Coeliac disease

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Coeliac disease is an autoimmune disorder that primarily affects the small intestine, and is caused by the ingestion of gluten in genetically susceptible individuals. Prevalence in the general population ranges from 0·5% to 2%, with an average of about 1%. The development of the coeliac enteropathy depends on a complex immune response to gluten proteins, including both adaptive and innate mechanisms. Clinical presentation of coeliac disease is highly variable and includes classical and non-classical gastrointestinal symptoms, extraintestinal manifestations, and subclinical cases. The disease is associated with a risk of complications, such as osteoporosis and intestinal lymphoma. Diagnosis of coeliac disease requires a positive serology (IgA anti-transglutaminase 2 and anti-endomysial antibodies) and villous atrophy on small-intestinal biopsy. Treatment involves a gluten-free diet; however, owing to the high psychosocial burden of such a diet, research into alternative pharmacological treatments is currently very active.

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Introduction

Coeliac disease is a permanent T-cell-mediated enteropathy, caused by the ingestion of gluten—the major protein fraction in wheat, rye, and barley—in genetically susceptible individuals.[1] Although previously considered to be a rare disease in children of European origin, coeliac disease is one of the most common lifelong disorders and affects people of all ages worldwide. A notable feature of coeliac disease is the wide variability in clinical presentation, which can be responsible for delayed or missed diagnoses and, consequently, long-term complications. The diagnostic algorithm, which was previously based mainly on the results of the small-intestinal biopsy, is currently evolving owing to the availability of simple and specific serological biomarkers. A gluten-free diet is an effective treatment for coeliac disease; however, given the psychosocial effect of avoiding common and enjoyable dietary components on a lifelong basis, adherence to a gluten-free diet can be incomplete, and new strategies for the prevention and treatment of coeliac disease are currently under investigation.

Coeliac disease has been the topic of previous Seminars in *The Lancet*.[2,3] The aim of this Seminar is to provide updated information for those who care for patients with coeliac disease, with particular focus on currently unsolved questions and research directions.

Epidemiology

In most countries, the overall prevalence of coeliac disease in the general population ranges from 0·5% to 2%, with an average of about 1%. Higher values have occasionally been reported (eg, 3% in Sweden and 5·6% in the Saharawi people), whereas coeliac disease is less common in countries where gluten-containing cereals are not the staple food and where diffusion of the major genes (HLA-DQ2 and HLA-DQ8) that predispose to the condition is low, in particular east Asia (eg, Japan and Vietnam) and part of sub-Saharan Africa.[4,5] Coeliac disease is more common in females than in males in both population screening (relative risk [RR]=1·13–1·79) and clinical studies (female-to-male ratio=1·85).[6] Longitudinal studies have shown that the prevalence of coeliac disease can change over time, and during the past 50 years an increasing trend has been observed in some countries (eg, Italy)[7] but not in others (eg, Israel).[8] These changes could reflect local exposure to as yet unidentified environmental cofactors, or ethnic or demographic variations.

Owing to increased awareness of the clinical polymorphisms of coeliac disease, and the identification of numerous simple and sensitive diagnostic serological biomarkers, the number of newly diagnosed cases of coeliac disease has increased exponentially in many countries over the past 30–40 years. In Europe, the USA, Canada, and New Zealand, the incidence of coeliac disease was less than two cases per 100 000 people per year in the 1980s and 1990s, increasing to more than 20 cases per 100 000 people per year in the 2010s.[9] However, due mainly to the high proportion of clinically silent cases (in which disease is asymptomatic but damage to the intestine is still occurring) and insufficient awareness of disease variability, coeliac disease is still largely underdiagnosed, particularly in countries with limited resources; calculations suggest that, on average, 70% of cases (the so-called submerged part of the coeliac iceberg) escape diagnosis and treatment.[7] The diagnosed fraction is very small in countries where active policies of case-finding (testing for the disease in at-risk groups) have not been extensively used so far, for instance in China[10] and India.[11]

Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 1990, and March 30, 2022, with no language restrictions, using the terms "celiac", "coeliac", and "gluten". In our selection of articles, we prioritised those published since 2015, but included older publications of scientific and historical relevance. We mostly selected cohort and case-control studies, randomised trials, international guidelines, meta-analysis and systematic reviews, and smaller, non-controlled clinical studies of particular relevance.

Pathogenesis

Necessary causes

Genetic factors

People with a family history of coeliac disease have a 10–15% risk of developing the disease in their lifetime, and a 50–75% concordance is seen among monozygotic twins. By far the most important genetic factors are MHC class II genes. Around 90% of patients with coeliac disease express HLA-DQ2.5 (alleles: *HLA-DQA1*05:01* and *HLA-DQB1*02:01*). With few exceptions, the remaining patients usually express either HLA-DQ2.2 (alleles: *HLA-DQA1*02:01* and *HLA-DQB1*02:02*; ~5%) or HLA-DQ8 (alleles: *HLA-DQA1*03:01* and *HLA-DQB1*03:02*; ~5%). Patients who are homozygous for HLA-DQ2 have a higher risk of disease development than do heterozygous individuals.[12,13] From genome-wide association studies, 41 additional non-HLA loci were found to be associated with coeliac disease.[14] These genetic factors, which individually have a small contribution to disease development, are involved in the regulation of various aspects of the immune system and barrier function, and could modulate disease presentation and phenotype.[15]

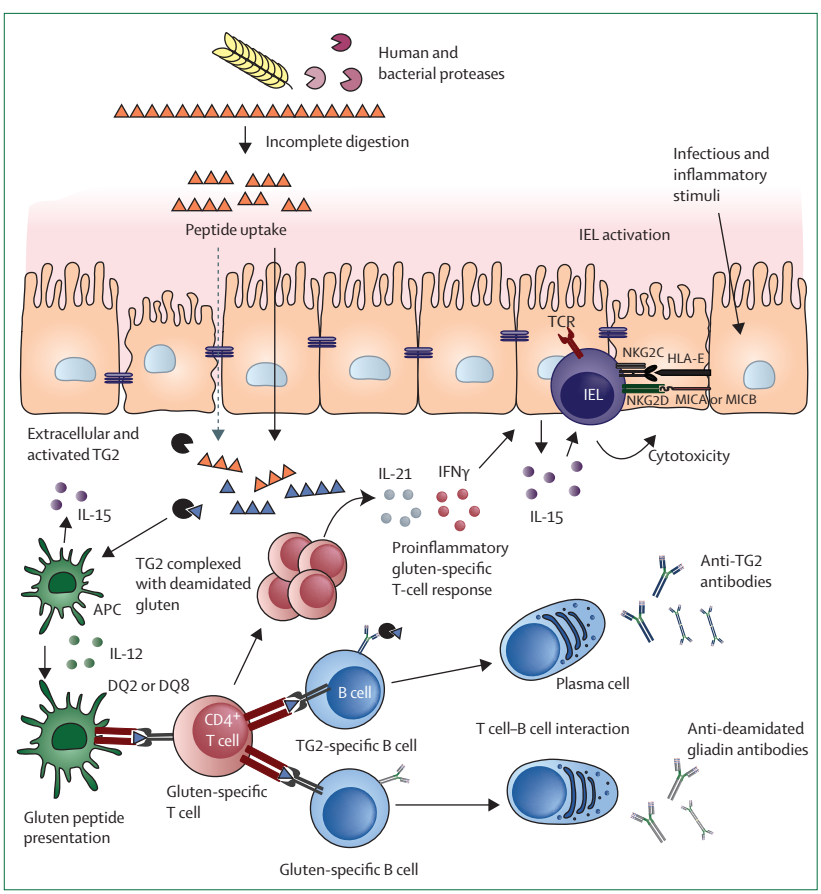


Figure 1: **Pathophysiology of coeliac disease**

Ingested gluten is partially digested by a combination of host (digestive) and microbial (small intestinal microbiota) enzymes, then transported mainly through transcellular, and possibly paracellular, pathways to the lamina propria. Activated transglutaminase 2 (TG2; also known as tissue transglutaminase)—an enzyme that is expressed in many cell types and is secreted during inflammatory conditions to the extracellular matrix—deamidates glutamine residues in gluten peptides, which enhances the efficiency of peptide binding to the HLA-DQ2 or HLA-DQ8 groove of antigen-presenting cells (APC). TG2 also mediates crosslinking, leading to TG2–gluten complexes that can activate B cells to produce autoantibodies. Gluten-specific $CD4^+$ T helper 1 cells secrete pro-inflammatory mediators such as interferon (IFN) γ, interleukin (IL)-12 and tumour necrosis factor. The interaction of extracellular TG2 with the gluten peptides induces TG2-specific B-cell clones that produce autoantibodies against TG2, which are used as a sensitive and specific serological diagnostic tool. B cells can also internalise TG2–gluten complexes, and release deamidated gluten peptides that bind to HLA-DQ2 or HLA-DQ8 and further activate the gluten-specific T cells. Infectious or inflammatory cues upregulate stress markers (MHC class I chain-related proteins A [MICA] and B [MICB], and HLA class I histocompatibility antigen, alpha chain E [HLA-E]) in intestinal epithelial cells. Cytotoxic transformation of intraepithelial lymphocytes (IELs) interact with intestinal epithelial cells through natural killer cell receptors. Pro-inflammatory cytokines, such as IL-15, drive IEL cytotoxicity, contributing to tissue destruction and intestinal atrophy.[18,19] TCR=T-cell receptor.

Dietary gluten

Gluten is a collective term for the storage proteins of wheat, rye, and barley. These proteins, which characteristically contain a high proportion of proline and glutamine residues, are named prolamins. Wheat prolamins include gliadins (α, γ, and ω gliadins) and glutenins (low-molecular-weight and high-molecular-weight fractions),[16] whereas rye prolamins are termed hordeins and barley prolamins are termed secalins. Gluten proteins drive the adaptive immune response in coeliac disease. Gastric and pancreatic enzymes are unable to fully break down these proteins, in part due to their unusual repetitive sequences,[17] and this proteolytic stability is a key factor for their immunogenicity.

Additional environmental triggers

Gluten intake and a genetic predisposition to coeliac disease are common in the general population. Additional environmental factors, such as infections and gluten dose, together with quantitative and qualitative changes in the intestinal microbiome, are likely to have a role in the development of disease, and are currently under investigation. The pathophysiological cascade of events that begins with an adaptive and innate immune response to gluten proteins and leads to the development of the coeliac autoimmunity and enteropathy is shown in figure 1.

Clinical picture

Coeliac disease is a so-called clinical chameleon, and can present at any age with various manifestations. Depending on the clinical features at the time of diagnosis, coeliac disease can be divided into classical, non-classical, and subclinical forms. The classical form, which is more common in children younger than 5 years, presents with chronic diarrhoea, poor appetite, weight loss, abdominal distension, muscle wasting, and mood changes.[1,20] A delay in diagnosis can rarely lead to a life-threatening coeliac crisis, which is characterised by watery diarrhoea, marked abdominal distension, dehydration, electrolyte imbalance, hypoalbuminaemia, hypotension, and lethargy. Acute or recurrent intestinal intussusception is another possible manifestation.[21] Non-classical coeliac disease is the most common presentation and is characterised by non-specific intestinal complaints (eg, recurrent abdominal pain, bloating, and diarrhoea or constipation), extraintestinal

	Clinical aspects	Diagnosis	Comments
Iron deficiency anaemia	Can present with fatigue, irritability, lethargy, concentration difficulties, dizziness, pallor, headache, alopecia, dry hair or skin, koilonychia, or atrophic glossitis	Full blood count shows anaemia and microcytic, hypochromic red blood cells, with an increased red blood cell distribution width (anisocytosis), and low ferritin concentrations	One of the most frequent extraintestinal manifestations of coeliac disease; can improve with gluten-free diet alone, but iron supplementation is sometimes necessary
Short stature	Height ≤2 SD score or below the third percentile of height for age	Anthropometric measures; growth hormone resistance with low concentrations of IGF-1 might be observed	Most common cause of disease-related short stature; catch-up growth is expected within 1–2 years of gluten-free diet
Coeliac hepatitis	Asymptomatic	Increased blood levels of aminotransferases; no specific histological changes	Promptly reversible with a gluten-free diet; should be differentiated from autoimmune hepatitis, which is sometimes associated with coeliac disease
Defects in dental enamel	Symmetrically affect deciduous and, more frequently, permanent teeth, and can range from colour defects (grade 1) to structural defects (grade 2–4)	Clinical examination by an experienced dentist	Early diagnosis of coeliac disease seems to prevent the development of dental defects
Osteopenia or osteoporosis	Can cause an increased risk of fractures	Dual x-ray densitometry shows reduced bone mineral density	In children, osteopenia or osteoporosis can be reversed by a gluten-free diet with restoration of normal peak densitometric values; in adults, bone-mineral density improves but rarely normalises
Unexplained fertility-related disorders	Delayed puberty, infertility, miscarriage, premature birth, or small-for-gestational-age infant	Obstetrics consultation	The prevalence of coeliac disease among patients with unexplained infertility ranges from 4% to 10·3%; hormonal imbalances and nutritional deficiencies could be responsible for infertility, which might resolve with a gluten-free diet
Epilepsy	Generally drug-resistant epilepsy; occipital calcifications might be found	Electroencephalogram and magnetic resonance imaging	A gluten-free diet could reduce seizure frequency or help to reduce the dose of or wean off of one or more antiseizure medications
Peripheral neuropathy	Generally presents with tingling, pain, and numbness, initially in the hands and feet	Electromyography	Adherence to a strict gluten-free diet can result in clinical improvement
Gluten ataxia	Difficulty with arm and leg control, gait instability, poor coordination, loss of fine motor skills such as writing, problems with talking, and visual issues; less than 10% of patients have intestinal symptoms	Neurological exam with combinations of either magnetic resonance imaging or magnetic resonance spectroscopy, or computed tomography; presence of antigliadin antibodies; only a third of patients have enteropathy on biopsy	Mean age at onset 53 years; 20% prevalence among all patients with ataxias and 40% among patients with sporadic ataxias
Dermatitis herpetiformis	An itchy rash usually occurring in the elbows, extensor surfaces of the forearms, knees, and buttocks, including the sacral area; the rash is polymorphic, consisting of small blisters, papules, and erythema; erosions, crusts, and postinflammatory hyperpigmentation often occur	Biopsy of adjacent unaffected skin showing granular deposits of IgA at the dermal-epidermal junction; IgA anti-transglutaminase 2 antibodies and duodenal villous atrophy	Reversed by a gluten-free diet, but drug treatment (dapsone) might be required; patients are often highly sensitive to traces of gluten
Hyposplenism	Causes susceptibility to infections, with increased risk especially of pneumococcal infections	Detection of thrombocytosis and pitted red cells by phase-interference microscopy on blood sample	Whether hyposplenism can be reversible with a gluten-free diet is still uncertain

Table 1: **Major extraintestinal manifestations and complications of coeliac disease, excluding refractory disease and malignancies**[22–26]

manifestations (eg, persistent iron deficiency, chronic fatigue, or hypertransaminasemia), or other systemic manifestations or complications (table 1) including nutritional deficiencies (eg, vitamin D, vitamin B12, folate, iron, or zinc), arthralgia or arthritis, alopecia, recurrent stomatitis, and chronic urticaria.[22–26] Subclinical (clinically silent) coeliac disease is identified through either screening programmes in the general population or case-finding in at-risk groups, such as relatives of individuals with coeliac disease. In adults, the higher prevalence of extraintestinal manifestations and associations at the time of diagnosis, and the development of long-term complications, seem to be the most notable differences from paediatric-onset coeliac disease.[27] The association of

Panel: **Conditions other than coeliac disease that can cause duodenal lymphocytosis (Marsh type 1 lesion) or villous atrophy (Marsh type 3a–c)**

Modified from Lauwers and colleagues[50] and Leonard and colleagues.[51]

Duodenal lymphocytosis

- Food allergy, non-coeliac gluten sensitivity
- Infection (eg, *Helicobacter pylori* or Giardiasis)
- Drugs (eg, non-steroidal anti-inflammatory drugs)
- Post-enteritis syndrome
- Immune deficiency (eg, selective IgA deficiency, common variable immune deficiency)
- Immune dysregulation (eg, autoimmune thyroiditis)
- Crohn's disease
- Pre-infiltrative intestinal T-cell lymphoma

Villous atrophy

- Environmental enteropathy
- Common variable immune deficiency
- Autoimmune enteropathy
- Drugs (eg, olmesartan or azathioprine)
- Food allergy
- Giardiasis
- Crohn's disease
- Eosinophilic enteritis
- Radiation enteritis

coeliac disease with some malignancies is seen almost exclusively in adults.[28]

Coeliac disease is significantly associated with other autoimmune diseases, in particular type 1 diabetes (associated coeliac disease in 4·5% of cases)[29] and Hashimoto's thyroiditis (odds ratio=4·0 of associated coeliac disease),[30] but also autoimmune hepatitis, primary biliary cholangitis,[31] Sjögren's syndrome, systemic lupus erythematosus, and systemic sclerosis.[32] Coeliac disease and autoimmune comorbidities are linked, at least in part, to HLA predisposing genes, but a possible role of gluten or other cofactors in triggering autoimmunity has also been suggested.[20] An increased risk of inflammatory bowel diseases is seen in patients with coeliac disease (RR=9·88); similarly, patients with inflammatory bowel diseases have a greater risk of coeliac disease (RR=3·96).[33] A strong association with microscopic colitis has also been reported; the condition was found to be 50 times more common in patients with coeliac disease than would be expected in the general population.[34] The prevalence of coeliac disease is also increased in people with genetic and chromosomal disorders, particularly selective IgA deficiency (associated coeliac disease in 15% of cases),[35] Down syndrome (9·8%),[36] Turner syndrome (3·8%),[37] and Williams syndrome (6·9%).[38]

All the previously mentioned manifestations, complications, and comorbidities are indications for a serological screen for coeliac disease.

Diagnosis

Serological markers

The development of coeliac disease is characterised by the appearance of serum autoantibodies, which nowadays have a central role in the diagnostic process. Anti-transglutaminase 2 (TG2) antibodies are directed against the major coeliac disease autoantigen. In people on a gluten-containing diet, the presence of IgA class anti-TG2 is highly sensitive and specific for active coeliac disease (>95%), and testing for these antibodies, together with or preceded by the measurement of total serum IgA to exclude selective IgA deficiency, is considered the best first-level screening test for coeliac disease.[39–43] A high concentration of serum IgA anti-TG2 is strongly associated with the presence of villous atrophy on small intestinal biopsy.[44] Testing for IgG anti-TG2, although less accurate for diagnostic purposes than testing for IgA anti-TG2, can be indicated in individuals with associated selective IgA deficiency. Different methods are currently available for the determination of anti-TG2 antibodies: ELISA, fluorescent immunoassay, radioimmunoassay, and chemiluminescence. The reported interassay variability can occasionally be responsible for diagnostic uncertainty.[45] IgA class anti-endomysial antibody (EMA) is directed against the TG2 antigen present in the endomysium in a tissue section. The EMA test is based on indirect immunofluorescence assays on a monkey oesophageal or human umbilical cord substrate. The specificity of IgA EMA is almost 100%, even higher than that of IgA anti-TG2.[20] Because the results of the EMA determination procedure can vary between operators, and the test requires a primate substrate, it is not suitable for first-level screening for coeliac disease, but is an excellent confirmatory test. IgG class anti-deamidated gliadin peptide (DGP) is slightly less sensitive (88%) and specific (94%) than is IgA anti-TG2;[46] however, testing for IgG anti-DGP can be suitable for patients with selective IgA deficiency and for children younger than 2 years, because the appearance of IgG anti-DGP can precede that of IgA anti-TG2.[47] Occasionally, screening for IgA anti-DGP and IgG anti-DGP can be helpful to identify cases of coeliac disease in anti-TG2-negative individuals.[48] Additionally, point-of-care tests for the determination of either IgA anti-TG2 or anti-DGP are available. Owing to lower sensitivity, such tests could find application as triage tests to decide whether the standard serological tests should be conducted.[49]

HLA determination

Screening for HLA-DQ2 and HLA-DQ8 can be useful in some circumstances. The risk of coeliac disease in the siblings of affected patients, for example, is almost absent in individuals who lack both HLA-DQ2 and HLA-DQ8, whereas this risk is 10–15% in siblings with a single copy of HLA-DQ2 or HLA-DQ8, and more than 20% in those with a double copy of HLA-DQ2.[12] Genotyping can also be

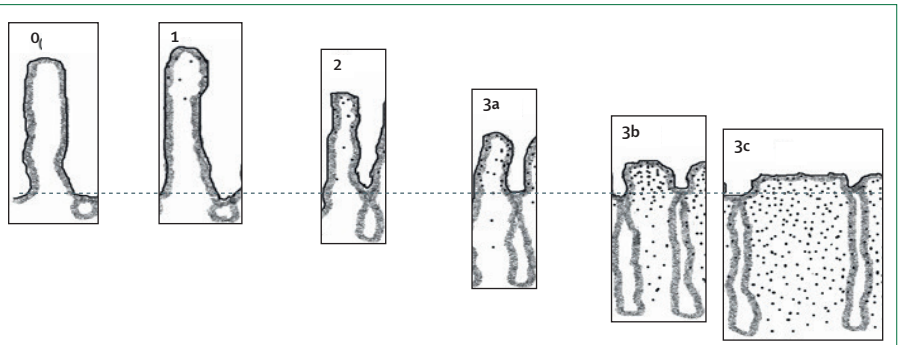
useful for individuals who are already on a gluten-free diet but whose diagnosis is uncertain.

Small intestinal biopsy

The typical histological picture of coeliac disease shows a severe villous atrophy with crypt hypertrophy and an increase in intraepithelial lymphocytes. However, the coeliac enteropathy is variable, ranging from duodenal lymphocytosis (an isolated increase of the intraepithelial lymphocyte count) to total villous atrophy (flat mucosa), and is not specific to coeliac disease, especially when the damage is not severe (panel).[20,50,51] The extent of intestinal damage can be graded using different scores, with the Marsh classification modified by Oberhuber[52] being the most widely used for this purpose (figure 2). When a precise quantification of small-intestinal damage is needed, intestinal morphometry is used as the reference method, including measurement of the intraepithelial lymphocyte count, villous height, crypt depth, and ratio of villous height to crypt depth.[54] Small intestinal biopsies are conducted by upper gastrointestinal endoscopy, and multiple biopsy samples are taken from the duodenal bulb (at least two samples; to increase the diagnostic yield of coeliac disease)[55] and from the descending portion of the duodenum (at least four samples). Proper handling and orientation of specimens is important to avoid artifacts (eg, the tangential cut) that can impair evaluation of the biopsy sample.

Diagnostic criteria

For children, owing to the tight correlation between high-titre IgA anti-TG2 plus IgA-EMA positivity and villous atrophy,[44,56] the current diagnostic guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition include the option of omitting the small intestinal biopsy in children with an IgA anti-TG2 concentration of more than ten times the normal upper limit, and a positive IgA-EMA on a second blood sample.[39] This algorithm avoids the risks and cost of an endoscopy in at least 50% of children with suspected coeliac disease.[56] Conversely, a small intestinal biopsy is considered always necessary by the North American Society of Paediatric Gastroenterology, Hepatology and Nutrition, a recommendation that is motivated by an absence of standardisation of serological tests, variation in antibody concentrations between commercial assays, and the potential for missing additional gastrointestinal disorders.[43] In adults, the finding of both a positive serology (particularly IgA anti-TG2) and the characteristic histological changes on small intestinal biopsy (Marsh type 3a–c) is still required for a diagnosis of coeliac disease.[41,42] However, this recommendation could change



	Marsh-Oberhuber grade					
	0	1	2	3a	3b	3c
Descriptor		Infiltrative	Hyperplastic	Partial villous atrophy	Subtotal villous atrophy	Total villous atrophy
Villous architecture	Normal	Normal	Normal	Shortened, blunt	Clearly atrophic	Complete loss
Crypt architecture	Normal	Normal	Enlarged	Enlarged	Enlarged	Severe hyperplasia
Intraepithelial lymphocytes	Normal (<25 per 100 enterocytes)	Increased	Increased	Increased	Increased	Increased
Vh:Cd ratio	≥3	≥3	≥2 to <3	≥1 to <2	≥0·5 to <1	<0·5

Figure 2: **Small intestinal histology in coeliac disease**
Classified according to the widely used Marsh-Oberhuber classification system.[52] Grade 0 is normal small intestinal mucosa, whereas grades 1–3c classify the variable degree of damage found in coeliac disease (grades 0–1 are usually found in potential coeliac disease, and grades 3a–c reflect the presence of coeliac disease-associated villous atrophy). A less subjective evaluation is the Quantitative-Mucosal Algorithmic Rule for Scoring Histology, which is based on the measurements of villous height (Vh) and crypt depth (Cd) and the intraepithelial lymphocyte count. Modified from Rostom and colleagues.[53]

in the near future, as studies have suggested that the biopsy-sparing algorithm could apply to adults as well as children.[57]

Potential coeliac disease

Potential coeliac disease is defined by positivity of coeliac disease serological markers (IgA anti-TG2 and EMA) without duodenal villous atrophy (Marsh type 0 or 1).[1] Progression to coeliac disease (ie, Marsh type 3) occurs in 15–45% of cases.[58,59] Patients with potential coeliac disease should be left on a normal gluten-containing diet and followed up at regular intervals by serology and, eventually, repetition of the small intestinal biopsy. A gluten-free diet might be recommended to patients who are symptomatic.[39,41] Long-term prospective studies are needed to clarify the possible triggers of progression to coeliac disease.

Difficult cases

In most cases, the diagnostic process for coeliac disease is straightforward and the results of diagnostic tests are readily interpreted; however, borderline cases are observed (usually <10% of cases in clinical practice). First, patients can have symptoms that are suggestive of coeliac disease, but test negative for serological markers and show villous atrophy on small intestinal biopsy. After other small bowel enteropathies have been excluded (panel), the possibility of seronegative coeliac disease should be considered.[41,42] Seronegative coeliac disease has been described in adults, with a low incidence (<2% of all cases).[51] IgA anti-TG2 intestinal deposits have been reported in seronegative coeliac disease, suggesting that the coeliac disease autoimmune reaction might be confined to the gut.[60] Confirmation of diagnosis requires the finding of coeliac-disease-permissive genes (HLA-DQ2, HLA-DQ8, or both), and clear-cut clinical and histological improvement after starting the gluten-free diet. Second, discrepancies can exist between the anti-TG2 and EMA test results. For patients who have a low isolated titre of IgA anti-TG2, a shift can occur over time either to a fully expressed coeliac disease serological pattern or to the normalisation of anti-TG2.[61] Conversely, EMA positivity with negative IgA anti-TG2 usually results from incorrect interpretation of the EMA test, sometimes related to positivity for anti-smooth-muscle antibodies. Third, the reliability of coeliac disease biomarkers can be poor in individuals with a very low intake of gluten-containing food (eg, relatives of a patient with coeliac disease[62] or individuals who have self-diagnosed an intolerance to gluten[63]). So far these situations have been managed by a gluten challenge (ie, repetition of the test after at least 1–3 months of increased gluten exposure). Finally, coeliac disease-predisposing genes (HLA-DQ2 and HLA-DQ8) can be absent. Although rare, this situation is still compatible with the diagnosis of coeliac disease (<1% of cases),[64] provided that clinical, serological, and histological findings are strongly suggestive.

Refractory coeliac disease

Refractory coeliac disease is a complication of adult coeliac disease that is characterised by persistent symptoms and mucosal damage despite following a strict gluten-free diet for 1 year.[1] Refractory coeliac disease can be primary (in patients who never respond to a gluten-free diet) or secondary (in patients who initially respond but subsequently worsen), and can be classified as type 1 (normal intraepithelial lymphocyte phenotype) or type 2 (abnormal intraepithelial lymphocyte phenotype).[65] Histological findings and risk of complications in type 1 refractory coeliac disease are similar to those of untreated coeliac disease, and some researchers define this condition as non-responsive coeliac disease, in which chronic gluten contamination should be explored—especially in patients who show a persistent increase in coeliac disease autoantibody concentrations.[66] In patients with type 2 refractory coeliac disease, a massive infiltration of the gut epithelium by lymphocytes with clonal T-cell receptor rearrangements is seen and, in most cases, an unusual immunophenotype that reflects the origin of these lymphocytes from a small subset of innate T-intraepithelial lymphocytes. Type 2 refractory coeliac disease is a pre-lymphoma state, and is always a cause for concern because of its severe course, development of enteropathy-associated T-cell lymphoma in 30–50% of cases within 5 years of diagnosis, and high mortality.[65] Most patients with type 2 refractory coeliac disease are homozygous for HLA-DQ2, and mutations in genes regulating cell growth and proliferation have been described in these patients. Mutations activating the JAK1–STAT3 pathway seem to be the primary drivers of coeliac-disease-associated lymphomagenesis in both type 2 refractory coeliac disease and aggressive enteropathy-associated T-cell lymphoma.[67,68] Environmental drivers such as persistent gluten introduction, infections, and proinflammatory stimuli that increase production of interleukin-15 (IL-15) could also have a role.[69] The reported prevalence of type 2 refractory coeliac disease is 1–4% of total cases of coeliac disease,[70] which is probably an overestimation of the true community prevalence. Most patients with type 2 refractory coeliac disease are older than 40 years, with a female predominance, and have severe malabsorption symptoms such as persistent weight loss and diarrhoea.[65,70] Despite persistent severe histological damage (Marsh type 3), most patients adhere to a strict gluten-free diet and show normal concentrations of coeliac disease autoantibodies. The type of refractory coeliac disease can be diagnosed according to the absence (type 1) or presence (type 2) of an abnormal phenotype of intraepithelial lymphocytes determined by immunohistochemistry, flow cytometry, or T-cell clonality analyses.[71] Type 2 refractory coeliac disease is characterised by clonal expansion of abnormal intraepithelial lymphocytes that lack surface markers CD3, CD8, and T-cell receptor ($CD3s^{-}CD8s^{-}TCR^{-}$) and preserved expression of intracellular CD3 ($CD3e^{+}$).[1,65] Ulcerative jejunitis is a common complication of type 2 refractory

coeliac disease that occurs in around 30% of patients.[65] In addition to enteropathy-associated T-cell lymphoma, other contributing factors to mortality include infections, severe malnutrition, and complications due to immunosuppressive therapy.

Malignancies and mortality risk associated with coeliac disease

Coeliac disease is associated with an increased risk (RR=3·1) of non-Hodgkin lymphoma, especially of the T-cell type and primarily localised in the gut.[28] With an incidence of approximately 0·10 cases per 100 000 people per year, enteropathy-associated T-cell lymphoma is a rare form of non-Hodgkin lymphoma that specifically arises in patients with coeliac disease, and is either pre-existing or concomitantly diagnosed. Enteropathy-associated T-cell lymphoma is more common in men, with a peak in the seventh decade of life.[72,73] Very few cases have been reported in children, and the condition has also been observed in patients on a strict gluten-free diet.[74] In many cases, enteropathy-associated T-cell lymphoma is the end stage of type 2 refractory coeliac disease. The tumour is more frequently localised in the jejunum than the ileum and is often multifocal with ulcerative lesions. The neoplastic cells of enteropathy-associated T-cell lymphoma are most commonly positive for CD3e, CD7, CD103, and cytotoxic markers (TIA-1, granzyme B, and perforin), and negative for CD4, CD5, CD8, and CD56. CD30 expression is common. Treatment of enteropathy-associated T-cell lymphoma is difficult when the disease spreads, and long-term survival is extremely low (13% at 30 months).[28]

Small bowel carcinoma is a relatively uncommon cancer in the general population and has been linked to coeliac disease. In a retrospective study in Sweden, the risk of small bowel carcinoma in coeliac disease patients was significantly increased (hazard ratio [HR]=3·05).[75] In some cases, coeliac disease is diagnosed at the time of, or subsequent to, the diagnosis of cancer. Most cases are found in the jejunum or duodenum, and the most common clinical features are pain, persistent iron deficiency anaemia, occult or overt haemorrhage, and obstructive signs. Non-compliance with a gluten-free diet is regarded as a risk factor for small bowel carcinoma. Early diagnosis leads to a better prognosis, and some studies have shown a high five-year survival (80%) depending on clinical, molecular, and histological phenotypic subtypes.[76]

Complications and risk of associated malignancies can increase overall mortality in coeliac disease.[77] A cohort-based study in Sweden found a small but significant increased mortality risk (HR=1·21 [95% CI, 1·17–1·25]) in nearly 50 000 patients with coeliac disease compared with healthy controls. Individuals with coeliac disease were at increased risk of death from cancer and respiratory and cardiovascular diseases.[72] The overall risk of cancer was higher, but was only significantly increased in the first year after diagnosis of coeliac disease (HR=2·47) and not subsequently, although the risks of haematological, lymphoproliferative, hepatobiliary, and pancreatic cancers persisted. By contrast, the prevalence of other malignancies (breast, pulmonary, and gynaecological cancers) seems to be lower in patients with coeliac disease than in the general population.[73]

Treatment

Treatment of coeliac disease is based on adherence to a gluten-free diet. Gluten is found in wheat and related species (ie, kamut, emmer, einkorn, spelt, and triticale), rye, barley, and derivatives (eg, wheat flour, pasta, couscous, and seitan), with the exception of purified ingredients such as deglutinated wheat starch. Naturally gluten-free grains, such as rice, corn, buckwheat, millet, teff, amaranth, and quinoa, are allowed in a gluten-free diet.[20] Oats, a cereal rich in important nutrients such as fibre, unsaturated fatty acids, and antioxidants,[78] are well tolerated by most patients with coeliac disease;[79] however, some oat cultivars might still contain a few coeliac T-cell-activating sequences that can occasionally be responsible for disease reactivation.[78] Purified oats can be included in a gluten-free diet after clinical remission has been obtained.[80] According to guidelines from international regulatory agencies, commercially available gluten-free items must contain less than 20 mg/kg (20 parts per million) of gluten to remain within the safety threshold.[78,81]

A gluten-free diet is a nutritionally safe intervention that enables remission of the disease, including mucosal healing, without any major risks. However, studies have shown that such a diet can lead to insufficient intake of some nutrients over the long term, especially fibre, calcium, iron, folate, and other vitamins.[82] Commercial gluten-free items can contain more simple sugars and fat than gluten-containing products; however, most studies have not found any increased risk of obesity or dyslipidaemia related to a gluten-free diet, most likely due to the restricted choice of food.[83] Because wheat is a staple food in many countries, eliminating gluten from the diet can have negative psychosocial effects and negative effects on quality of life.[84] The need to constantly consider the diet could be responsible for psychological disturbances, particularly during vulnerable periods such as adolescence.[85]

The complete elimination of gluten from the diet is more complex than it might seem. Naturally gluten-free items, such as oats and lentils,[86] can be cross-contaminated with gluten at different steps of the food-processing chain. Furthermore, gluten is a pervasive ingredient that is often added for its viscoelastic and stabilising properties and can be found in many unexpected items such as hamburgers, soy sauce, ready soups, dressings, and ice cream. Dining out (eg, at a restaurant, workplace, or school) also increases the risk of inadvertent gluten

exposure.[78] Incomplete adherence to a gluten-free diet is more common in males, adolescents, and clinically silent cases.[87] The repeated ingestion of traces of gluten is often symptomless but can cause deterioration of the small intestinal mucosa.[81] Over the long term, incomplete mucosal healing has been associated with an increased risk of osteoporotic fractures and lymphoproliferative malignancies, but not mortality.[88]

Therapies in addition to a gluten-free diet

Treatment of dysbiosis associated with coeliac disease has been attempted with administration of probiotics. A 2020 meta-analysis[89] investigated the efficacy of probiotics in coeliac disease and concluded that, although probiotics can improve persistent gastrointestinal symptoms in a subset of patients with coeliac disease on a gluten-free diet, the overall quality of data and evidence was low. New-generation probiotic therapies for coeliac disease that target specific mechanisms of disease, such as gluten metabolism or defective microbial-regulated pathways, or genetically engineered bacterial strains producing immune-regulatory molecules of interest, could show efficacy in the future. Nevertheless, many patients with coeliac disease regularly consume over-the-counter probiotics, mostly because of persistent symptoms.[90] Some of these products could be contaminated with gluten and patients should be advised to verify their gluten-free status.

Currently recommended treatment options of refractory coeliac disease include nutritional support, pharmacological agents (oral budesonide and azathioprine in type 1; oral budesonide or intravenous prednisone and cladribine in type 2) and autologous haemopoietic stem-cell transplantation in non-responsive type 2 cases.[41,91,92] A phase 2a randomised controlled trial of anti-IL-15 antibody (AMG 714) showed no reduction in aberrant intraepithelial lymphocyte populations (primary outcome), but found improvement in symptoms and other secondary endpoints, suggesting that further research is needed.[93]

Follow-up

After diagnosis, periodic follow-up is recommended to monitor progress and wellbeing, evaluate compliance with a gluten-free diet, provide education about the disease, and ensure social support.[39–43] Patients on a strict gluten-free diet usually show improvement or resolution of symptoms during the first 6 months of treatment. However, persistence of symptoms is a common finding and can result from continuing ingestion of gluten or the emergence of conditions such as irritable bowel syndrome, lactose intolerance, small intestinal bacterial overgrowth, pancreatic insufficiency, or microscopic colitis.[42]

An expert dietician should be involved at diagnosis and during follow-up visits to assess the patient's current nutritional status, identify macronutrient and micronutrient intake, detect deficiencies and excesses, analyse eating habits and potential factors that affect access to a gluten-free diet, and monitor and evaluate dietary compliance.[39–43] Patient questionnaires (eg, Biagi questionnaire,[94] Coeliac Dietary Adherence Test,[95] and Wessels questionnaire[96]) are available to standardise dietary evaluations. Haematological profiles, particularly iron and folate status, 25-hydroxyvitamin D concentrations, and other abnormal results at diagnosis, should be checked and any anomalies corrected. Persistence of iron deficiency is common and can be due to low iron intake, increased iron requirements secondary to catch-up growth, or persistent mucosal damage. Some patients with coeliac disease are refractory to oral iron supplementation and might require intravenous iron administration.[23] Bone density should be measured at diagnosis in adults, especially women, and in younger patients who have additional risk factors for osteoporosis.[41]

IgA anti-TG2 should be monitored, ideally by the same assay used at diagnosis. A considerable reduction of IgA anti-TG2 titre is seen after a few months of a gluten-free diet; however, full normalisation of coeliac disease serology can take more than 2 years, particularly in individuals with very high IgA anti-TG2 levels at diagnosis.[97] A lack of progressive decline in antibody concentrations, or an increase in antibody concentrations at any stage, requires careful review of the diet. Owing to the frequent association with autoimmune thyroid disease, measurement of thyroid-stimulating hormone is advisable, especially in females. Other autoimmunity screening (eg, for type 1 diabetes autoantibodies) is not recommended. Adults should be vaccinated against pneumococci, *Haemophilus influenzae*, and meningococci, because of possible hyposplenism or functional asplenia associated with coeliac disease.[41,42] Patients with coeliac disease can have a weaker than normal response to hepatitis B vaccination;[98] however, an increased risk of infection with hepatitis B virus has not been reported in patients with coeliac disease.[99] The necessity and the timing of a follow-up small intestinal biopsy is still debated, although conducting this investigation after 1–2 years of a gluten-free diet is reasonable for patients who are older than 40 years at diagnosis or who have persistent symptoms.[41,42]

Online consultations for patients with coeliac disease save money, increase disease-specific health-related quality of life, and are satisfactory for most patients.[100] The COVID-19 pandemic strongly encouraged the implementation of E-healthcare for coeliac disease follow-up.[101]

Hot topics and research areas

Despite great advances in the knowledge of coeliac disease, many questions remain unanswered and are currently the target of intense research activities.

Environmental triggers

Why only a small percentage of individuals who are positive for HLA-DQ2 or HLA-DQ8 and who eat

gluten-containing food develop coeliac disease is unclear. Environmental factors besides gluten must be important at any age, including the amount and type of other wheat proteins consumed—in particular the amylase trypsin inhibitors, which are potent activators of innate immunity.[102] Notably, ancient wheat varieties (such as einkorn) can contain different types and lower concentrations of amylase trypsin inhibitors, suggesting that the currently high frequency of coeliac disease could be facilitated by the widespread use of modern wheat varieties that are rich in amylase trypsin inhibitors.[103] Starting in the early 2000s, several longitudinal, multicentre cohort studies on genetically at-risk newborn babies, such as TEDDY (USA, Sweden, Finland, and Germany),[104] Prevent-CD (Spain, Italy, the Netherlands, Poland, Romania, and Croatia),[105] CELIPREV (Italy),[106] MoBa[107] and MIDIA[108] (Norway), and CD-GEMM (the USA, Italy, and Spain)[109] are shedding a light on possible environmental determinants of coeliac disease other than gluten. In terms of prenatal factors, maternal smoking[107] and high maternal gluten consumption[110] have been reported to increase the risk of coeliac disease, whereas high maternal fibre consumption reduces this risk.[110] The method of delivery (vaginal or caesarean) does not influence the risk of developing coeliac disease.[104,111] With the exception of a single study, which suggests that early gluten introduction (at 4 months of age) reduces the risk of coeliac disease later in life,[112] most available data show that breastfeeding and the timing of the introduction of gluten into the diets of infants has no role in the development of disease.[105,106] Higher gluten intake during the first 5 years of life and shifts in the intestinal microbiome seem to be positively associated with the development of coeliac disease.[113,114] Viral infections, such as with rotavirus,[115] reovirus,[116] enterovirus,[117] and paraechovirus,[108] could trigger the development of coeliac disease.[118] Vaccination against rotavirus infection could be protective, although data are inconclusive.[118,119] The use of antibiotics or proton-pump inhibitors in early infancy has been found to be associated with an increased risk of subsequent coeliac disease in some studies[120,121] but not in others.[122] A better knowledge of the environmental triggers of coeliac disease could pave the way to the development of policies for the primary prevention of coeliac disease.

Role of the intestinal microbiome

Longitudinal studies investigating predisease changes in the stool microbiome in children at risk of developing coeliac disease have identified several species that increase or decrease in abundance before disease onset.[123] Similar to other chronic diseases, such as inflammatory bowel disease, a unique microbiome signature of coeliac disease has not been definitively identified. Variability is high across studies, due to a combination of factors such as clinical trial design, sampling site (duodenum *vs* faeces), population under study, and analytical methods.[18] For this reason, and the fact that inferences on causality are difficult to draw from clinical studies, basic and translational studies have proven a valuable tool to increase mechanistic insight into the role of the microbiome in coeliac disease. Bacterial proteases (such as elastase) from opportunistic pathogens increase gluten antigenicity and enhance the immune reactivity of gluten-specific T cells in coeliac disease. Conversely, commensal bacteria such as *Lactobacillus* aid in the full digestion of gluten peptides, reducing their immunogenicity.[124] The essential amino acid tryptophan is poorly metabolised by gut microbes present in the duodenum of patients with coeliac disease, leading to impaired activation of the aryl hydrocarbon receptor in the intestinal mucosa and subsequent inflammation.[125] Microbiome-driven mechanisms include pathways that are independent of bacterial elastase, such as the T-cell receptor cross-reactivity between gliadin and *Pseudomonas* peptides in HLA-DQ2.5-positive individuals.[126] With the rapid advances in microbiome analysis, the next decade should reveal crucial information on proinflammatory and protective species and mechanisms involved in coeliac disease, which could lead to novel biotherapeutics.[127]

New diagnostic tools

Tests that are currently used for the diagnosis of coeliac disease, including testing for coeliac disease autoantibodies, have limitations—in particular poor reliability in individuals on a low-gluten or gluten-free diet. A new HLA-DQ–gluten tetramer-based assay detects gluten-reactive T cells and identifies patients with coeliac disease with a high level of accuracy, regardless of whether they are on a gluten-free diet.[128] Similarly, microRNAs (miRNAs; small, single-stranded, non-coding RNA molecules involved in RNA silencing and post-transcriptional regulation of gene expression) are consistently increased in patients with untreated and patients with treated coeliac disease, independent of gluten intake.[129] Intestinal histology and concentrations of serum coeliac disease autoantibodies change slowly (over weeks or months) during gluten challenge, which can be a problem for clinical trials that test the efficacy of alternative treatments to a gluten-free diet. Measuring the mobilisation of gluten-specific T cells into the blood, originally with an enzyme-linked immunoabsorbent spot assay and more recently with whole-blood cytokine release assays, is useful because the concentration of these T cells changes quickly after gluten exposure.[130] After the administration of gluten peptides in patients treated for coeliac disease, the concentrations of at least 15 plasma cytokines, in particular IL-2, IL-8, and IL-10, increased within a few hours.[131] IL-2 is the earliest, most sensitive marker of acute gluten exposure, and is consistently increased only 4 h after a 3–6 g gluten challenge.[132]

Monitoring adherence to a gluten-free diet

A reliable and non-invasive tool for monitoring adherence to a gluten-free diet is still lacking. New biomarkers of gluten exposure in people on a gluten-free

	Trial number	Clinical stage	Comments
Microbial (*Aspergillus niger*) prolyl endoprotease enzyme cleaving proline-rich regions in gluten			
AN-PEP	NCT00810654	Phase 2 completed	Insufficient evidence of efficacy
AN-PEP	NCT04788797	Phase 3 not done; phase 4 study ongoing	Commercially available as food supplement (eg, GliadinX)
Barley-derived, glutamine-specific cysteine and microbial (*Sphingomonas capsulata*) prolyl endoproteases (single or combination)			
EP-B2 (ALV001); SC-PEP (ALV002)	..	Phase 1 completed	Modest degrading effect; no clinical data available
Latiglutinase IMGX003 (EP-B2 + SC-PEP; previously ALV003, now synthetic derivate)	NCT01917630	Phase 2 completed	No effect on symptoms and intestinal histology in treated coeliac disease when compared with placebo;[145] symptomatic improvement restricted to seropositive patients[146]
Engineered computationally designed enzyme			
TAK-062 (formerly kuma062)	..	Phase 1 completed	Rapid degradation of gluten;[147] no clinical data available yet
Tight junction modulator			
Larazotide acetate (formerly AT-1001)	NCT01396213 and NCT00492960	Phase 2b completed	Improvement of coeliac disease symptoms on a gluten-free diet;[148] no effect on permeability
Larazotide acetate (formerly AT-1001)	NCT03569007	Phase 3 ongoing	..
TG2 blocker			
ZED1227	2017-002241-30	Phase 2a completed	Attenuated gluten-induced duodenal mucosal damage and possible improvement of coeliac disease symptoms on a gluten-free diet; no assessment of long-term side-effects[149]
ZED1227	2020-004612-97	Phase 2b ongoing	..
Anti-IL-15 monoclonal antibody			
PRV-015 (formerly AMG 714)	NCT02637141	Phase 2a completed	Did not prevent mucosal damage induced by gluten challenge; improvement of diarrhoea; some side effects[150]
PRV-015 (formerly AMG 714)	NCT04424927	Phase 2b ongoing	Ongoing study in non-responsive coeliac disease
Restoration of oral tolerance to gluten using nanoparticle technology			
TAK-101 (TIMP-GLIA)	NCT03486990	Phase 1 completed	No serious adverse effects reported[151]
TAK-101 (TIMP-GLIA)	NCT03738475	Phase 2a completed	~90% reduction in gliadin-specific IFNγ-producing cells and improved histology after gluten challenge[151]
TAK-101 (TIMP-GLIA)	NCT04530123	Phase 2b not yet recruiting	..

Table 2: **Novel pharmacological therapies for coeliac disease**

diet are currently under investigation (eg, serum alkilresorcinol,[133] intestinal fatty acid binding protein,[134] citrullin,[135] and miRNAs[136]). Measurement of gliadin immunogenic peptides in stool or urine has been introduced to detect recent gluten ingestion in patients on a gluten-free diet.[137,138] Several studies have shown that this assay is more sensitive than others for the detection of inadvertent gluten ingestion[139] and to predict mucosal healing.[140] However, the accuracy of gliadin immunogenic peptide analysis is currently under scrutiny, as data have shown a high rate of false positive and false negative results.[141]

New treatment strategies

The selection of wheat varieties that contain no or reduced immunogenic gluten proteins could improve the quality of life of people on a gluten-free diet and possibly introduce new methods for the primary prevention of coeliac disease. Conventional mutation and breeding methods have not been successful, but new techniques of gene silencing (eg, RNA interference) or gene editing (eg, CRISPR-Cas9) represent an interesting new approach.[142,143] A pilot study showed that a low-gluten RNA interference wheat line did not elicit an immune response after a short-term oral challenge in patients with treated coeliac disease.[144]

Recognition that a gluten-free diet is an imperfect therapy, combined with a detailed insight into the major pathogenesis steps in coeliac disease (figure 1), has led to considerable interest in the development of pharmacological agents. The main candidates that are currently in advanced clinical drug development include gluten-degrading enzymes,[145–147] tight junction modulators,[148] specific inhibitors of TG2,[149] antibodies against key cytokines (eg, IL-15),[150] and strategies to induce tolerance to gluten.[151] In table 2, we show the stage of clinical development, the target mechanisms, and the results achieved by the most promising pharmacological therapies according to our evaluation.[145–151] A 2021 review dealt with this topic in detail.[152] One or more of these therapies are expected to be used as adjuncts to, rather than replacements for, a gluten-free diet, and so decrease complications due to accidental chronic gluten contamination.

Conclusions

Coeliac disease is a common disorder in most countries. From a pathophysiological perspective, coeliac disease is a unique model of interaction between a known external dietary antigen (gluten) and other environmental factors with an individual's genetic and metabolic make-up, leading to the development of an autoimmune process. The availability of specific biomarkers of coeliac disease, coupled with the small intestinal biopsy, has improved the detection of a disease that shows great variability in clinical manifestations. Patients with complicated cases of coeliac disease, particularly those with refractory coeliac disease or enteropathy-associated T-cell lymphoma, require in-depth evaluation in specialised centres. A gluten-free diet is the treatment of choice for coeliac disease; however, new dietary and pharmacological therapies that could improve the health and the quality of life of patients with coeliac disease are currently under investigation.

Contributors

CC conceptualised, administered, and supervised the project. All authors searched the literature, selected articles, and wrote, reviewed, and edited the manuscript.

Declaration of interests
CC serves as a scientific consultant for Dr Schaer Food and has received grants from Noos; EFV holds a Canada Research Chair, is funded by the Canadian Institutes of Health Research grant PJT-168840, serves on the advisory board of the Biocodex Microbiota Foundation, and receives grants from Gilead Sciences, Kalyoppe, and the Biocodex Microbiota Foundation, outside of the submitted work. All other authors declare no competing interests.

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