ8, which is inherited in families. The reason these genes produce an increase in risk of coeliac disease is that the receptors formed by these genes bind to [gliadin](#) peptides more tightly than other forms of the antigen-presenting receptor. Therefore, these forms of the receptor are more likely to activate [T lymphocytes](#) and initiate the autoimmune process.^[21]

Most coeliac patients bear a two-gene HLA-DQ2 [haplotype](#) referred to as [DQ2.5 haplotype](#). This haplotype is composed of two adjacent gene [alleles](#), DQA1*0501 and [DQB1*0201](#), which encode the two subunits, DQ α^5 and DQ β^2 . In most individuals, this DQ2.5 isoform is encoded by one of two [chromosomes 6](#) inherited from parents (DQ2.5cis). Most coeliacs inherit only one copy of this DQ2.5 haplotype, while some inherit it from *both* parents; the latter are especially at risk for coeliac disease, as well as being more susceptible to severe complications.^[23]

Some individuals inherit DQ2.5 from one parent and an additional portion of the haplotype (either DQB1*02 or DQA1*05) from the other parent, increasing risk. Less commonly, some individuals inherit the DQA1*05 allele from one parent and the DQB1*02 from the other parent (DQ2.5trans), called a trans-haplotype association, and these individuals are at similar risk for coeliac disease as those with a single DQ2.5-bearing chromosome 6, but in this instance, disease tends not to be familial. Among the 6% of European coeliacs that do not have DQ2.5 (cis or trans) or DQ8 (encoded by the [haplotype](#) DQA1*03:DQB1*0302), 4% have the [DQ2.2](#) isoform, and the remaining 2% lack DQ2 or DQ8.^[24]

The frequency of these genes varies geographically. DQ2.5 has high frequency in peoples of North and Western Europe ([Basque Country](#) and Ireland^[25] with highest frequencies) and portions of Africa and is associated with disease in India,^[26] but is not found along portions of the West Pacific rim. DQ8 has a wider global distribution than DQ2.5, and is particularly common in South and Central America; up to 90% of individuals in certain Amerindian populations carry DQ8 and thus may display the coeliac [phenotype](#).^[27]

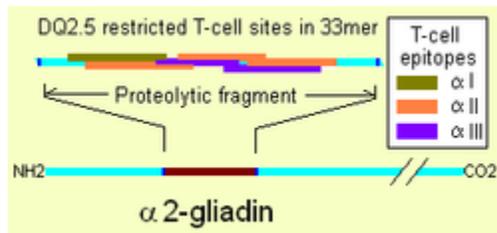
Other genetic factors have been repeatedly reported in CD, however, involvement in disease has variable geographic recognition. Only the HLA-DQ loci show a consistent involvement over the global population.^[28] Many of the loci

detected have been found in association with other autoimmune diseases. One locus, the [LPP](#) or lipoma-preferred partner gene is involved in the adhesion of extracellular matrix to the cell surface and a minor variant ([SNP](#) = rs1464510) increases the risk of disease by approximately 30%. This gene strongly associates with coeliac disease ($p < 10^{-39}$) in samples taken from a broad area of Europe and the US. ^[28]

The prevalence of CD genotypes in the modern population is not completely understood. Given the characteristics of the disease and its apparent strong heritability, it would normally be expected that the genotypes would undergo negative selection and to be absent in societies where agriculture has been practised the longest (compare with a similar condition, [Lactose intolerance](#), which has been negatively selected so strongly that its prevalence went from ~100% in ancestral populations to less than 5% in some European countries.) This expectation was first proposed by Simoons (1981). ^[29] By now, however, it is apparent that is not the case; on the contrary, there is evidence of *positive* selection in CD genotypes. It is suspected that some of them may have been beneficial by providing protection against bacterial infections. ^{[30][31]}

[\[edit\]](#) Prolamins

The majority of the proteins in food responsible for the immune reaction in coeliac disease are the [prolamins](#). These are storage proteins rich in [proline](#) (*prol-*) and [glutamine](#) (*-amin*) that dissolve in alcohols and are resistant to [proteases](#) and [peptidases](#) of the gut. ^{[2][32]} Prolamins are found in cereal grains with different grains having different but related prolamins: wheat ([gliadin](#)), [barley](#) ([hordein](#)), rye ([secalin](#)), [corn](#) ([zein](#)) and as a minor protein, [avenin](#) in oats. One region of [α-gliadin](#) stimulates membrane cells, [enterocytes](#), of the intestine to allow larger molecules around the sealant between cells. Disruption of [tight junctions](#) allow peptides larger than three [amino acids](#) to enter circulation. ^[33]

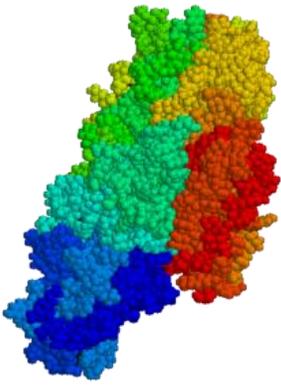


^[34] Illustration of deamidated α-2 gliadin's 33mer, amino acids 56–88, showing the overlapping of three varieties of T-cell epitope ^[34]

Membrane leaking permits peptides of gliadin that stimulate two levels of immune response, the innate response and the adaptive (T-helper cell mediated) response. One protease-resistant peptide from α-gliadin contains a region that stimulates lymphocytes and results in the release of [interleukin-15](#). This [innate response to gliadin](#) results in immune-system signalling that attracts inflammatory cells and increases the release of inflammatory chemicals. ^[2] The strongest and most common adaptive response to gliadin is directed toward an [α2-gliadin fragment](#) of 33 amino acids in length. ^[2]

The response to the 33mer occurs in most coeliacs who have a [DQ2 isoform](#). This peptide, when altered by intestinal transglutaminase, has a high density of overlapping T-cell epitopes. This increases the likelihood that the DQ2 isoform will bind and stay bound to peptide when recognised by T-cells. ^[34] Gliadin in wheat is the best-understood member of this family, but other prolamins exist, and [hordein](#) (from barley) and [secalin](#) (from rye) may contribute to coeliac disease. ^{[2][35]} However, not all prolamins will cause this immune reaction, and there is [ongoing controversy](#) on the ability of [avenin](#) (the prolamins found in oats) to induce this response in coeliac disease.

[\[edit\]](#) Tissue transglutaminase



[Tissue transglutaminase](#), drawn from [PDB 1FAU](#)

[Anti-transglutaminase antibodies](#) to the enzyme [tissue transglutaminase](#) (tTG) are found in an overwhelming majority of cases.^[36] Tissue transglutaminase modifies gluten [peptides](#) into a form that may stimulate the immune system more effectively.^[2] These peptides are modified by tTG in two ways, deamidation or transamidation.^[37]

Deamidation is the reaction by which a glutamate residue is formed by cleavage of the epsilon-amino group of a glutamine side chain. Transamidation, which occurs three times more often than deamidation, is the cross-linking of a glutamine residue from the gliadin peptide to a lysine residue of tTg in a reaction which is catalysed by the transglutaminase. Crosslinking may occur either within or outside the active site of the enzyme. The latter case yields a permanently, covalently linked complex between the gliadin and the tTg.^[38] This results in the formation of new epitopes which are believed to trigger the primary immune response by which the autoantibodies against tTg develop.^{[39][40][41]}

Stored biopsies from suspected coeliac patients have revealed that [autoantibody](#) deposits in the [subclinical](#) coeliacs are detected prior to clinical disease. These deposits are also found in patients who present with other autoimmune diseases, anaemia or malabsorption phenomena at a much-increased rate over the normal population.^[42] Endomysial components of antibodies (EMA) to tTG are believed to be directed toward cell-surface transglutaminase, and these antibodies are still used in confirming a coeliac disease diagnosis. However, a 2006 study showed that EMA-negative coeliac patients tend to be older males with more severe abdominal symptoms and a lower frequency of "atypical" symptoms including autoimmune disease.^[43] In this study, the anti-tTG antibody deposits did not correlate with the severity of villous destruction. These findings, coupled with recent work showing that gliadin has an innate response component,^[44] suggests that gliadin may be more responsible for the primary manifestations of coeliac disease, whereas tTG is a bigger factor in secondary effects such as allergic responses and secondary autoimmune diseases. In a large percentage of coeliac patients, the anti-tTG antibodies also recognise a [rotavirus](#) protein called VP7. These antibodies stimulate [monocyte](#) proliferation, and rotavirus infection might explain some early steps in the cascade of [immune cell](#) proliferation.^[45]

Indeed, earlier studies of rotavirus damage in the gut showed this causes a villous atrophy.^[46] This suggests that viral proteins may take part in the initial flattening and stimulate self-crossreactive anti-VP7 production. Antibodies to VP7 may also slow healing until the gliadin-mediated tTG presentation provides a second source of crossreactive antibodies.

[edit] Villous atrophy and malabsorption

The inflammatory process, mediated by [T cells](#), leads to disruption of the structure and function of the small bowel's mucosal lining and causes [malabsorption](#) as it impairs the body's ability to absorb [nutrients](#), minerals and fat-soluble [vitamins](#) A, D, E and K from food. [Lactose intolerance](#) may be present due to the decreased bowel surface and reduced production of [lactase](#) but typically resolves once the condition is treated.

Alternative causes of this tissue damage have been proposed and involve release of [interleukin 15](#) and activation of the innate immune system by a shorter gluten peptide (p31–43/49). This would trigger killing of [enterocytes](#) by

lymphocytes in the [epithelium](#).^[2] The villous atrophy seen on biopsy may also be due to unrelated causes, such as [tropical sprue](#), [giardiasis](#) and [radiation enteritis](#). While positive serology and typical biopsy are highly suggestive of coeliac disease, lack of response to diet may require these alternative diagnoses to be considered.^[9]

[\[edit\]](#) Risk modifiers

There are various theories as to what determines whether a genetically susceptible individual will go on to develop coeliac disease. Major theories include infection by [rotavirus](#)^[47] or human intestinal [adenovirus](#).^[48] Some research has suggested that smoking is protective against adult-onset coeliac disease.^[49]

A 2005 prospective and [observational study](#) found that timing of the exposure to gluten in childhood was an important risk modifier. People exposed to wheat, barley, or rye before the [gut barrier](#) has fully developed (within the first three months after birth) had five times the risk of developing coeliac disease relative to those exposed at four to six months after birth. Those exposed even later than six months after birth were found to have only a slightly increased risk relative to those exposed at four to six months after birth.^[50]

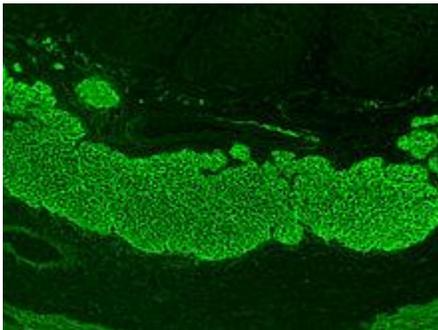
A study conducted in 2006 showed that early introduction of grains was protective against grain allergies; however, this study explicitly excluded any participants found to have coeliac disease and therefore offers no help in this regard.^[51] Breastfeeding may also reduce risk. A [meta-analysis](#) indicates that prolonging [breastfeeding](#) until the introduction of gluten-containing grains into the diet was associated with a 52% reduced risk of developing coeliac disease in infancy; whether this persists into adulthood is not clear.^[52]

[\[edit\]](#) Diagnosis

There are several tests that can be used to assist in [diagnosis](#). The level of [symptoms](#) may determine the order of the tests, but *all* tests lose their usefulness if the patient is already taking a [gluten-free diet](#). [Intestinal](#) damage begins to heal within weeks of gluten being removed from the diet, and [antibody](#) levels decline over months. For those who have already started on a gluten-free diet, it may be necessary to perform a re-challenge with some gluten-containing food in one meal a day over 2–6 weeks before repeating the investigations.^[17]

Combining findings into a prediction rule to guide use of [endoscopic](#) biopsy reported a [sensitivity](#) of 100% (it would identify all the cases) in a population of subjects with a high index of suspicion for coeliac disease, with a concomitant [specificity](#) of 61% (a [false positive](#) rate of 39%). The prediction rule recommends that patients with high-risk symptoms *or* positive serology should undergo endoscopic biopsy of the second part of the duodenum. The study defined high-risk symptoms as [weight loss](#), [anaemia](#) ([haemoglobin](#) less than 120 g/l in females or less than 130 g/l in males), or diarrhoea (more than three loose stools per day).^[53]

[\[edit\]](#) Blood tests



[Immunofluorescence](#) staining pattern of endomysial antibodies on a monkey oesophagus tissue sample.

[Serological](#) blood tests are the first-line investigation required to make a diagnosis of coeliac disease. IgA antiendomysial antibodies can detect coeliac disease with a [sensitivity](#) and [specificity](#) of 90% and 99% according to a [systematic review](#). The systematic review estimates that the prevalence of coeliac disease in primary care patients with gastrointestinal symptoms to be about 3%.^[54] [Serology](#) for [anti-tTG antibodies](#) was initially reported to have a high [sensitivity](#) (99%) and [specificity](#) (>90%) for identifying coeliac disease; however, the systematic review found the two tests were similar.^[54] Modern anti-tTG assays rely on a human [recombinant protein](#) as an [antigen](#).^[55] tTG testing should be done first as it is an easier test to perform. An equivocal result on tTG testing should be followed by antibodies to endomysium.^[17]

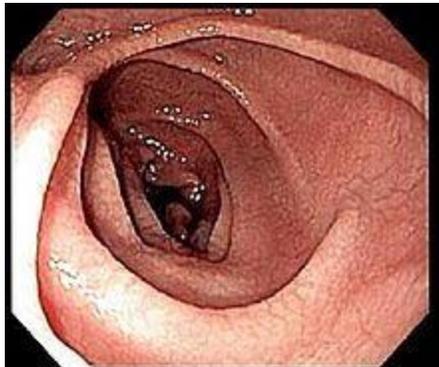
Because of the major implications of a diagnosis of coeliac disease, professional guidelines recommend that a positive [blood test](#) is still followed by an [endoscopy/gastroscopy](#) and [biopsy](#). A negative serology test may still be followed by a recommendation for endoscopy and [duodenal](#) biopsy if clinical suspicion remains high due to the 1 in 100 "[false-negative](#)" result. As such, tissue biopsy is still considered the [gold standard](#) in the diagnosis of coeliac disease.^{[9][17][56]}

Historically three other antibodies were measured: anti-[reticulin](#) (ARA), anti-[gliadin](#) (AGA) and anti-[endomysium](#) (EMA) antibodies. Serology may be unreliable in young children, with anti-[gliadin](#) performing somewhat better than other tests in children under five.^[57] Serology tests are based on [indirect immunofluorescence](#) (reticulin, gliadin and endomysium) or [ELISA](#) (gliadin or tissue [transglutaminase](#), tTG).^[58]

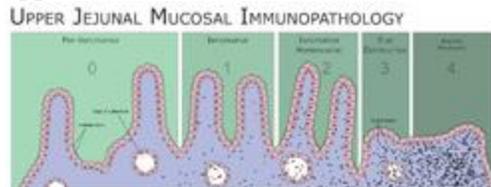
Guidelines recommend that a total serum IgA level is checked in parallel, as coeliac patients with IgA deficiency may be unable to produce the antibodies on which these tests depend ("[false negative](#)"). In those patients, IgG antibodies against transglutaminase (IgG-tTG) may be diagnostic.^{[17][59]}

Antibody testing and [HLA](#) testing have similar accuracies.^[21] However, widespread use of HLA typing to rule out coeliac disease is not currently recommended.^[17]

[\[edit\]](#) Endoscopy



[Endoscopic](#) still of [duodenum](#) of patient with coeliac disease showing scalloping of folds and "cracked-mud" appearance to mucosa



Schematic of the Marsh classification of upper [jejunal](#) pathology in coeliac disease.

An [upper endoscopy](#) with [biopsy](#) of the [duodenum](#) (beyond the [duodenal bulb](#)) or [jejunum](#) is performed. It is important for the physician to obtain multiple samples (four to eight) from the duodenum. Not all areas may be equally affected; if biopsies are taken from healthy bowel tissue, the result would be a false negative.^[9]

Blood HLA tests for coeliac disease^[21]

Test	sensitivity	specificity
HLA-DQ2	94%	73%
HLA-DQ8	12%	81%

Most patients with coeliac disease have a [small bowel](#) that appears normal on endoscopy; however, five concurrent endoscopic findings have been associated with a high specificity for coeliac disease: scalloping of the small bowel folds (*pictured*), paucity in the folds, a [mosaic](#) pattern to the [mucosa](#) (described as a "cracked-mud" appearance), prominence of the [submucosa blood vessels](#), and a nodular pattern to the mucosa.^[60]

Until the 1970s, biopsies were obtained using metal capsules attached to a suction device. The capsule was swallowed and allowed to pass into the small intestine. After [x-ray](#) verification of its position, suction was applied to collect part of the intestinal wall inside the capsule. Often-utilised capsule systems were the [Watson capsule](#) and the [Crosby-Kugler capsule](#). This method has now been largely replaced by [fibre-optic](#) endoscopy, which carries a higher sensitivity and a lower frequency of errors.^[61]

[\[edit\]](#) Pathology

The classic pathology changes of coeliac disease in the small bowel are categorised by the "Marsh classification":^[62]

- Marsh stage 0: normal mucosa
- Marsh stage 1: increased number of intra-epithelial [lymphocytes](#), usually exceeding 20 per 100 [enterocytes](#)
- Marsh stage 2: proliferation of the [crypts of Lieberkuhn](#)
- Marsh stage 3: partial or complete [villous atrophy](#)
- Marsh stage 4: [hypoplasia](#) of the [small bowel](#) architecture

Marsh's classification, introduced in 1992, was subsequently modified in 1999 to six stages, where the previous stage 3 was split in three substages.^[63] Further studies demonstrated that this system was not always reliable and that the changes observed in coeliac disease could be described in one of three stages—A, B1 and B2—with A representing lymphocytic infiltration with normal villous appearance and B1 and B2 describing partial and complete villous atrophy.^{[4][64]}

The changes classically improve or reverse after [gluten](#) is removed from the diet. However, most guidelines do not recommend a repeat biopsy unless there is no improvement in the symptoms on diet.^{[9][56]} In some cases, a deliberate gluten challenge, followed by biopsy, may be conducted to confirm or refute the diagnosis. A normal biopsy and normal serology after challenge indicates the diagnosis may have been incorrect.^[9]

[\[edit\]](#) Other diagnostic tests

At the time of diagnosis, further investigations may be performed to identify complications, such as [iron deficiency](#) (by [full blood count](#) and iron studies), [folic acid](#) and [vitamin B₁₂](#) deficiency and [hypocalcaemia](#) (low calcium levels, often due to decreased [vitamin D](#) levels). [Thyroid function tests](#) may be requested during blood tests to identify [hypothyroidism](#), which is more common in people with coeliac disease.^[10]

[Osteopenia](#) and [osteoporosis](#), mildly and severely reduced bone mineral density, are often present in people with coeliac disease, and investigations to measure bone density may be performed at diagnosis, such as [dual energy X-ray absorptiometry](#) (DXA) scanning, to identify risk of fracture and need for bone protection medication.^{[9][10]}

[\[edit\]](#) Screening

Due to its high sensitivity, [serology](#) has been proposed as a [screening](#) measure, because the presence of antibodies would detect previously undiagnosed cases of coeliac disease and prevent its complications in those patients.^[9] There is significant debate as to the benefits of screening. Some studies suggest that early detection would decrease the risk of osteoporosis and anaemia. In contrast, a [cohort study](#) in [Cambridge](#) suggested that people with undetected coeliac disease had a beneficial risk profile for [cardiovascular disease](#) (less [overweight](#), lower [cholesterol](#) levels).^[2] There is limited evidence that screen-detected cases benefit from a diagnosis in terms of morbidity and mortality; hence, population-level screening is not presently thought to be beneficial.^[4]

In the United Kingdom, the [National Institute for Health and Clinical Excellence](#) (NICE) recommends screening for coeliac disease in patients with newly diagnosed [chronic fatigue syndrome](#)^[65] and [irritable bowel syndrome](#),^[8] as well as in type 1 diabetics, especially those with insufficient weight gain or unexplained weight loss.^{[17][66]} It is also recommended in [autoimmune thyroid disease](#), [dermatitis herpetiformis](#), and in the first-degree relatives of those with confirmed coeliac disease.^[17]

There is a large number of scenarios where testing for coeliac disease may be offered given previously described associations, such as the conditions mentioned above in "[miscellaneous](#)".^{[4][17]}

[\[edit\]](#) Diet

Main article: [Gluten-free diet](#)

At present, the only effective treatment is a lifelong [gluten-free diet](#).^[19] No medication exists that will prevent damage or prevent the body from attacking the gut when gluten is present. Strict adherence to the diet allows the intestines to heal, leading to resolution of all symptoms in most cases and, depending on how soon the diet is begun, can also eliminate the heightened risk of osteoporosis and intestinal cancer and in some cases sterility.^[67] [Dietitian](#) input is generally requested to ensure the patient is aware which foods contain gluten, which foods are safe, and how to have a balanced diet despite the limitations. In many countries, gluten-free products are available on [prescription](#) and may be reimbursed by [health insurance](#) plans.

The diet can be cumbersome; failure to comply with the diet may cause relapse. The term *gluten-free* is generally used to indicate a supposed harmless level of gluten rather than a complete absence.^[68] The exact level at which gluten is harmless is uncertain and controversial. A recent [systematic review](#) tentatively concluded that consumption of less than 10 mg of gluten per day is unlikely to cause histological abnormalities, although it noted that few reliable studies had been done.^[68]

Regulation of the label *gluten-free* varies widely by country. In the United States, the [FDA](#) issued regulations in 2007 limiting the use of "gluten-free" in food products to those with less than 20 ppm of gluten.^{[69][70]} The current international [Codex Alimentarius](#) standard allows for 20 ppm of gluten in so-called "gluten-free" foods.^[71] Gluten-free products are usually more expensive and harder to find than common gluten-containing foods.^[72] Since ready-made products often contain traces of gluten, some coeliacs may find it necessary to cook from scratch.^[73]

Even while on a diet, health-related [quality of life](#) (HRQOL) may be lower in people with coeliac disease. Studies in the United States have found that quality of life becomes comparable to the general population after staying on the diet, while studies in Europe have found that quality of life remains lower, although the surveys are not quite the same.^[74] Men tend to report more improvement than women.^[75] Some have persisting digestive symptoms or [dermatitis herpetiformis](#), mouth ulcers, osteoporosis and resultant fractures. Symptoms suggestive of [irritable bowel syndrome](#) may be present, and there is an increased rate of anxiety, fatigue, [dyspepsia](#) and musculoskeletal pain.^[76]

[\[edit\]](#) Refractory disease

A tiny minority of patients suffer from refractory disease, which means they do not improve on a gluten-free diet. This may be because the disease has been present for so long that the intestines are no longer able to heal on diet alone, or because the patient is not adhering to the diet, or because the patient is consuming foods that are inadvertently contaminated with gluten. If alternative causes have been eliminated, [steroids](#) or [immunosuppressants](#) (such as [azathioprine](#)) may be considered in this scenario.^[9]

[\[edit\]](#) Epidemiology

The disease is thought to affect between 1 in 1750 (with CD defined as clinical cases including [dermatitis herpetiformis](#)) to 1 in 105 (CD defined by presence of IgA TG in blood donors) people in the United States.^[3] The prevalence of clinically diagnosed disease (symptoms prompting diagnostic testing) is 0.05–0.27% in various studies. However, population studies from parts of Europe, India, South America, Australasia and the USA (using serology and biopsy) indicate that the prevalence may be between 0.33 and 1.06% in children (5.66% in one study of [Sahrawi children](#)^[77]) and 0.18–1.2% in adults.^[2]

People of African, Japanese and Chinese descent are rarely diagnosed;^[78] this reflects a much lower prevalence of the genetic [risk factors](#), such as [HLA-B8](#).^[79] Population studies also indicate that a large proportion of coeliacs remain undiagnosed; this is due, in part, to many clinicians being unfamiliar with the condition.^[80]

Coeliac disease is more prevalent in women than in men.^[81]

A large multicentre study in the U.S. found a prevalence of 0.75% in not-at-risk groups, rising to 1.8% in symptomatic patients, 2.6% in second-degree relatives of a patient with coeliac disease and 4.5% in first-degree relatives. This profile is similar to the prevalence in Europe.^[82] Other populations at increased risk for coeliac disease, with prevalence rates ranging from 5% to 10%, include individuals with [Down](#) and [Turner syndromes](#), [type 1 diabetes](#), and autoimmune thyroid disease, including both [hyperthyroidism](#) (overactive [thyroid](#)) and [hypothyroidism](#) (underactive thyroid).^[83]

Historically, coeliac disease was thought to be rare, with a prevalence of about 0.02%.^[83] Recent increases in the number of reported cases may be due to changes in diagnostic practice.^[84]

[\[edit\]](#) Christian churches & the Eucharist

Speaking generally, the various denominations of Christians celebrate a [Eucharist](#) in which a wafer or small piece of wheat bread is blessed and then eaten (see [Sacramental bread](#)). A typical wafer weighs about half a gram^[85] [Wheat flour](#) contains around 10 to 13% gluten, so a single communion wafer may have more than 50 mg of gluten, an amount which will harm the health of many coeliac patients especially if consumed every day (see Diet above). Many Christian churches offer their communicants gluten-free alternatives, usually in the form of a rice-based cracker or gluten-free bread. These include [United Methodist](#), [Christian Reformed](#), [Episcopal](#), and [Lutheran](#). [The Church of Jesus Christ of Latter-day Saints](#) also offers gluten-free alternatives to its communicants.^[86]

[\[edit\]](#) Roman Catholic position

Roman Catholic [doctrine](#) states that for a valid [Eucharist](#), the bread to be used at Mass must be made from wheat. In 2002, the [Congregation for the Doctrine of the Faith](#) approved German-made low-gluten [hosts](#), which meets all of the Catholic Church's requirements, for use in Italy; although not entirely gluten-free, they were also approved by the Italian Celiac Association.^[87] Some Catholic coeliac sufferers have requested permission to use rice wafers; such petitions have always been denied.^[88]

The issue is more complex for priests. Though a Catholic (lay or ordained) receiving the [Eucharist](#) under either form (bread or wine) is receiving Christ "whole and entire"—his body, blood, soul, and divinity—the priest, who is acting *in persona Christi*, is required to receive under both species when offering Mass—not for the validity of his Communion, but for the fullness of the sacrifice of the Mass. On 24 July 2003, the [Congregation for the Doctrine of the Faith](#) stated, "Given the centrality of the celebration of the Eucharist in the life of a priest, one must proceed with great caution before admitting to Holy Orders those candidates unable to ingest gluten or alcohol without serious harm."^[89]

By January 2004, extremely low-gluten Church-approved hosts had become available in the United States, Italy and Australia.^[90]

[\[edit\]](#) **Passover**

The Jewish festival of [Pesach](#) (Passover) may present problems with its obligation to eat [matzo](#), which is unleavened bread made in a strictly controlled manner from wheat, barley, [spelt](#), oats, or rye. This rules out many other grains that are normally used as substitutes for people with gluten sensitivity, especially for [Ashkenazi Jews](#), who also avoid rice. Many kosher-for-Passover products avoid grains altogether and are therefore gluten-free. [Potato starch](#) is the primary starch used to replace the grains. Consuming [matzo](#) is mandatory on the first night of Pesach only. Jewish law holds that one should not seriously endanger one's health in order to fulfil a commandment. Thus, a person with severe coeliac disease is not allowed, let alone required, to eat any matzo other than gluten-free matzo. The most commonly used gluten-free matzo is made from oats.^[9]^[1]

[\[edit\]](#) **Research directions**

Various other approaches are being studied that would reduce the need of dieting. All are still under development, and are not expected to be available to the general public for a while.^[2]

Using [genetically engineered](#) wheat species, or wheat species that have been [selectively bred](#) to be minimally immunogenic, may allow the consumption of wheat. This, however, could interfere with the effects that gliadin has on the quality of dough. Alternatively, gluten exposure can be minimised by the ingestion a combination of [enzymes](#) ([prolyl endopeptidase](#) and a barley glutamine-specific [cysteine endopeptidase](#) ([EP-B2](#))) that degrade the putative 33-mer peptide in the [duodenum](#).^[2]

Alternative treatments under investigation include the inhibition of [zonulin](#), an endogenous signalling protein linked to increased permeability of the bowel wall and hence increased presentation of gliadin to the immune system, and other modifiers of other well-understood steps in the pathogenesis of coeliac disease, such as the action of HLA-DQ2 or tissue transglutaminase and the MICA/NKG2D interaction that may be involved in the killing of enterocytes.^[2]

[\[edit\]](#) **History**

Humans first started to cultivate grains in the [Neolithic](#) period (beginning about 9500 BCE) in the [Fertile Crescent](#) in Western Asia, and it is likely that coeliac disease did not occur before this time. [Aretaeus of Cappadocia](#), living in the second century in the same area, recorded a malabsorptive syndrome with chronic diarrhoea. His "Cœliac Affection" (*coeliac* from Greek κοιλιακός *koiliakos*, "abdominal") gained the attention of Western medicine when [Francis Adams](#) presented a translation of Aretaeus's work at the Sydenham Society in 1856. The patient described in Aretaeus' work had stomach pain and was atrophied, pale, feeble and incapable of work. The diarrhoea manifested as loose stools that were white, malodorous and flatulent, and the disease was intractable and liable to periodic return. The problem, Aretaeus believed, was a lack of heat in the stomach necessary to digest the food and a reduced ability to distribute the digestive products throughout the body, this incomplete digestion resulting in the diarrhoea. He regarded this as an affliction of the old and more commonly affecting women, explicitly excluding children. The cause, according to Aretaeus, was sometimes either another chronic disease or even consuming "a copious draught of cold water."^[5]^[6]

The [paediatrician Samuel Gee](#) gave the first modern-day description of the condition in children in a lecture at [Hospital for Sick Children, Great Ormond Street](#), London, in 1887. Gee acknowledged earlier descriptions and terms for the disease and adopted the same term as Aretaeus (coeliac disease). He perceptively stated: "If the patient can be cured at all, it must be by means of diet." Gee recognised that milk intolerance is a problem with coeliac children and that highly starched foods should be avoided. However, he forbade rice, sago, fruit and vegetables, which all would have been safe to eat, and he recommended raw meat as well as thin slices of toasted bread. Gee highlighted particular success with a child "who was fed upon a quart of the best Dutch [mussels](#) daily." However, the child could not bear this diet for more than one season.^[6]^[9]^[2]

[Christian Archibald Herter](#), an American physician, wrote a book in 1908 on children with coeliac disease, which he called "intestinal [infantilism](#)." He noted their growth was retarded and that fat was better tolerated than carbohydrate.

The [eponym](#) *Gee-Herter disease* was sometimes used to acknowledge both contributions.^{[93][94]} [Sidney V. Haas](#), an American paediatrician, reported positive effects of a diet of bananas in 1924.^[95] This diet remained in vogue until the actual cause of coeliac disease was determined.^[6]

While a role for carbohydrates had been suspected, the link with wheat was not made until the 1940s by the Dutch paediatrician Dr. [Willem Karel Dicke](#).^[96] It is likely that clinical improvement of his patients during the [Dutch famine of 1944](#) (during which flour was scarce) may have contributed to his discovery.^[97] Dicke noticed that the shortage of bread led to a significant drop in the death rate among children affected by CD from greater than 35% to essentially zero. He also reported that once wheat was again available after the conflict, the mortality rate soared to previous levels.^[98] The link with the gluten component of wheat was made in 1952 by a team from [Birmingham](#), England.^[99] Villous atrophy was described by British physician John W. Paulley in 1954 on samples taken at surgery.^[100] This paved the way for biopsy samples taken by endoscopy.^[6]

Throughout the 1960s, other features of coeliac disease were elucidated. Its hereditary character was recognised in 1965.^[101] In 1966, [dermatitis herpetiformis](#) was linked to [gluten sensitivity](#).^{[6][13]}

May has been designated as "Coeliac Awareness Month".^{[102][103]}

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- [^] See [American and British English spelling differences](#).
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