Coeliac disease

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Abstract | Coeliac disease is an immune-mediated enteropathy against dietary gluten present in wheat, rye and barley and is one of the most common lifelong food-related disorders worldwide. Coeliac disease is also considered to be a systemic disorder characterized by a variable combination of gluten-related signs and symptoms and disease-specific antibodies in addition to enteropathy. The ingestion of gluten leads to the generation of harmful gluten peptides, which, in predisposed individuals, can induce adaptive and innate immune responses. The clinical presentation is extremely variable; patients may have severe gastrointestinal symptoms and malabsorption, extraintestinal symptoms or have no symptoms at all. Owing to the multifaceted clinical presentation, diagnosis remains a challenge and coeliac disease is heavily underdiagnosed. The diagnosis of coeliac disease is achieved by combining coeliac disease serology and small intestinal mucosal histology during a gluten-containing diet. Currently, the only effective treatment for coeliac disease is a lifelong strict gluten-free diet; however, the diet is restrictive and gluten is difficult to avoid. Optimizing diagnosis and care in coeliac disease requires continuous research and education of both patients and health-care professionals.

Coeliac disease is generally defined as a chronic immune-mediated enteropathy driven by dietary gluten, which is present in grains including wheat, rye and barley[1]. In addition to the ingestion of gluten, the development of coeliac disease requires genetic susceptibility and the disorder almost exclusively occurs in individuals with the human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 haplotypes[2]. However, as only a fraction of HLA-DQ2-positive and/or HLA-DQ8-positive individuals consuming gluten develop the disorder, it is likely that other genetic and/or environmental factors play a role in the disease onset. Coeliac disease is more prevalent in females, may develop at any age after the introduction of dietary gluten and can affect almost any ethnicity[3].

Coeliac disease primarily affects the small intestinal mucosa, and the ingestion of gluten by predisposed individuals results in the development of a mucosal immune response, including an increased intraepithelial lymphocyte (IEL) count, and such immune responses eventually lead to structural changes in the gut, characterized by villous atrophy (blunting or flattening of the villi) and crypt hyperplasia (elongation of the crypts)[1]. Coeliac-disease-associated enteropathy is often accompanied by gastrointestinal symptoms and signs of malabsorption. However, the clinical manifestations of coeliac disease are broad, and in addition to gastrointestinal problems, patients may experience various extraintestinal symptoms or even remain asymptomatic[4,5]. Such clinical heterogeneity complicates the diagnostic work-up, which may delay diagnosis or allow the disease to remain unrecognized. Unsurprisingly, coeliac disease is heavily underdiagnosed worldwide[3]. Moreover, untreated coeliac disease may be associated with severe health complications, increased morbidity and mortality, considerable burdens to health-care systems and decreased patient quality of life (QOL)[6–8]. Currently, the only effective treatment is a lifelong strict gluten-free diet, which results in the recovery of mucosal damage in the small intestine along with improvements to clinical symptoms[9]. Evidence exists that suggests that early treatment with a gluten-free diet might also prevent the development of complications associated with coeliac disease[7,10].

In this Primer, we discuss the epidemiology, pathophysiology, diagnosis, screening and prevention, as well as the management and QOL issues associated with this gluten-induced disease entity, coeliac disease.

Epidemiology

Prevalence and incidence

Before the 1990s, coeliac disease was considered an uncommon disorder that mainly affected children and was limited to western Europe. Improved diagnostics, including the implementation of coeliac-disease-specific serological tests (transglutaminase 2 antibodies (TG2-Abs) and endomysial antibodies (EmAs); see below), have led to increased recognition of coeliac disease, in addition to making it possible to estimate the true prevalence of the disorder in the general population[11–13].

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A 2015 systematic review of screening studies indicates that coeliac disease is now a major public health problem, as the pooled global seroprevalence measured by TG2-Abs or EmAs in the general population can be as high as 1.4% (95% CI: 1.1–1.7%)[3]. Most screening studies have been performed in Europe, and the findings show variation between different countries (FIG. 1). High-prevalence countries in Europe include Sweden, Finland, Turkey, the United Kingdom, Italy, the Czech Republic and Portugal, whereas in Russia, Estonia, Iceland, Poland and Switzerland, coeliac disease is less common. Altogether, coeliac disease has been estimated to affect ~1% of the European population[14–16]. Similar studies performed in areas with high levels of European ancestry such as North America, South America and Oceania have yielded prevalence figures comparable to those in Europe[17–19]. Population-based data on the prevalence of coeliac disease have also been reported from India and some countries in middle-eastern Asia and Africa[20,21] (FIG. 1). Of the world's top ten most populated countries, population-based prevalence data on coeliac disease are available from India, the United States, Brazil and Russia but are largely lacking from China, Indonesia, Pakistan, Nigeria, Bangladesh and Japan[22,23]. Taken together, coeliac disease is now known to affect people worldwide. In some geographical areas such as Far East Asia and sub-Saharan Africa, the disease is still rare, although large epidemiological studies from these sites are still lacking.

Most population-based epidemiological studies on coeliac disease prevalence are based on serological data, and the diagnosis of coeliac disease in all seropositive patients has not been confirmed by invasive small intestinal mucosal biopsies. Therefore, the global pooled prevalence of biopsy-proven coeliac disease, which is 0.7% (95% CI: 0.5–0.9%), is lower than the seroprevalence[3]. Interestingly, on the basis of serological data, the prevalence of coeliac disease is increasing over time. Two studies reported a 2-fold increase in seroprevalence of coeliac disease over two decades[24,25], and a further study with ~50 years of follow-up indicated a 4–4.5-fold increase over time[26]. A recent meta-analysis also confirmed a parallel increase in the prevalence of biopsy-proven coeliac disease[3].

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Although the prevalence of coeliac disease in the general population has increased, the disorder still remains heavily unrecognized. The seroprevalence figures of coeliac disease suggest that for each clinically diagnosed patient with coeliac disease, an average of five to ten seropositive individuals remain undiagnosed, usually because of atypical, minimal or even absent symptoms[15–17,24]. The diagnostic rate mostly depends on the level of physician awareness, and with an active search for patients, a clinical prevalence for coeliac disease of up to 0.7% may be reached[27], which still clearly falls behind the corresponding seroprevalence[28].

Risk factors

The factors that explain the varying and increasing prevalence of coeliac disease remain obscure. Variation exists in the frequency of the coeliac-disease-predisposing HLA haplotypes worldwide, but the prevalence of coeliac disease also varies in populations with a similar HLA background[1]. Such variance may be explained by environmental factors rather than genetics. Potential environmental factors include the consumption of gluten-containing cereals, infection in the early years of life and lower economic status as well as an inferior hygienic environment[29–31]. When considering the prevalence figures of coeliac disease, it is important to note that the age of the individuals in the study population may affect the results[12,28,32]. Also noteworthy is that the prevalence of coeliac disease varies according to sex, being more common in female individuals[3]. Finally, the presence of certain disorders is associated with an increased risk of developing coeliac disease[33,34] (BOX 1).

Mechanisms/pathophysiology

The driver antigen: dietary gluten

Gluten commonly refers to the main storage proteins, the prolamins, of wheat, rye and barley, which are harmful for patients with coeliac disease. As a major structural component of these cereals, gluten is also essential for dough formation owing to its unique viscoelastic properties[35,36]. Wheat gluten is a complex mixture of alcohol-soluble gliadins (divided up into α-gliadins, γ-gliadins and ω-gliadins) and alcohol-insoluble glutenin (divided into high-molecular-mass and low-molecular-mass glutenins) (FIG. 2). Gliadins and glutenins are particularly rich in proline and glutamine amino acids; the high proline content renders these proteins fairly resistant to proteolytic processing by gastric and pancreatic enzymes as well as mammalian small intestinal brush-border membrane enzymes[37,38] (FIG. 3). As a result, various long gliadin peptides are generated in the gastrointestinal tract that are capable of activating the detrimental immune responses seen in patients with coeliac disease. Of these, the most extensively studied is the '33mer', which contains 6 partly overlapping, potentially harmful epitopes and is frequently described as the most important coeliac immunogenic sequence within gluten[37]. In addition to triggering an immune response in patients with coeliac disease, the undigested peptides become available for intestinal bacterial gluten metabolism as they constitute an attractive source of energy, which may affect the intestinal microbiota (discussed below)[39].

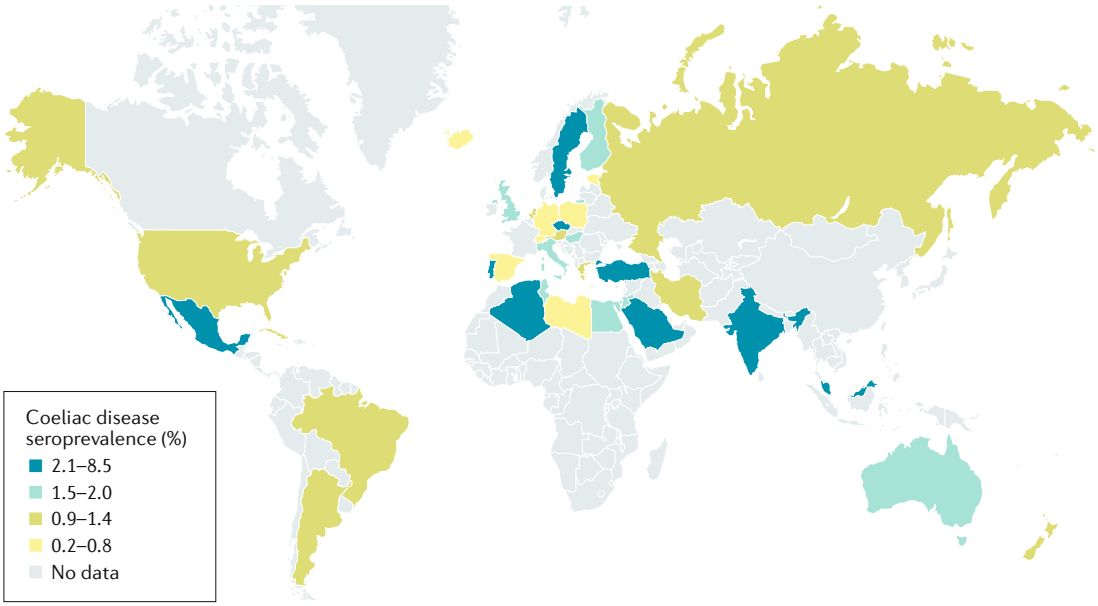

Fig. 1 | **The global seroprevalence of coeliac disease.** The map shows coeliac disease seroprevalence as determined by positive serum transglutaminase 2 and/or endomysial autoantibodies. More intensive colour indicates higher prevalence. Countries where no studies on the prevalence of coeliac disease have been conducted are presented without colour[3].

Avena spp. (oats) are taxonomically closely related to Triticeae cereals (wheat, rye and barley) (FIG. 2b), but the corresponding prolamin content in oats (that is, avenin) is substantially lower[36]. Moreover, there are fewer proline and glutamine residues in avenins than in prolamins, which are harmful to patients with coeliac disease[36]. These features probably account for the safety of dietary oats for the majority of patients with coeliac disease, as discussed later[40].

Genetics

The development of coeliac disease requires both the ingestion of gluten and genetic predisposition. The genetic susceptibility of coeliac disease is evidenced by the fact that the average prevalence of coeliac disease among first-degree relatives of patients exceeds that of the general population, being ~8%[33]. Of the genetic factors identified to date, the HLA-DQ haplotypes HLA-DQ2 and HLA-DQ8 impart the strongest risk, and these variants have been estimated to contribute ~25–40% of the genetic risk[41–43]. Notably, ~40% of the North American and European populations also carry these haplotypes, and the great majority of them never develop coeliac disease; as such, HLA-DQ2 or HLA-DQ8 is necessary but not sufficient for coeliac disease to develop.

HLA-DQ2 and HLA-DQ8 are dimeric class II major histocompatibility complex molecules expressed on the surface of antigen-presenting cells (APCs); they consist of an α-chain and a β-chain encoded by specific variants of the *HLA-DQA1* and *HLA-DQB1* genes, respectively. HLA-DQ2 is encoded by the *HLADQA1*05:01* and *HLADQB1*02:01* (also called *HLA-DQ2.5*) alleles, whereas HLA-DQ8 is encoded by the *HLADQA1*03* and *HLADQB1*03:02* alleles. More than 90% of patients with coeliac disease are HLA-DQ2 positive and almost all of the rest carry HLA-DQ8. Other HLA-DQ variants that are rarely associated with coeliac disease are HLA-DQ2.2 and HLA-DQ7.5 (REFS[2,44]). Interestingly, the gene dosage of HLA-DQ is associated with the risk of coeliac disease; accordingly, individuals homozygous for *HLA-DQ2.5* have the highest risk of the disease[45].

In addition to HLA, 42 non-HLA regions have been associated with coeliac disease[41,42,46,47]; interestingly, many of these loci harbour genes in particular pathways enriched in coeliac disease (TABLE 1). However, the risk effect of these non-HLA variants is fairly modest, and they have been estimated to account for ~15% of the genetic coeliac disease risk[41,42,46,47]. Collectively, all the genetic variants identified to date including HLA explain only ~50% of the genetic variance in coeliac disease, and additional hereditary factors, may potentially exist that await identification.

Immune mechanisms

Gluten peptides that result from incomplete digestion in the gut lumen gain access to the lamina propria through the epithelial barrier via the transcellular or paracellular route. In patients with coeliac disease, these harmful peptides launch the activation of both adaptive and innate immune responses[1,38].

Generation of gluten-specific T cell responses. The adaptive immune response in coeliac disease is characterized by small intestinal mucosal gluten-specific $CD4^+$ T cell responses[48,49] and antibodies towards wheat gliadin and the enzyme TG2 (encoded by *TGM2*) (FIG. 4). In 1997, the discovery of TG2 as a major autoantigen[50] enabled better understanding of coeliac disease pathogenesis and the development of highly specific serological assays for diagnosis (discussed below). Native gluten peptides contain the amino acid glutamine at key positions, and these can be selectively deamidated by TG2 (REF.[51]).

Box 1 | **Risk groups and associated disorders**

- First-degree relative with coeliac disease (2–20%)
- Type 1 diabetes mellitus (3–12%)
- Selective IgA deficiency (2–8%)
- Autoimmune thyroiditis (4–7%)
- Sjögren syndrome (4–12%)
- Down syndrome (5–12%)
- Addison disease (5%)
- Turner syndrome (3–4%)
- Williams syndrome (2–4%)

Percentages in parentheses indicate the prevalence of coeliac disease in each group. Data are from REFS[33,34].

This biochemical modification leads to glutamine residues being replaced by glutamic acid, which increases the binding affinity of gluten peptides to HLA-DQ2 or HLA-DQ8 molecules on APCs[52] (FIG. 3b,c). The HLA-bound gliadin peptides are further presented to gluten-specific CD4$^+$ T helper cells[48,49].

Historically, pro-inflammatory dendritic cells, which readily express HLA-DQ molecules, have been considered as the key APCs in coeliac disease. However, it has been proposed that gliadin-specific and TG2-specific B cells might exert similar functions[1,44]. Gluten-specific CD4$^+$ T cells recognize the HLA-presented gliadin peptides by cell surface T cell receptors (TCRs). Interestingly, gluten-specific T cells carrying a TCR with distinct gliadin epitope recognition modes have been identified only in patients with coeliac disease[53]. As TCRs are generated in a random process, high-affinity TCRs specific for gliadin may be produced only in a minority of HLA-DQ2-positive or HLA-DQ8-positive individuals, thereby providing a potential explanation why only a subset of these individuals develop coeliac disease[53]. Once activated, the gluten-specific CD4$^+$ T cells secrete various cytokines, including IFNγ and IL-21 (REF.[54]), thereby creating an inflammatory milieu in the small intestinal lamina propria that is conducive to tissue damage (FIG. 4).

Generation of autoantibodies. In addition to contributing to the pro-inflammatory cytokine network in the small intestine, gluten-specific CD4$^+$ cells have been implicated in the generation of the antibody responses that are characteristic for coeliac disease (FIG. 4). After encountering HLA-bound gliadin on an APC and becoming activated, a CD4$^+$ cell might provide help signals to both gluten-specific and TG2-specific B cells, thereby promoting their activation and differentiation into plasma cells that secrete antibodies against deamidated gliadin peptides (DGPs) and TG2 (REF.[55]). Both antibody populations can be detected in the circulation of patients with coeliac disease; in addition, TG2-Abs are present in the small intestinal mucosa, deposited at the subepithelial basement membrane and around mucosal blood vessels[56]. Historically, both the circulating and intestinally deposited TG2-Abs were thought to be produced in the small intestine by local plasma cells. However, recent data indicate that serum TG2-Abs are secreted by plasma cells that are clonally related to intestinal TG2-specific plasma cells but reside outside the gut[57,58]. Regardless of their origin, both gliadin antibodies and TG2-Abs have been proposed to play a part in the pathogenesis of coeliac disease. For example, these antibodies are thought to increase the permeability of the epithelial barrier, allowing gliadin peptides to access the lamina propria and affecting epithelial cell biology[59]. Interestingly, autoantibody responses targeting other members of the transglutaminase family have been associated with specific manifestations of coeliac disease. Antibodies targeting TG3 and TG6, which occur in the context of dermatitis herpetiformis and gluten ataxia, respectively, have been considered as potential contributors in the pathogenesis of these extraintestinal manifestations[59].

Cytokines in the intestinal mucosal immune response. A subset of the cytokines including IFNγ and IL-21 produced by gluten-specific CD4$^+$ T cells as a result of adaptive immune activation serve as links between adaptive and innate immunity[60]. In coeliac disease, innate immune responses are hallmarked by increased mucosal expression of IL-15, IL-18 and type I interferons, which are thought to be produced by stressed intestinal epithelial cells and/or dendritic cells[1,61,62]. Of these cytokines, IL-15 is known to contribute to disease development in multiple ways — for example, by inhibiting the regulatory effects of regulatory CD4$^+$ T (T_{reg}) cells, thus promoting loss of oral tolerance and immune regulation, and by licensing IELs to kill intestinal epithelial cells[63] (FIG. 5).

Intraepithelial lymphocytes. IELs are a heterogeneous population of T cells that patrol the mucosal barrier and can exert effector functions without antigen-specific priming; they interact directly with intestinal epithelial cells and can induce apoptosis when required. In coeliac disease, the number of IELs is increased and their amount correlates with the severity of mucosal atrophy[64]. Interestingly, IELs in the mucosa of patients with coeliac disease are not driven by TCR-dependent antigens[63]. Instead, these cells display cytotoxic transformation, which is central to the induction of intestinal epithelial cell apoptosis driven by mechanisms involving Fas ligand[65], perforin, granzyme B[66] and type II integral membrane protein NKG2D[67]. The latter, NKG2D, is an activating receptor on the surface of IELs and its expression is increased in coeliac disease in response to IL-15 (REF.[67]). The main ligand for NKG2D expressed on intestinal epithelial cells is an unconventional stress-induced HLA class I molecule MICA, the expression of which is upregulated in coeliac disease. The interaction of NKG2D and MICA directly induces intestinal epithelial cell death[68] along with the aforementioned apoptotic pathways. These mechanisms contribute to the development of small intestinal mucosal villous atrophy (FIG. 5), but the relative contributions of each pathway in the induction of intestinal epithelial cell death in coeliac disease still remain unclear.

Innate immune activation. Researchers are keen to understand the upstream mechanisms that lead to the dysregulated production of IL-15 and the activation of the innate response in coeliac disease; as such, many different candidates have been proposed. These include

distinct gluten peptides such as P31-43, which was suggested to induce epithelial cell stress[68] and pro-inflammatory events[69], although this remains controversial. In addition, enteric infections, including viral and bacterial pathogens (for example, *Campylobacter*)[70], could directly induce the release of innate immune cytokines and cause intestinal epithelial cell stress[71] or programme a pro-inflammatory signature in APCs[72]. Moreover, non-gluten proteins such as α-amylase-trypsin inhibitors (ATIs; pest-resistant endogenous molecules), present in wheat, may be able to induce innate immune responses via Toll-like receptor 4 (TLR4)-dependent mechanisms[73]. However, the clinical relevance of ATIs in coeliac disease remains to be determined. Finally, post-infection or inflammatory changes in the microbiota may induce imbalances that promote intestinal epithelial cell stress and innate immune activation[74]. All in all, it is likely that more than one of these factors acting through different pathways are involved in the pathogenesis of coeliac disease (FIG. 5).

Environmental factors

Dietary gluten is the most important environmental factor involved in the development of coeliac disease. However, the great majority of humans are exposed to gluten, and only a subset of individuals who carry the genetic risk alleles will develop the disease. Therefore, other environmental factors have been suggested to be involved. Of these, microorganisms have been the target of recent research.

Microorganisms. In 2004, the intestinal microbiota was first linked to coeliac disease when a study described the presence of rod-shaped bacteria associated with the mucosa of patients with active or treated coeliac disease[75]. A follow-up study determined increases in the abundance of *Clostridium*, *Prevotella* and *Actinomyces* species in patients with coeliac disease[76]. More recently, several studies report intestinal dysbiosis (that is, a state caused when the intestinal microbiota becomes unbalanced) in patients with coeliac disease[77,78] and an increased prevalence of specific microbial virulence genes isolated from patient samples[79]. In addition to bacteria, viruses, including rotavirus and reovirus, have been implicated in the onset of coeliac disease[30,73,80]. Results obtained from in vitro studies and animal experiments performed with different mouse models relevant for coeliac disease support the role of microorganisms, including viruses, in the pathogenesis of coeliac disease[39,73], but direct causality remains to be proved. Evidence suggests that some microorganisms (for example, *Helicobacter pylori* or cytomegalovirus) might actually protect individuals from the development of coeliac disease through unclear mechanisms[81].

The concept that microorganisms play a part in the development of coeliac disease is also supported by epidemiological studies. For example, a recent birth cohort study showed that gastrointestinal infections generally increase the risk of developing coeliac disease[30], although this was not verified in another prospective cohort study[82]. An indirect role of dysbiosis in coeliac disease pathogenesis has also been addressed in epidemiological studies that focus on factors that might be involved in modulating the intestinal microbiota. For example, there are contradictory reports on associations of coeliac disease with birth by elected caesarean section (which affects the colonization of the infant intestinal microbiota)[83,84], repeated antibiotic exposure[85,86] or therapy with proton pump inhibitors[87]. Notably, however, some studies have only investigated patients with clinically diagnosed coeliac disease, which might have an effect on the findings.

Other environmental factors. Other environmental factors have also been implicated in the development of coeliac disease, such as early-life feeding practices. This association was first recognized owing to the Swedish epidemic of coeliac disease, which occurred after changes in infant feeding practices in 1984–1996 (REF.[88]). During this time period, the prevailing feeding practice was to postpone the introduction of dietary gluten from 4–6 months of age to an age when breastfeeding was often discontinued. At the same time, the gluten content of commercially available milk cereal drinks and porridges was increased, which may have contributed to the high prevalence of coeliac disease. After recognition of the epidemic, parents were recommended to introduce gluten gradually, preferably while

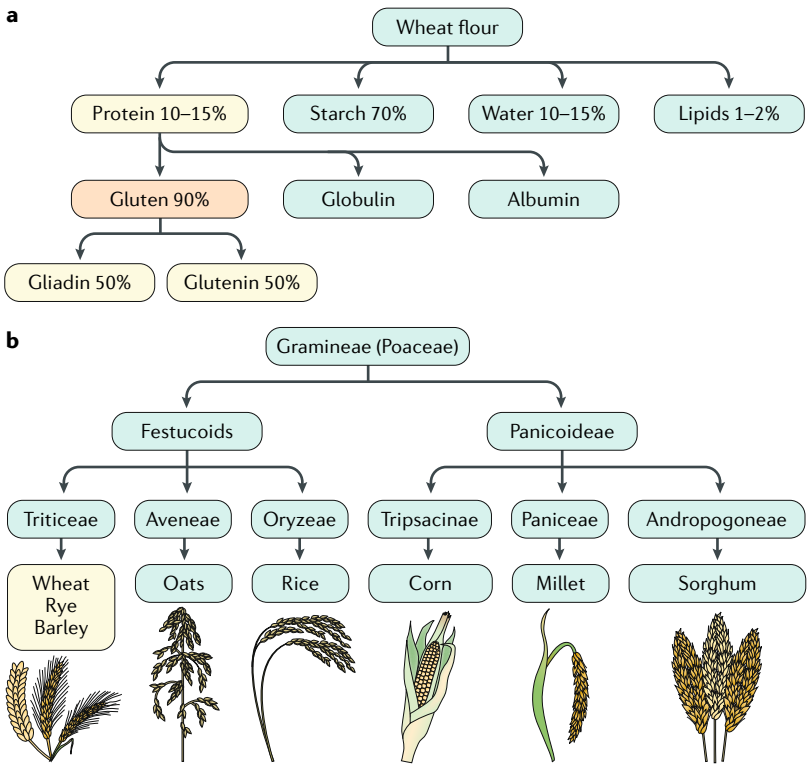

Fig. 2 | **Cereals harmful for patients with coeliac disease. a** | The content of wheat flour prepared from the grain endosperm. Wheat gluten proteins that are toxic to patients with coeliac disease are the major storage proteins of the grain and can be further divided into gliadins and glutenins. The harmfulness of gluten in coeliac disease is mostly related to gliadins, although evidence suggests that glutenins are also toxic for patients. Gliadins are monomeric and can be separated into α-gliadins, γ-gliadins and ω-gliadins on the basis of their amino acid composition. Yellow and/or orange indicate fractions that are harmful for patients with coeliac disease. **b** | Taxonomic classification of harmful species (Triticeae: wheat, rye and barley) and presumably non-harmful species of the cereals Festucoids and Panicoideae for patients with coeliac disease. Harmful cereals are indicated in yellow.

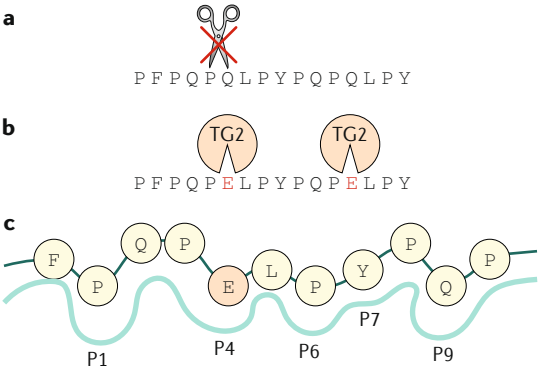

Fig. 3 | **Gluten peptide presentation by HLA-DQ2.** **a** | Gluten peptides contain a considerable number of proline residues, which render the peptides resistant to proteolytic degradation by gastrointestinal enzymes. **b** | The coeliac disease autoantigen transglutaminase 2 (TG2) converts distinct glutamine residues in gluten peptides to glutamic acid in a deamidation reaction. **c** | Deamidation enhances the binding of gluten peptides by increasing their affinity to human leukocyte antigen (HLA)-DQ2 on antigen-presenting cells. Figure adapted from REF.[38], Springer Nature Limited.

still breastfeeding, and the gluten content was reduced in commercially available infant foods, factors which have been hypothesized to have contributed to the end of the epidemic[88]. However, recent meta-analyses have not shown an effect of breastfeeding on the risk of coeliac disease[89]. Furthermore, according to large prospective studies, the timing of gluten introduction in a genetically high-risk group is not associated with coeliac disease[82,90]. Large doses of gluten in infancy were linked with increased disease risk in one study[31]; however, contradictory findings have also been reported[91], therefore further research is required.

Additional environmental factors may be involved in coeliac disease. Smoking, which has been implicated in inflammatory bowel disease, has also been suggested to modulate the development of coeliac disease. It has been reported that the diagnosis of coeliac disease is less frequent in smokers than in non-smokers[92], but it is unclear whether this relates to the possibility of smoking masking the clinical manifestations of coeliac disease rather than preventing it. Taken together, the development of coeliac disease requires a complex interplay between the host, dietary gluten and other environmental factors that is currently far from being fully understood.

Diagnosis, screening and prevention

Clinical signs and symptoms

Coeliac disease is heavily underdiagnosed, partially owing to the variable clinical signs and symptoms (FIG. 6). Over time, the most common clinical presentation of coeliac disease has shifted from symptoms of malabsorption in childhood to milder multi-organ manifestations that present in both childhood and adulthood, reflecting the systemic nature of the disease[4,5,34,93]. Abdominal symptoms are still common, but patients often experience only mild symptoms, including loose stools, abdominal discomfort or flatulence, or may even have no gastrointestinal problems at all. Improved diagnostic methods and increased clinician knowledge of coeliac disease probably explain most of the changes seen in the clinical presentation of coeliac disease[5].

Importantly, extraintestinal symptoms comprise a substantial proportion of the clinical manifestations of coeliac disease (FIG. 6). Dermatitis herpetiformis, which is present in up to 10% of adults with coeliac disease, is the best characterized extraintestinal manifestation and is defined by itching blisters, particularly on the elbows, knees, buttocks and scalp[94]. Other extraintestinal manifestations, such as arthritis, neurological symptoms (for example, peripheral neuropathy) and anaemia, are also frequent[4,5,34,95]. Owing to this diverse presentation and the lack of awareness among health-care professionals, diagnostic delays can reach up to 10 years in resource-rich countries[6,96]. In resource-poor settings, this delay might be considerably longer, although data on this are scant. For these reasons, the key to coeliac disease diagnosis is augmented awareness of the wide spectrum of symptoms (FIG. 6). In addition, coeliac disease may be asymptomatic, in which case patients can be found by active screening in risk groups (for example, in the family members of patients and in patients with autoimmune disorders such as type 1 diabetes mellitus)[33,34] (BOX 1).

Coeliac disease serology

A combination of coeliac disease serology testing and the determination of small intestinal mucosal morphology forms the basis for the diagnosis of coeliac disease. If coeliac disease is suspected, various serological tests, including EmAs (antibodies specific for TG2 in the endomysium, which is a form of perivascular connective tissue) and TG2-Ab assays, can support the diagnostic procedure in selecting patients for endoscopy, upon which diagnostic duodenal biopsy samples are taken. EmAs and TG2-Abs have excellent sensitivity (90–100%) and close to 100% specificity for coeliac disease[97–99]. EmA testing has been regarded as the gold-standard method to detect coeliac disease autoantibodies. However, as this test is based on indirect immunofluorescence, it is subjective, low throughput, laborious and expensive. By contrast, the operator-independent enzyme-linked immunosorbent assay (ELISA) and radiobinding assay for TG2-Abs can be performed on automated instruments and has become more popular in clinical practice. However, the performance of commercial tests for TG2-Abs may vary depending on the quality of the TG2 antigen (for example, the conformation of the molecule), and, as such, some tests may yield false-negative and false-positive results. In particular, low TG2-Ab values are sometimes associated with autoimmune diseases such as type 1 diabetes mellitus and infectious diseases in general[100].

First-generation anti-gliadin antibody assays, which use native gliadin peptides as an antigen, are considered inaccurate, and, as such, they are no longer recommended for the diagnosis of coeliac disease. More recently developed tests use DGPs as an antigen to detect DGP-specific antibodies; these tests may recognize some patients with coeliac disease that are not detected by the established EmA and TG2-Ab tests[101,102]. However, tests

for DGP antibodies are not yet in common usage in clinical practice. Notably, the most accurate serological tests for coeliac disease are for IgA isotype EmAs and TG2-Abs, and only in the case of selective IgA deficiency are IgG isotype antibody tests needed[102,103]. In addition, ~10% of patients with coeliac disease are seronegative[101] and thus cannot be identified by any of the current serological methods[104]. In seronegative cases, the diagnosis is based on detection of small intestinal mucosal damage, which, similar to symptoms, responds to the gluten-free diet[104].

Table 1 | **Non-HLA regions associated with coeliac disease**

Chromosomal region	Candidate genes[a]	Pathway enriched for target genes
2q12.1	*IL18R1* and *IL18RAP*	• Inflammatory bowel disease • Cytokine–cytokine receptor activation
2q32.2–32.3	*STAT4*	• Inflammatory bowel disease • JAK–STAT signalling pathway
2q33.2	*CD28*	• Cell adhesion molecules • T cell receptor signalling • Autoimmune thyroid disease • Intestinal immune network for IgA production • Allograft rejection • Type 1 diabetes mellitus
	CTLA4	• Cell adhesion molecules • T cell receptor signalling • Autoimmune thyroid disease
	ICOS	• Cell adhesion molecules • T cell receptor signalling • Intestinal immune network for IgA production
3p22.3	*CCR4*	• Chemokine signalling pathway • Cytokine–cytokine receptor activation
3p21.31	*CCR1*, *CCR2* and *CCR3*	• Chemokine signalling pathway • Cytokine–cytokine receptor activation
3q25.33	*IL12A*	• JAK–STAT signalling pathway • Allograft rejection • Type 1 diabetes mellitus • Inflammatory bowel disease • Cytokine–cytokine receptor activation
4q27	*IL2*	• JAK–STAT signalling pathway • Inflammatory bowel disease • Cytokine–cytokine receptor activation • Allograft rejection • Type 1 diabetes mellitus • Autoimmune thyroid disease • Intestinal immune network for IgA production • T cell receptor signalling
	IL21	• JAK–STAT signalling pathway • Inflammatory bowel disease • Cytokine–cytokine receptor activation
6q23.3	*TNFAIP3*	NF-κB signalling
7p14.1	*ELMO1*	Chemokine signalling pathway
10p15.1	*PRKCQ*	• NF-κB signalling • T cell receptor signalling
16p13.13	*SOCS1*	JAK–STAT signalling pathway
21q22.3	*ICOSLG*	• Cell adhesion molecules • Intestinal immune network for IgA production
Xq28	*IRAK1*	NF-κB signalling

HLA, human leukocyte antigen; JAK, Janus kinase; NF-κB, nuclear factor-κB; STAT, signal transducer and activator of transcription. [a]Candidate genes within each region involved in particular pathways enriched in coeliac disease. Data are from REFS[41–43,46,47].

Currently, there are several commercial point-of-care rapid tests available for the detection of anti-DGPs and TG2-Abs[16,105]. These tests offer immediate results in a primary care setting and could be useful in resource-poor settings with limited health-care personnel and laboratory resources. However, data on the performance of these rapid tests are still limited[105], and further studies are needed before recommending the use of these tests in everyday clinical practice.

Small intestine biopsy

In individuals who are seropositive for coeliac-disease-specific autoantibodies or when the clinical suspicion of coeliac disease is high owing to severe symptoms, further diagnostic procedures are implemented. The diagnosis of coeliac disease is historically based on the demonstration of small bowel mucosal villous atrophy, intraepithelial lymphocytosis and crypt hyperplasia in biopsy samples obtained upon gastroscopy[1,34]. However, there are several challenges in the biopsy-based diagnostic method. First, comparable villous atrophy can occur upon treatment with certain medications, during viral and bacterial infections and as a consequence of autoimmune enteropathy (BOX 2). As such, villous atrophy per se is not a specific pathognomic finding for coeliac disease[104]. Second, in the context of coeliac disease, villous atrophy is the end stage of the gradual destruction of the intestinal villi and may take years or even decades to develop (FIG. 7). However, patients may already experience various symptoms before development of the overt small intestinal lesion[106,107]. Moreover, patients have been shown to benefit from a gluten-free diet even at an early phase in the development of disease, which supports the concept that coeliac disease extends beyond villous atrophy[106,107]. Such a condition with positive serum coeliac-disease-specific antibodies but normal small intestinal mucosal morphology is often termed as potential coeliac disease. There is no consensus whether all such cases, especially asymptomatic ones, should be treated with a gluten-free diet or monitored during continued gluten consumption[106]. Third, the mucosal damage in coeliac disease may be patchy and thus detectable only in specific areas of the small intestine (for example, the duodenal bulb)[108]. However, the determination of intestinal morphology from bulb biopsy samples is particularly challenging as biopsy samples are often of poor quality and may contain many Brunner's glands, which are racemose glands in the submucosal layer of the duodenum that secrete alkaline mucus and a potent proteolytic enzyme[108]. Regardless of biopsy site, the interpretation of mucosal histology should be done from high-quality, well-oriented and correctly cut samples to avoid misclassification and erroneous diagnosis[109,110].

Additional diagnostic tools

In diagnostically challenging cases, such as seronegative patients or patients with borderline villous damage, additional non-conventional tools are needed to reliably identify patients with coeliac disease. HLA typing is useful for the exclusion of coeliac disease, as the

disorder is highly unlikely to arise in individuals who are not carrying either HLA-DQ2 or HLA-DQ8 (REF.[111]). Quantification of inflammatory cells in the small intestinal mucosa might also provide useful information for the diagnostic work-up. Although an increased number of CD3$^+$ lymphocytes in the small intestinal mucosa by itself is not a specific finding for coeliac disease, determination of increased numbers of these cells from villus tips or the quantification of γδ-positive IELs may have additional value in borderline cases[112]. Moreover, the detection of intestinal TG2-targeted coeliac IgA isotype autoantibody deposits in intestinal mucosal tissue samples is helpful in unequivocal cases but requires frozen biopsy samples[56,112]. The presence of gluten-specific T cells in the circulation may provide a potential means for diagnosis even in cases in which an individual has reduced their intake of dietary gluten. A 3-day gluten challenge induces the mobilization of memory T cells reactive against gliadin, which can be detected by IFNγ enzyme-linked immunospot (ELISPOT) assay[113]. However, although the assay is highly specific for coeliac disease, it is not able to identify all patients. Alternatively, flow cytometry, using HLA-DQ–gluten tetramers, can be used[114]. The technology is able to identify patients with coeliac disease with a high level of accuracy, regardless of whether the individuals are on a gluten-free diet[115]. Thus far, the only additional tools used outside of a research setting are HLA typing and immunohistochemistry for IEL subsets and sometimes intestinal IgA deposits.

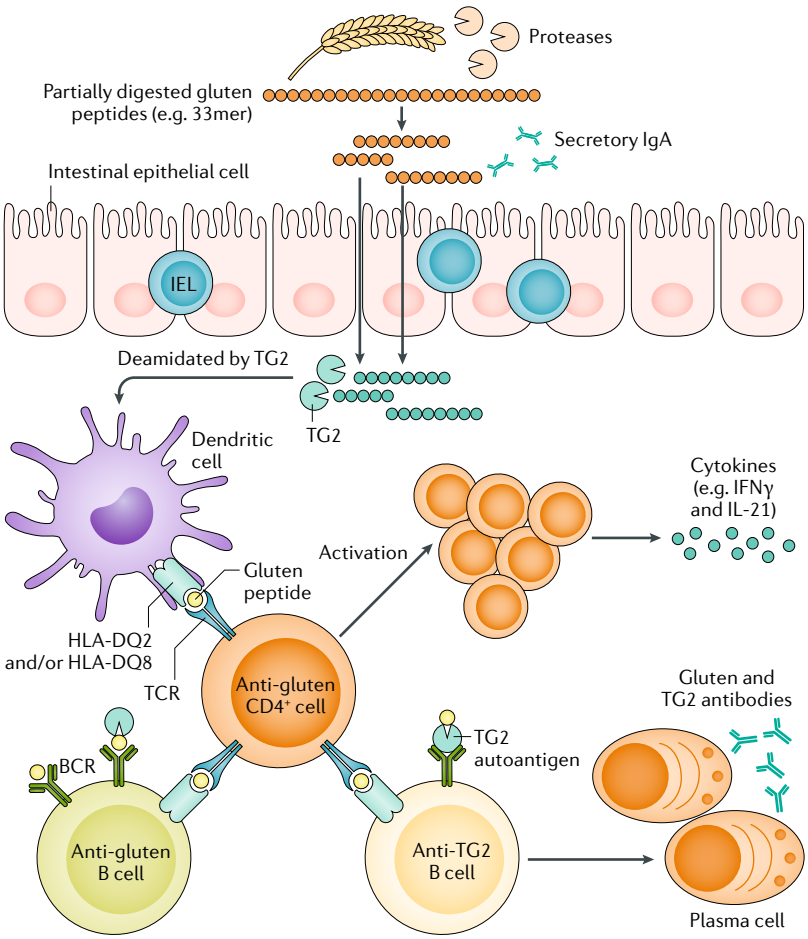

Fig. 4 | **Adaptive immune responses involved in coeliac disease.** Owing to a high proline content, gluten is fairly resistant to proteolytic degradation by mammalian and microbial digestive enzymes, which leads to the appearance of fairly long gliadin peptides, including the 33mer, in the small intestinal lumen. These peptides access the lamina propria either actively through the transepithelial route or passively by paracellular flux caused by compromised epithelial barrier function. In the lamina propria, the immunogenic gliadin peptides are modified by transglutaminase 2 (TG2), which deamidates distinct glutamine residues into glutamic acid, increasing their affinity to human leukocyte antigen (HLA)-DQ2 or HLA-DQ8. These modified epitopes are taken up by antigen-presenting cells, including dendritic cells that present them to gluten-specific CD4$^+$ T cells in the context of HLA-DQ2 or HLA-DQ8 molecules. Moreover, both gluten-specific and TG2-specific B cells have been suggested to act as antigen-presenting cells in coeliac disease. B cells recognize their antigens (gliadin peptides and TG2–gliadin complexes) via surface B cell receptors (BCRs), internalize them and present the processed gluten peptides to gluten-specific CD4$^+$ cells. Upon the interaction of HLA-DQ2 or HLA-DQ8, gliadin peptides and distinct T cell receptors (TCRs), both the T cells and the B cells would be activated. Once activated, gluten-specific CD4$^+$ T cells start secreting inflammatory cytokines, including IFNγ and IL-21, thereby creating an inflammatory milieu in the small intestinal lamina propria. Moreover, the activated B cells can differentiate into plasma cells that secrete antibodies against gluten and TG2. IEL, intraepithelial lymphocyte.

Non-coeliac gluten sensitivity

The symptoms of coeliac disease are far from being disease specific, and patients with, for example, irritable bowel syndrome or cereal allergy, may present with similar abdominal symptoms. Interestingly, it has long been known that a large number of patients experiencing functional gastrointestinal symptoms benefit from the avoidance of wheat even in the absence of coeliac disease (TABLE 2). Recent randomized intervention studies indicate that some patients experiencing symptoms from gluten-containing cereals have a true non-coeliac gluten sensitivity (NCGS)[116–120]. The prevalence of NCGS probably exceeds that of coeliac disease, as it has been estimated to affect ~2–5% of individuals in the general population. Currently, there is no reliable biomarker for NCGS, and NCGS diagnosis requires the careful exclusion of coeliac disease. Patients with NCGS have normal small intestinal mucosal morphology and are seronegative for coeliac autoantibodies. Gluten dependency of symptoms needs to be proved by double-blind gluten challenge, which renders the diagnostic work-up laborious[121]. Interestingly, recent studies indicate that NCGS might be associated with other triggers in addition to gluten (for example, fructans might be involved)[122].

Prevention

As stated above, the incidence and prevalence of coeliac disease have risen over time, and the disease causes considerable health burdens for individuals and for society. Coeliac disease may be considered as a public health problem as it increases the overall mortality risk[123], reduces QOL[124,125] and yields extensive negative economic consequences[126]. Once diagnosed and treated with a gluten-free diet, the health status of a patient does improve; however, preventing the onset of coeliac disease entirely would be even more beneficial[127].

The best-studied possible primary prevention strategy derives from data presented in a Swedish epidemiological study of coeliac disease in the mid-1980s[88]. This

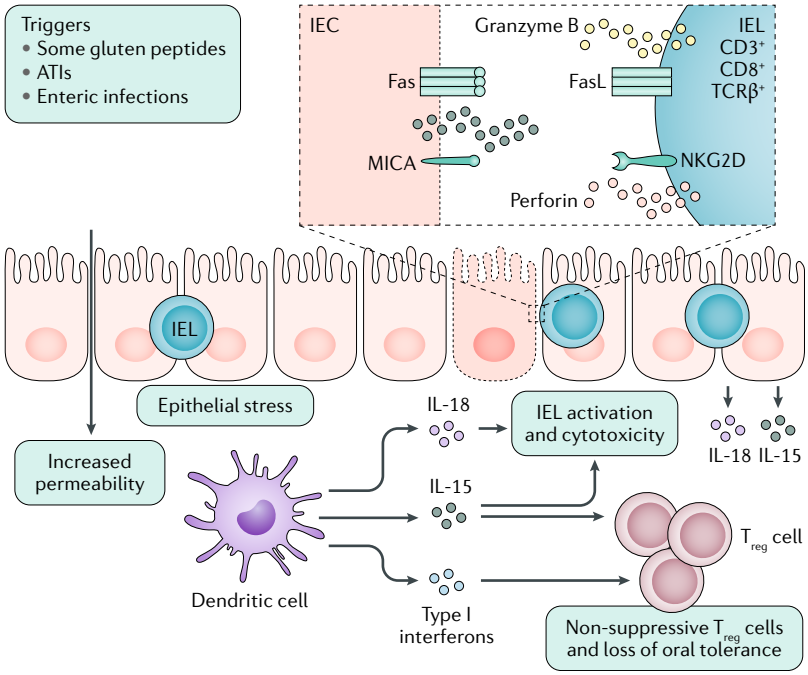

Fig. 5 | **Innate immune responses involved in coeliac disease.** Innate immune mechanisms involved in coeliac disease pathophysiology may evolve as a response to certain gluten peptides, enteric infections or α-amylase-trypsin inhibitors (ATIs) present in wheat. The small intestine mucosal epithelium in coeliac disease is populated by numerous intraepithelial lymphocytes (IELs) that take part in innate immune responses. These cells display cytotoxic properties involving molecules such as Fas ligand (FasL), perforin, granzyme B and NKG2D. These cytotoxic responses require the expression of a stress-induced human leukocyte antigen (HLA) class I molecule, MICA, on adjacent intestinal epithelial cells (IECs). IL-15 is an important regulator of the NKG2D–MICA pathway as it increases the expression of NKG2D on IELs. As a result, IEC apoptosis is augmented and epithelial permeability is increased. In addition, IL-15 can also inhibit the regulatory effects of regulatory $CD4^+$ T (T_{reg}) cells, which also contributes to loss of oral tolerance. Additional hallmarks of the innate immune response in coeliac disease are the secretion of type I interferons and IL-18. TCRβ, T cell receptor-β.

study suggests that coeliac disease may be prevented by the early introduction of small quantities of gluten into the diet of young children, particularly while breastfeeding[128]. However, two gluten intervention randomized controlled trials[82,90] analysing the timing of introduction of gluten into the diet of young children from families with coeliac disease and three prospective observational studies[129–131] have shown that these early-life feeding practices do not prevent coeliac disease. Moreover, two systematic reviews and meta-analyses concluded that the timing of gluten introduction and the duration or maintenance of breastfeeding do not influence the development of coeliac disease[89,132]. Data from The Environmental Determinants of Diabetes in the Young (TEDDY) cohort indicate that a high intake (>5.0 g per day) of gluten during the first 2 years of life was associated with an increased risk of coeliac disease in Swedish children[31]. However, a similar analysis of the data in the international PREVENTCD study showed that the amount of gluten consumed at 11–36 months of age did not influence the risk of coeliac disease development[91]. Thus, this topic remains open to further evaluation.

Early-life intestinal infections have been associated with the development of coeliac disease, but the topic of infections is controversial: some prospective studies have shown an association between early-life infections and the risk of coeliac disease[30,133], whereas others have not[82]. In addition to this, discrepant findings have been published on the mode of delivery (vaginal birth versus caesarean section) and risk of coeliac disease[84,134]. Taken together, none of the primary strategies for the prevention of coeliac disease has been shown to prevent the disease, and early diagnosis and treatment are currently the only way to achieve secondary prevention by halting disease progression and the emergence of symptoms. There are two approaches to achieve this — screening or case-finding.

Screening strategies

Most national and international guidelines on coeliac disease advise screening in high-risk groups, including first-degree relatives of patients with coeliac disease and those with associated high-risk disorders (BOX 1) to increase the diagnostic rate[34,135]. Active case-finding refers to low-threshold serological testing followed by confirmatory biopsy for seropositive cases. Such testing of patients with various coeliac-associated symptoms has led to the early diagnosis of a large number of patients with coeliac disease[136,137]. However, this strategy will not identify all patients; thus, mass screening by serology in the general population has been suggested. In principle, coeliac disease fulfils the WHO criteria for mass screening because it is an important health problem, there is an accepted treatment, facilities for diagnosis and treatment are available, there is a recognizable latent or early symptomatic stage and a suitable test exists for disease detection. Furthermore, coeliac disease mass screening research projects in Europe and the United States show that screening is well accepted by the general population[138–140]. Moreover, the natural history of the condition, from early phases of disease development through to the latent phase and to the manifest symptomatic disease with overt villous atrophy, is increasingly being understood by researchers and health-care professionals. Evidence also exists for health improvements by early treatment in asymptomatic individuals[141–145]. However, there are still few data on the complications that can occur from undiagnosed and untreated coeliac disease. Furthermore, additional data on the cost-effectiveness of mass screening in the general population are needed. In 2017, a US preventive services task force reviewed the evidence for the mass screening of coeliac disease and concluded that more research is needed to understand the effectiveness of screening and treatment for coeliac disease, the accuracy of screening tests in asymptomatic individuals and optimal strategies[146].

Management

Gluten-free diet

The mainstay of treatment for coeliac disease remains lifelong strict adherence to a gluten-free diet. The gluten-free diet has been the documented therapy for coeliac disease since just after World War II. It remains one

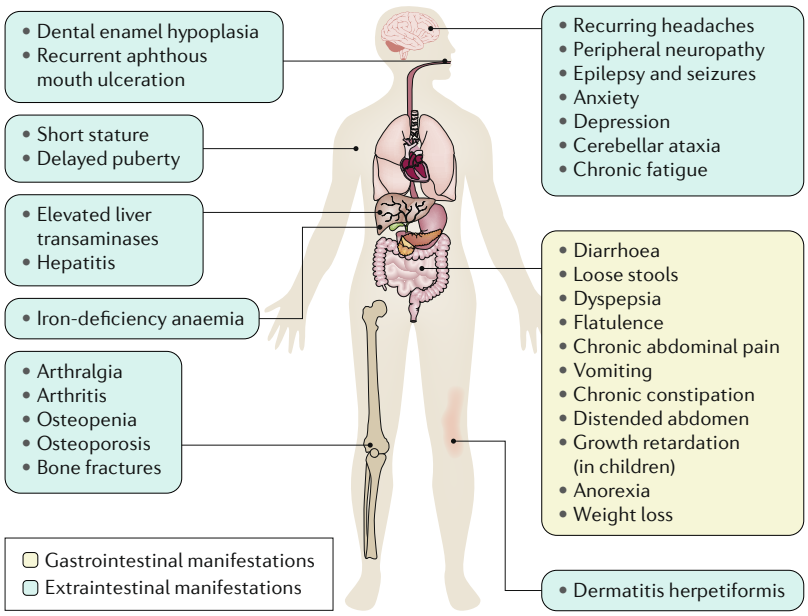

Fig. 6 | **The clinical manifestations of coeliac disease.** Coeliac disease can have diverse clinical presentations in addition to the classically anticipated gastrointestinal symptoms.

of the very few causative treatments in medicine, with overall excellent results. The term gluten-free diet is used for a diet devoid of harmful gluten peptides; in practice, this means avoiding all food based on or containing wheat, rye, barley and all cross-breeds of these cereals[147]. Primitive wheat varieties such as kamut, einkorn and others may be less toxic for patients with coeliac disease[148], but this has not been convincingly shown in proper trials. Spelt is a wheat variety believed by many to be a 'primitive' wheat, but this is actually not true as it contains many of the toxic peptide sequences and must therefore be avoided by patients[149]. As wheat is the basis of most grain-based foods, including breads, pasta, pastries and many snack foods, and is often used as a thickener for sauces and gravies and as an additive for stabilizing, flavouring and other functions, its complete avoidance is very difficult.

Although a strict gluten-free diet is vital for patients with coeliac disease, studies suggest that the nutritional composition of such a diet might not be ideal[150]. As such, a gluten-free diet should always have medical grounds. A gluten-free diet is often associated with a higher carbohydrate and lower fibre and mineral intake[150]. Furthermore, the avoidance of gluten may result in reduced consumption of beneficial whole grains (beneficial for cardiovascular health), which may increase cardiovascular risk[151]. Even if the popularity of gluten-free dieting has increased considerably among the general population during recent years, owing to the above-mentioned reasons, the promotion of a gluten-free diet among people without coeliac disease should not be encouraged.

Standards for gluten-free products. The legislation of gluten-free products is based on the WHO Codex Alimentarius standard[152]. On the basis of these guidelines, the European Commission in 2012 and the US FDA in 2013 issued regulations defining foods labelled 'gluten free' as containing <20 parts per million (ppm) of gluten (equal to 20 mg per kg of food) when measured by an approved system for testing[147]. Wheat-starch-based gluten-free products, which might contain minute amounts of residual gluten, are favoured by many patients with coeliac disease. Previous randomized and long-term follow-up studies show that these products are safe and well tolerated in the majority of patients[153]. In 2018, industrially purified wheat-starch-based gluten-free products contain <20 ppm of gluten and, thus, are widely allowed for patients with coeliac disease, particularly in northern Europe and the United Kingdom. By contrast, Australia and New Zealand have stricter rules that allow no gluten in gluten-free products. A zero-gluten diet would be ideal; however, in the real world, such a diet is impossible to achieve and analytical methods might not be available to check products[147].

To meet the requirements of the regulations for gluten-free food and to guarantee accurate food labelling, a gluten-analysis R5 ELISA (Mendez) is currently used as the official gold standard for measuring the gluten level in food[154]. The assay recognizes a pentapeptide (QQPFP) and the homologous sequences that occur repetitively in the prolamins from wheat, rye and barley. However, the test has some important limitations as it fails to detect barley contamination in oat products, high-molecular-weight glutenins of wheat and hydrolysed gluten peptides[147]. As such, more accurate tests to detect gluten contamination in food are currently under development.

Dietary lapses. In coeliac disease, dietary adherence is essential to achieve small intestinal mucosal healing and the alleviation of symptoms. Adherence to a gluten-free diet is dependent on a high level of knowledge and motivation in patients. However, as mentioned above, a diet completely devoid of gluten is difficult, if not impossible, to maintain. On the basis of limited data from a few small patient series, it appears that wide variation exists in gluten sensitivity between patients with coeliac disease. However, a daily intake of 10–20 mg of gluten appears harmless, whereas daily consumption of >200–500 mg seems to induce small intestinal villous damage and inflammation[153,155,156]. By contrast, the standard Western diet contains 10–20 g gluten per day[157].

Although a range of good products are now available, many individuals find the gluten-free diet less palatable than a regular diet. Gluten-free products are also often more expensive and inadequately labelled, all of which hamper the strict adherence to the lifelong diet and predispose to dietary lapses. In accordance with this, a considerable proportion of patients with coeliac disease report advertent dietary lapses, and the proportion of patients reporting to adhere to a strict diet ranges between 42% and 96%[147]. Factors that may possibly be associated with poor adherence include diagnosis in adolescence, lower socioeconomic status, local food culture and travelling and eating out in restaurants[158,159]. Furthermore, those patients with no symptoms might be more prone to occasional gluten ingestion[160].

Interestingly, several studies show an incomplete histological normalization of small intestinal mucosa despite patients adhering to a strict gluten-free diet, which suggests inadvertent gluten intake[9]. Therefore, the food industry and legislators have a responsibility to pay special attention to ensure the purity of gluten-free products. Moreover, patients are encouraged to be cautious with their food selection and to avoid all sources of possible gluten contamination. To achieve this, knowledge is required by all individuals participating in gluten-free cooking, including family members without coeliac disease and chefs and caterers in restaurants, schools and workplaces[161,162]. All in all, owing to the challenges in gluten-free dieting, a considerable portion of patients with coeliac disease state that they would be willing to take a drug or some kind of vaccine or immunotherapy rather than to adhere to a gluten-free diet[163].

Oats in gluten-free diet. Although oats contain <20 ppm gluten and fulfil the Codex Alimentarius standard for gluten-free products, the inclusion of oats in gluten-free dieting has remained a controversial issue[40]. The potential advantages of incorporating oats into the gluten-free diet relate to several nutritional benefits, such as contributing a source of soluble fibre, minerals and vitamins, as well as lowering post-prandial blood glucose and low-density lipoprotein levels[164]. Moreover, the addition of oats would diversify the otherwise restrictive diet[165]. Ample evidence shows that oats are well tolerated by the majority of patients with coeliac disease and they have no detrimental effects on small intestinal mucosal morphology or clinical symptoms, even after long-term consumption[40]. However, controversial results also exist that indicate that, in some patients, the consumption of oats may trigger clinical symptoms, induce mucosal inflammation and hamper normalization of the intestinal immune response[9,166–168]. Moreover, in experimental models of coeliac disease, oats have shown biological responses[169,170] with possible differences in toxic effects between different varieties of oats[169]. Owing to these discrepant results, alongside the fear of contamination of oat products with other gluten-containing cereals, oats have been restricted in the gluten-free diet. Currently, the inclusion of oats in the gluten-free diet varies between different countries; for example, oats are accepted in Scandinavia, the United Kingdom, the United States and Canada but not recommended in Australia and New Zealand. Evidently, these issues require further clarification, along with further research into the possible differences in the tolerance to oats between individuals and genetically different populations. Altogether, although most of the current evidence supports the clinical safety of oats in coeliac disease, more high-quality prospective studies are needed[40].

Patient follow-up

Follow-up in coeliac disease is considered important to confirm the response and adherence to a gluten-free diet and to detect possible complications[34,171]. However, current scientific evidence on the optimal implementation and frequency of patient follow-up in coeliac disease is limited[159,172,173]. It remains unclear who would be responsible for patient follow-up[174,175] and whether follow-up should be more personalized[176]. Owing to this ambiguity, variation exists within the current guidelines. Nevertheless, according to all guidelines, clinical and dietary evaluation and serological testing are recommended, often annually or biannually. Testing positive for serum antibodies in follow-up often indicates poor dietary adherence and ongoing small intestinal mucosal damage; however, testing negative for coeliac antibodies during a gluten-free diet does not always signify adequate histological recovery[9,176]. Although a repeat biopsy during a gluten-free diet is currently the only reliable tool to demonstrate small intestinal mucosal healing, there is no consensus on the routine use of biopsy in adults, and follow-up biopsy is not performed in children[34,171]. Furthermore, the interpretation of small intestine biopsy samples is challenging, as discussed above[108–110]. In children, demonstration of clinical and serological response is sufficient, together with the continuous monitoring of growth and development. Moreover, follow-up should ensure that possible nutritional deficiencies (for example, iron, folic acid and vitamin B_{12}) present at the time of diagnosis of coeliac disease have been corrected, although the necessity to routinely monitor these parameters might not be needed[177]. In patients with an inadequate response to a gluten-free diet, a careful evaluation by a clinical dietician is of paramount importance[147].

Box 2 | **Causes of small intestinal villous atrophy**

Immune disorders
- Coeliac disease
- Autoimmune enteropathy
- Inflammatory bowel disease

Immune deficiencies
- Common variable immunodeficiency

Infections
- *Helicobacter pylori*
- Giardiasis
- Cryptosporidiosis
- HIV
- Viral gastroenteritis

Nutritional deficiencies
- Malnutrition
- Vitamin B_{12}, folic acid or zinc deficiencies

Malignancies
- Enteropathy-associated T cell lymphoma

Other
- Peptic duodenitis
- Eosinophilic gastroenteritis
- Olmesartan medication and other angiotensin II blockers
- NSAIDs
- Radiation and chemotherapy
- Allergy to cow's milk
- Small intestine bacterial overgrowth

Data are from REFS[104,219,220].

Refractory coeliac disease

The clinical effects of a gluten-free diet are in most cases rapid and convincing, but the recovery of the intestinal mucosal morphology can take months or even years[9,178,179]. However, in some patients, the mucosa fails to heal, and in even rarer cases, a patient may develop villous atrophy after an initial clinical and morphological improvement. In these circumstances, refractory coeliac disease (RCD) should be considered[27]. RCD is defined by persistent or recurrent villous atrophy and malabsorptive symptoms despite adherence to a strict gluten-free diet[180]. Some patients with RCD may never have responded to a gluten-free diet (primary RCD) or may have relapsed despite adherence and initial response to the gluten-free diet (secondary RCD). If RCD is suspected, the original diagnosis of coeliac disease should be reconsidered. In addition to inadvertent or advertent gluten intake, other causes of villous atrophy (BOX 2) must be excluded before the diagnosis of RCD can be established[181]. According to recent population-based studies, RCD affects 0.3% of patients with diagnosed coeliac disease and its prevalence in the general population is 0.002%[27,182]. RCD is a serious disorder with the potential to develop into ulcerative jejunitis and further to enteropathy-associated T cell lymphoma. The symptoms are often severe and require additional therapeutic intervention in addition to a gluten-free diet. The condition can be subdivided into type I (RCDI) and type II (RCDII), the latter being characterized by a massive accumulation of abnormal IELs expressing cytoplasmic CD3ε but lacking surface expression of T cell markers CD3, CD4 and CD8 or containing clonal T cell rearrangement or rearrangements[180,183]. Furthermore, RCDII is non-responsive to any treatments and has poor prognosis[180,183]. Several factors predisposing to the later development of RCD have been identified and they include older age, symptoms of malabsorption and seronegativity at the time of coeliac disease diagnosis as well as a history of poor dietary adherence[27,184]. In coeliac disease, persistent villous atrophy can also occur in the absence of clinical symptoms, and this condition is more common than RCD, affecting 4–79% patients with coeliac disease[9]. However, even in the absence of symptoms, the prognosis of the disorder is not ideal, and these individuals may be predisposed to severe complications, including osteoporosis and malignancies[185].

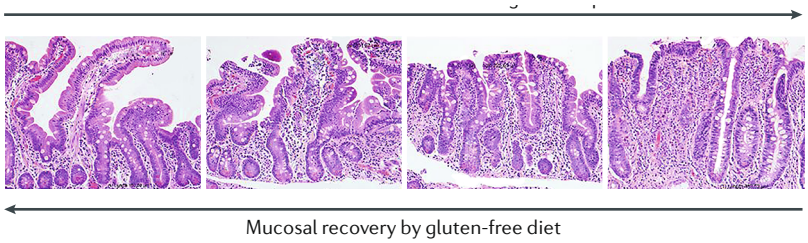

Fig. 7 | **The continuum of small intestinal mucosal damage in coeliac disease.** In coeliac disease, gluten-induced small intestinal mucosal lesions develop over time, from normal villous architecture (far-left panel) to mucosal inflammation with crypt hyperplasia (middle-left panel) and finally progressing to villous atrophy with crypt hyperplasia (middle-right and far-right panels). Images are mucosal sections cut perpendicular to the luminal surface from biopsy samples from patients with coeliac disease. Damage to the mucosa reverses upon the initiation of a strict gluten-free diet. Figure adapted from REF.[221], Springer Nature Limited.

Symptoms without villous atrophy on diet

About 20–50% of patients with coeliac disease have persistent or recurrent symptoms despite a long-term gluten-free diet[77,186]. Only a minor fraction of symptoms in these patients are explained by RCD, but its exclusion is mandatory[181]. In the majority of symptomatic patients with treated coeliac disease, the small bowel mucosal morphology is actually normal. Common factors associated with such symptoms include inadvertent gluten exposure, other concomitant gastrointestinal disorders such as irritable bowel syndrome, lactose intolerance and coeliac-disease-related autoimmune conditions (TABLE 3; BOX 1). Interestingly, patients who experience severe symptoms before diagnosis or those with a long diagnostic delay are particularly prone to persistent symptoms during a gluten-free diet[187]. Moreover, altered intestinal microbial composition[77] and low fibre intake[188] may play a role in poor symptom response. Altogether, gluten-free dietary treatment is not always sufficient by itself and individualized supplementary therapeutic approaches should be considered.

Prognosis

The prognosis of coeliac disease has been a matter of research and debate for decades. All clinicians working with these patients regularly see the vast majority of patients experience a very good and long life after the diagnosis of coeliac disease has been established. By contrast, a subgroup of patients do develop complications such as cancer[7]. In addition to enteropathy-associated T cell lymphoma, coeliac disease is associated with an increase in other types of non-Hodgkin lymphoma and adenocarcinoma of the intestine[7,189,190]. However, for unclear reasons, breast cancer is less frequently seen in women with coeliac disease[189,191]. Importantly, the aforementioned cancer types that have increased prevalence in patients with coeliac disease are also rarely found in the general population.

One non-neoplastic complication of coeliac disease is splenic hypofunction, which might predispose patients to increased numbers of infections[192]. However, hyposplenism is often associated with more severe forms of coeliac disease (for example, RCD[27]), but studies on this issue are limited in number.

An association between coeliac disease and increased mortality is well documented[7,123]. Very large epidemiological registry studies from Sweden suggest an increased mortality, but only as low as 1.4 times that of the general population, indicating that the mortality is only marginally increased in individuals with coeliac disease[193]. The increased risk of death was specifically due to cardiovascular and respiratory diseases as well as cancer. However, a recent population-based study in the United Kingdom suggested that patients with coeliac disease diagnosed close to or after 2000 have no major excess risk of mortality, although a 0.15% excess risk of dying from non-Hodgkin lymphoma still exists[194].

All in all, the complications of coeliac disease are unpredictable. Clinicians do not have any tools to

Table 2 | **Differential diagnostics of disorders related to gluten and cereal consumption**

Disease	Causative agent	Symptoms	Prevalence	Small intestinal mucosal morphology	Antibodies	Genetics	Mechanisms	Age of diagnosis	Treatment
Coeliac disease	Gluten	• GI • Malabsorption • Extraintestinal • Some asymptomatic	1–2%	• Villous atrophy • Crypt hyperplasia	IgA, EmAs and TG2-Abs	HLA-DQ2 and HLA-DQ8	Immune mediated	Children and adults	Lifelong GFD
Cereal allergy	Cereal proteins	• GI • Respiratory symptoms • Mouth and skin symptoms • Rarely anaphylaxis	• 1% in children • Often resolves by adulthood	Normal	IgE cereal RAST in some cases	Genetic susceptibility	IgE or non-IgE mediated	Often children	Avoidance of symptom-causing cereals
NCGS	• Gluten • Fructose • Other	• GI • Extraintestinal	0.5–8%	Normal	Some with IgA and/or IgG anti-gliadin	Unknown	• Innate • Unknown	Mostly adults	• Avoidance of gluten-containing cereals and FODMAPs • Length of the diet: no data
IBS	Unknown	GI	10–20%	Normal	Unknown	Unknown	• Multifactoral • Unknown	Children and adults	• Avoidance of gluten-containing cereals and FODMAPs • Length of the diet: according to symptoms

EmAs, endomysial antibodies; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; GFD, gluten-free diet; GI, gastrointestinal; HLA, human leukocyte antigen; IBS, irritable bowel syndrome; NCGS, non-coeliac gluten sensitivity; RAST, radioallergosorbent test; TG2-Abs, transglutaminase 2 antibodies.

predict which patients with coeliac disease will develop complications; therefore, our clinical advice to patients will always be to adhere strictly to their diet.

Quality of life

Similar to other chronic disorders, coeliac disease is a challenging condition that affects the QOL of patients as well as that of partners and caregivers. Historically, nonspecific scales were used to measure QOL in coeliac disease, but since 2007, several disease-specific questionnaires have been developed for both children[124,195] and adults[196,197].

At diagnosis, symptomatic patients often report a lower QOL than do control populations[125,198]. The gluten-free diet may impose social restrictions, but on the whole, QOL has been shown to improve in most patients with coeliac disease when commencing a gluten-free diet. The most evident factor improving QOL is the alleviation of symptoms[198]. Nevertheless, there is evidence that, compared with the population in general, QOL remains worse in many individuals with treated coeliac disease, particularly women[199,200]. Notably, at the time of diagnosis, the QOL of patients who are diagnosed by serological screening and asymptomatic patients may be superior to that of patients with symptoms. Importantly, in asymptomatic individuals, the burdensome dietary treatment does not impair QOL; instead, many studies suggest beneficial effects[10,16,143,198]. When interpreting QOL results, it is important to keep in mind that QOL depends on the environment and cultural aspects; thus, the results may not always be applicable for different populations.

Finding a means to improve QOL in coeliac disease is challenging. Managing the disease involves an active effort from the patient to regulate feelings, actions and reactions during any social activity that involves food. Management strategies have been investigated to increase QOL, for example, by the development of the locus of control (locus control is a psychological concept that refers to the extent to which a person believes that his or her own actions influence events in the surrounding environment)[201], which favours 'primary control' (for example, patients may bring their own gluten-free food to social events) and discourages 'passive or disengagement coping' (for example, denial of the presence of disease)[202]. Moreover, an additional tool for improved disease management might be online consultation for children and young adults[203]. Despite these tools, many individuals with coeliac disease manage their disease with scarce support from health-care providers. Although many patients with coeliac disease eventually adapt to their disease over time, it seems that there is still a great need for training of health-care professionals and food industry workers to improve the QOL of patients[204].

Table 3 | **Differential diagnostics of persistent symptoms in treated coeliac disease**

Aetiological factor	Villous atrophy	Further information
Ongoing gluten consumption (advertent and inadvertent)	Often	Most common reason for ongoing symptoms
Lactose intolerance	No	• Frequent • May be secondary to active coeliac disease
Functional gastrointestinal disorder (for example, irritable bowel syndrome)	No	• Common • Other reasons should be excluded (for example, concomitant diseases or low fibre in diet)
Microscopic colitis	No	Presenting with watery diarrhoea
Infections	Rarely	For example, giardiasis or HIV
Small intestine bacterial overgrowth	Rarely	Frequent, challenging diagnosis
Exocrine pancreatic insufficiency	No	Presenting with steatorrhoea
Coeliac-disease-related autoimmune conditions	No	For example, autoimmune thyroid disease (hyperthyroidism or hypothyroidism)
Medication induced	Yes	For example, induced by olmesartan or NSAIDs
Malignancies	No	Prevalence increases with age
Psychiatric comorbidities	No	For example, depression or anxiety
Refractory coeliac disease	Yes	Presenting with malabsorptive symptoms

Outlook

Pathogenesis of coeliac disease

Substantial progress has been made in our understanding of the pathogenesis of coeliac disease. Currently, the dietary-gluten-driven immune response occurring in the small intestinal mucosa has been well characterized, and the role of HLA-DQ2 and/or HLA-DQ8 and the coeliac disease autoantigen TG2 in these processes has been established[1]. Owing to this and the knowledge that exclusion of gluten from the diet reverses pathology, coeliac disease can be regarded as a model to study the mechanisms involved in other autoimmune disorders[205]. Evidence suggests that other environmental factors in addition to gluten, such as the intestinal microbiota and infections, may shape the host immune response to gluten[30,31,73]; however, detailed cause–effect relationships and the precise interplay between host genetics, nutrition and the microbiota are yet to be unravelled. Animal models are convenient tools to investigate the pathogenesis of a disorder, and several models currently exist that enable the functional interrogation of specific components of coeliac disease pathogenesis[206–208]. New animal models are likely to be developed in the future that enable investigation of gluten responsiveness, coeliac disease HLA type, disease-specific autoantibodies and the gluten-induced adaptive and innate immune responses, which may allow a deeper insight into the pathogenesis of disease. The mechanisms of extraintestinal manifestations of coeliac disease are unknown and currently speculative; therefore, more work is needed to uncover them in the future.

Diagnosis

The clinical diagnosis of coeliac disease is proceeding towards non-invasive procedures; for example, in a subgroup of children, the diagnosis can be established without the need for small intestine biopsy[34,209]. In 2012, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) suggested that, in symptomatic children who have high serum TG2-Abs levels (≥10× upper limit of normal) in two independent measurements coupled with seropositivity for EmAs and coeliac-associated HLA haplotypes, the diagnosis of coeliac disease can be established without biopsy samples taken upon invasive endoscopy[34]. Prospective evaluation of these ESPGHAN diagnostic criteria show that they have a positive predictive value of 99.7% for coeliac disease in this group of children[209]. However, the inclusion of HLA haplotype analysis did not increase the accuracy of diagnosis[209], and the ESPGHAN guidelines are presently being re-evaluated. The performance of these guidelines has been insufficiently tested in all patient subgroups; therefore, further prospective studies are warranted to clarify whether a similar non-invasive approach can be adopted for adults and asymptomatic individuals.

The incorporation of non-HLA genetic data into the diagnostic work-up is an interesting future scenario. For example, genotyping of HLA and a few other dozen genetic variants (TABLE 1) could provide a useful and cost-efficient means to define those at risk of developing coeliac disease and be a step towards personalized medicine. Moreover, the HLA-DQ–gluten tetramer blood test might prove useful in the future as a diagnostic tool, allowing individuals with suspected coeliac disease to avoid gluten challenge and duodenal biopsy[114,115]. The determination of small intestinal mucosal morphology from biopsy samples obtained upon endoscopy will probably still be needed in problematic cases. However, alternative methods to supplement or even replace conventional histology would be welcomed.

Management

A strict gluten-free diet has been the only effective treatment for coeliac disease for many years, and owing to the efficacy, safety and low price, this diet is likely to remain important in disease management in the future. Improved technologies for the detection of gluten in the food and to monitor recent gluten exposure (for example, the detection of gluten in urine by quantitative lateral flow technique[210]) will enable the food industry to provide a safer and broader food supply for patients with coeliac disease. Unfortunately, some patients do not respond to a gluten-free diet, and even responsive patients have expressed the wish for alternative therapies owing to the restrictive nature of the diet[163]. Although no drugs thus far have been approved for coeliac disease, several pipelines are under investigation. These include drugs that aim to correct the impaired epithelial intestinal barrier (so-called leaky gut) (larazotide acetate)[211,212]; enzyme pills that digest gluten during and after intake (latiglutenase)[213,214]; drugs that inhibit the chemical modification of gluten by TG2 in the mucosa (ZED1227); and monoclonal antibodies targeting IL-15,

which aim to block the licensing of IELs to kill epithelial cells (AMG 714). Two drugs, larazotide acetate and latiglutenase, have progressed through phase II clinical studies, showing that larazotide acetate was effective in reducing gluten-triggered symptoms[212] and latiglutenase attenuated gluten-induced injury[213]. In addition to drugs, a vaccine is under development (Nexvax2) that consists of epitopes for gluten-specific T_{reg} cells to induce immune tolerance[215] and currently has completed phase I clinical trials.

As the new drugs move towards phase II clinical trials, reliable non-invasive surrogate markers for gluten-induced small intestinal damage and effective patient-related outcome measures would be useful[216]. Such non-invasive surrogate markers include, for example, serum intestinal fatty acid-binding protein (a marker for intestinal epithelial cell damage)[217] as well as alkylresorcinols[218] and urine gluten peptides (both markers for gluten exposure)[210]; these biomarkers are currently being developed and might prove useful in the future. The academic community, patient organizations and support groups and the food industry must cooperate innovatively to achieve a better life for patients with coeliac disease.

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Competing interests
None of the authors declares any financial competing interests. The authors have the following non-financial competing interests. K. Kaukinen, K.L. and K. Kurppa are members of the Scientific Advisory Board of the Finnish Coeliac Society. K. Kaukinen and K. Kurppa are members of the Finnish Coeliac Disease Current Care Guidelines committee. K. Kaukinen is a vice chairman of the Finnish Society of Internal Medicine. G.K.M. holds the post of Secretary General of the Indian Society of Gastroenterology, is a board member of the International Society for Studies on Coeliac Disease, is Co-Chair of the Research Committee of the World Gastroenterology Organization, serves as Coordinator of the Indian National Taskforce on Inflammatory Bowel Disease and is co-inventor of a device for faecal incontinence. J.A.M. is Section Editor for *Mayo Clinic Proceedings*. E.F.V. holds a Canada Research Chair and is an advisory board member of Innovate Pharmaceuticals, is President of the Society for the Study of Coeliac Disease, is Treasurer of the Canadian Association of Gastroenterology (CAG) and is an executive board member of CAG and the Canadian Digestive Health Foundation.

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