

Original Article

Celiac Disease: Against the Grain in Gastroenterology

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Abstract

The incidence of celiac disease has risen quickly and has a worldwide distribution in Europe, North and South America, Asia, the Middle East and Africa. This is attributed in part to increased availability in screening but also to the fast-rising gluten consumption and perhaps unknown environmental factors. In daily practice, this means that more subclinical cases and very young and elderly patients are diagnosed. The pathogenesis of celiac disease is a T-cell driven process initiated by gluten, leading to increased intestinal permeability and villous atrophy. The process requires HLA genotypes DQ2, DQ8 or both. Additional non-HLA alleles have been identified in genome-wide association studies. Serological testing, followed by duodenal biopsies, are still required to confirm the diagnosis. Advances are in the making for novel biomarkers to monitor disease and for pharmacological support of celiac disease. Medical costs and patient-perceived disease burden remain high in celiac disease, which point to the need for ongoing research in drug development to improve quality of daily life. Drugs undergoing phase I and phase II clinical trials include intraluminal therapies and vaccines to restore immune tolerance. These therapies aim to reduce symptoms and mucosal injuries as adjunct therapies to a gluten-free diet.

Keywords: *Celiac disease; Gluten; Gluten-free diet; HLA DQ2 and DQ8; Tissue Transglutaminase*

Celiac disease (CeD) is an autoimmune enteropathy generated from exposure to gluten in genetically predisposed individuals (1–3). Gluten is naturally present in wheat as gliadin, in barley as hordein and in rye as secalin (4). The classic view on CeD pathogenesis requires human leukocyte antigen (HLA) Class II genes and tissue transglutaminase (TTG). Gluten and gluten peptides increase intestinal permeability via the zonulin signaling pathway to allow an influx of these peptides by crossing the intestinal epithelium. Tissue transglutaminase deamidates gluten, allowing high affinity binding to HLA DQ2/DQ8+ antigen-presenting cells (APC), which turns on DQ2 and DQ8 restricted CD4+ T cells to produce pro-inflammatory cytokines (4). Celiac disease causes mucosal tissue damage of the upper small bowel, with villous atrophy being the hallmark of the disease, leading to malabsorption and its complications. The risk of small bowel lymphoma in celiac disease is increased (5). Extra-luminal manifestations include neuropsychiatric disease, dermatitis herpetiformis, arthritis and hyposplenism (6).

The condition is associated with cryptogenic hypertransaminemia, type 1 diabetes mellitus, osteoporosis, iron deficiency anemia, autoimmune liver disease and autoimmune thyroid disease (7). This review discusses the current global prevalence of celiac disease, newest insights on pathogenesis, diagnosis, treatment and the economic impact on daily living. Celiac disease is an example of a complex interaction between the environment, genetic predisposition, the human immune system and potential roles from the gut microbioma.

EPIDEMIOLOGY

In the first half of the 20th century, celiac disease was detailed in textbooks by physicians from Great Britain and the Netherlands who studied the same constellation of symptoms in children characterized by malabsorption and malnutrition in their respective countries (8–10). These symptoms were ameliorated by the withdrawal of bread and cereal and

recurred when challenged with these compounds. In the 21st century, the global map of celiac disease has changed both in distribution and its presentation, paralleling the growth in knowledge and public awareness of the disease (8, 11). Less than 36% are diagnosed in childhood, and the average age of diagnosis is around 44 to 52 (12). The reported incidence and prevalence of celiac disease is no longer gauged by symptoms alone but rather with an emphasis on serological testing or small-bowel biopsy results in adults and children. The incidence of biopsy-proven villous atrophy in celiac disease is always lower than the diagnosis made by serological testing. In Europe, wheat and cereal consumption remains high, and there is a common genetic predisposition toward a high prevalence of HLA DQ2 and HLA DQ8, which is present in 30% to 40% of the general population (13, 14). In Western Europe, 0.7% to 1% of the population may have celiac disease based on serological screenings (3, 13, 15, 16). In Northern European countries, the prevalence is estimated at 2% to 3% (13, 15). Gender distribution shows a female to male ratio of about two to one (15, 17, 18).

The spectrum of celiac disease presentation varies significantly across various time periods and by geography. In mid-to late-20th century, celiac disease was mainly diagnosed in those with classical symptoms (Table 1), usually in children and adults ages 20 to 40 years (12, 19). This is still true in countries like China and India but less so in Europe and North America, where nonclassical and silent celiac disease (Table 1) is rising fast (19). In Ireland, classical presentation decreased from 85% before 1985 to 48% after 2010, while nonclassical or silent presentation increased from 15% to 51% in the same period (18). This may reflect the disparity in celiac disease screening practices and access to gluten-free foods across the globe. Currently, the average age at diagnosis in resource-rich countries has increased to 50 years of age, and the time diagnostic delay is about 10 to 12 years. An increasing number of new cases has occurred in patients over age 60 in up to 25% of all cases in the

United Kingdom, North America and Sweden (20). In the pediatric population, the prevalence has increased from 0.10% to 0.17% between 2010 and 2014, respectively (21). Only 34% of the pediatric cohort presented with classical symptoms at the time of diagnosis, while 43% had nonclassical presentations, and 23% were asymptomatic (21).

A very recent meta-analysis on the global prevalence of CeD has exposed the ongoing need for population-based prevalence studies (11). In most Asian countries, data on celiac disease are scarce due to the lack of biopsies or serological tests performed in local hospitals (13, 15, 22). In one Chinese study, the prevalence of CeD among patients presenting with diarrhea-predominant irritable bowel-like syndrome (IBS-D) was 1%; CeD might be present in 0.28% of the general Chinese population (22). Recent meta-analysis shows CeD prevalence in North Africa, the Middle East, and India (8) is approaching the Western world prevalence (15). We can expect a rapidly growing incidence rate in countries where wheat is a staple food, such as in the Middle East and North Africa. In India, we see a difference in prevalence from the 'wheat belt' region in northern India where CeD prevalence is high (23) and rice consumption is low versus its southern region, where rice is still the staple food (8, 13, 15). In the northern community of India, the prevalence of CeD is 1% based on positive serology and positive duodenal biopsies (24).

Data on the prevalence of CeD among First Nations in Canada are currently also lacking. Although evidence suggests primary biliary cholangitis and other autoimmune liver disease has a high prevalence among Canadian First Nation communities (25), it remains unknown how celiac disease affects them. An association between primary biliary cholangitis and CeD has been recognized (26). A study from South America suggested that 51% of Amerindians carried at-risk HLA genotypes and that 2.7% of the studied subjects had strongly positive auto-antibodies that met a serological diagnosis (27).

Table 1. Classical versus nonclassical presentations of celiac disease

	Small Bowel Histology	Clinical Symptoms	Response to Gluten Withdrawal or Challenge	Serology: anti-TTG antibody
Classical	Villous atrophy	Diarrhea, weight loss, vitamin deficiency	Positive	Positive
Nonclassical	Villous atrophy	IDA, osteoporosis, neurological symptoms, dental enamel defects, elevated liver enzymes, infertility	Positive	Positive
Silent	Villous atrophy or crypt hyperplasia in majority	None in majority	Usually positive	Positive
Latent	Increased intraepithelial lymphocytes	None	Usually positive	Sometimes positive

DIAGNOSIS

It is controversial whether population screening for celiac disease should be considered. Cost-benefit analysis does not support mass screening in all children and adults (28). However, a new study from 2018 challenged the existing screening guidelines on the basis of underdiagnosis (29). Current guidelines, including those from the American College of Gastroenterology (ACG) and the European Society of Pediatric Gastroenterology Hepatology and Nutrition (30), recommend serological testing in adults with classical or nonclassical symptoms associated with celiac disease and otherwise not explained (Table 1), with a history of type 1 diabetes with possible signs and symptoms related to celiac disease, and in first degree relatives of confirmed celiac disease patients, especially if they are symptomatic (31). The initial test of choice is IgA based antitissue transglutaminase antibody (anti-TTG) in individuals older than two years old and with concomitant IgA level assessment. IgA deficiency occurs in 2% of patients with celiac disease, making the IgA based anti-TTG test falsely negative in them (32). In confirmed IgA-deficient individuals (IgA < 0.2 g/L), IgG-based tests, such as IgG-based deamidated gliadin peptides (DGP) or IgG antitissue transglutaminase, should be done (31). In children younger than two years old, combined DGP (IgA and IgG) may be recommended (31). In all adults and in the majority of children, positive serology should be confirmed by a duodenal biopsy (31). The exceptions are those subjects with confirmed dermatitis herpetiformis by a skin biopsy and children who have very high serology titers (anti-TTG titer >10 times upper limit of normal), where duodenal biopsy may be avoided (30). The typical and validated histological findings are outlined by the modified Marsh Classification (Table 2). A simpler classification by Corazza et al. is another used histological classification (33).

If patients suspected of having celiac disease are already on a gluten-free diet, aforementioned serological tests are still the first tests of choice. If negative, these should be followed by HLA DQ2/8 genotyping, which has a high negative predictive value at 98% (34). Potential patients with celiac disease with positive HLA genotypes should be subjected to 3 g/day gluten challenge for two to eight weeks (31). Positive serology should

then be followed by duodenal biopsies to confirm the diagnosis in adults.

There are a few points to ponder when interpreting a negative or positive histology. Small bowel disease may be patchy, and in a small percentage the abnormality is present only in the duodenal bulb (35). At least one bulb (D1) and four D2 biopsies should be sampled and graded according to modified Marsh classification for any evidence of increased intra-epithelial lymphocytes, villous atrophy, crypt elongation, and assessment of villous-crypt ratio (36, 37).

While the normalization of anti-TTG antibody titer is a conventionally used indicator of adherence to GFD, there is currently no consensus for repeating duodenal biopsies to assess mucosal healing in all newly diagnosed cases after one or two years of GFD. A retrospective study found that repeat biopsies were more commonly performed in those with severe disease at diagnosis (38). Histological normalization time may take years, and although mucosal healing is achievable in the majority of patients on GFD, up to 6% to 40% may not achieve histological remission, which may be linked to recurrent gluten exposure (39–41). In one pediatric study, normalization of serology generally took more than one year to achieve in the majority of children (42). Another reason for failure of mucosal healing is that at least 30% of patients do not adhere to strict GFD. However, true refractory CeD, which is defined by persistent symptoms despite strict GFD adherence for at least six to twelve months, occurs in less than 1% (43). The majority of refractory cases are Type 1, with normal intraepithelial CD3, CD4, CD8 lymphocyte phenotype, and a response to thiopurine or steroids. Clonal expansions of aberrant intraepithelial lymphocyte and T-cell receptor gamma gene rearrangement are seen in refractory CeD Type 2, which carries an increased risk of enteropathy T-lymphocyte type lymphoma (43).

CELIAC DISEASE GENETICS

Celiac disease is an inheritable, HLA haplotype-associated autoimmune disease (17, 44). Major genetic association is strongly linked within the major histocompatibility complex (MHC) locus; 88% of celiacs are positive with HLA DR3-DQ2.5, 4% with HLA DR3-DQ2.2, and 6% with HLA DR4-DQ8 (17). The

Table 2. Modified Marsh classification

	Increased Intraepithelial Lymphocytes (>40/100 enterocytes)	Crypt Hyperplasia	Villous Atrophy
0	No	No	None
1	Yes	No	None
2	Yes	Yes	None
3a	Yes	Yes	Partial
3b	Yes	Yes	Subtotal
3c	Yes	Yes	Total

prevalence of these alleles in the general Caucasian population is about 40%. Cumulative risks of developing celiac disease can be predicted from an individual's HLA haplotype (44). The cumulative incidence of CeD in the first 15 years was highest among those carrying DR3-DQ2 allele in homozygosity, followed by DQ2/DQ8 heterozygosity (44). When newborns with any of the susceptible genotypes for celiac disease and Type 1 diabetes were followed for 20 years, 5% developed CeD, and another 3.5% developed CeD auto-antibodies without villous atrophy (44-46). In DR3-DQ2/DR3-DQ2 homozygous newborns, autoimmunity was seen in 26%, and 11% developed CeD by the age five (46). In contrast, HLA DR3-DQ2 prevalence is below 5% in South Korea (47), while it is 5% to 20% in Turkey, 5% to 10% in Malaysia and China, compared with 20% to 30% in India and the Middle Eastern countries (8, 15). However, HLA DQ8 is prevalent in 5% to 10% of Iran, and 1% to 5% in Japan, India and China (47). HLA-DQ9.3 is a susceptible allele associated with celiac disease unique to the Chinese population (22).

Genome-wide association studies (GWAS) also identified more than 40 non-HLA loci linked to the disease, including many noncoding regions (14, 17). Among those, a 70 kb LD region in intron two of LPP gene is strongly associated with the development of celiac disease. Lower expression of LPP gene, involved in cell motility and cell-cell adhesion, is seen in Marsh 3 celiac disease (48). A recent study shows that Inc13, a non-coding RNA (IncRNA), is significantly downregulated in celiac disease (48). Decreased Inc13 as a regulator of pro-inflammatory genes can potentiate inflammation (48). Single nucleotide polymorphism (SNP) variants, like Inc13, have also identified SNP's overlapping B lymphocyte transcription factor binding sites and regulatory sites (48). The role of B cells in the pathogenesis of CeD is highlighted through these studies (48, 49).

Biomarkers for Gluten Exposure and Disease Monitoring

Seronegative CeD occurs in about 1.7% to 15% of the celiac population (50). This poses additional challenges for diagnosis and disease monitoring. Etiologies for seronegativity are multifactorial, including IgA deficiency, immunosuppressant use, self-imposed gluten restriction, early and late stage of celiac disease, and mild enteropathy (50). For example, in patients with proven dermatitis herpetiformis, up to 50% were seronegative with routine IgA- and IgG-based serology tests when duodenal biopsies were normal at the time of testing (51). Similarly, patients with suspected neuro-celiac disease were more likely to be seronegative when there was no or minor intestinal involvement, suggesting that enteropathy is necessary to yield positive serological results (52). More importantly, the IgA anti-TTG antibody test has been reported to poorly predict dietary compliance to GFD (53). The utility of anti-TTG antibody in monitoring histological recovery in patients on GFD was questioned, due to high false negativities, as reported to be greater than 66% when compared

with the gold standard duodenal biopsy (54). On the other hand, one cannot diagnose CeD based on villous atrophy alone. There are many nonceliac causes of duodenal villous atrophy, and the differentials range from combined variable immunodeficiency and infectious agents to drug-induced villous atrophy (55). Drug-induced villous atrophy is well documented in non-steroidal anti-inflammatory medications (e.g., mycophenolate, olmesartan and losartan) (55).

As a result of false negative anti-TTG tests in many scenarios, there has been an increased effort to find other noninvasive biomarkers of celiac disease. Urinary volatile organic compounds (VOC) analysis was reported to successfully differentiate classical CeD from irritable bowel syndrome (56). Serum intestinal fatty acid-binding protein (I-FABP), a marker of enterocyte damage, was shown to correlate with the Marsh severity grade in uncontrolled CeD, compared with healthy controls ($r=0.265$) (57). Intestinal fatty acid-binding protein may become a non-invasive marker for monitoring mucosal healing in CeD in children and adults on GFD (58).

New Understanding on Pathogenesis

In the classic view of CeD pathogenesis, the key ingredients are HLA DQ2/DQ8 genes and tissue transglutaminase 2 (TG2). Ingested gluten peptides (i.e., gliadin) increase intestinal permeability by activating zonulin signaling in the enterocytes. Zonulin modulates the permeability of the intestinal tight junctions, thereby allowing gluten peptides to enter the lamina propria. Intestinal barrier-forming claudins are downregulated and channel-forming claudins are upregulated in CeD (49). This leads to increased permeability to gluten, furthering immunogenic injury to the intestinal mucosa. The theory was tested in an in vivo study, where intestinal permeability was measured using the urine lactulose to mannitol ratio. Patients with celiac disease had the highest intestinal permeability compared with healthy controls (59).

Gluten peptides are deamidated by TG2 (60), a key step required to amplify affinity for APC carrying HLA-DQ2/HLA-DQ8 antigens, which in turn activates CD4+ T cells (61). In vitro, CD4+ T cells barely responded to minimally deamidated gluten peptides (62). CD4+ T cells, when activated, produce interferon- γ and interleukin-13, which attract cytotoxic CD8+ T cells to attack intestinal mucosa, resulting in villous atrophy, crypt hyperplasia, and inflammation. Gluten peptides also upregulate interleukin-15 (IL-15) expression in lamina propria and intestinal epithelium, a feature seen in active CeD and not in those on GFD (63). The role of IL-15 is multifaceted. Under the influence of IL-15, pro-inflammatory T-cell response is promoted; regulatory response is prevented at the level of T helper cell differentiation, and oral tolerance is lost (63). Interaction between IL-15 and NKG2D promotes cytolysis via arachidonic acid release, resulting in tissue injury (Figure 1). Interleukin-15 also plays a role in prolonging intraepithelial

lymphocyte survival and causing a subset of intraepithelial lymphocyte to expand (CD3- lymphocytes) (63).

Early or delayed gluten feeding pattern among newborns was explored in multicentred, randomized, placebo-controlled studies such as PreventCD and CELIPREV (64). The PreventCD study randomized 944 infants who were at high genetic risk for celiac disease into an early gluten feeding group by introducing daily gluten into their diets between four and six months old versus a placebo group. This study found no association of early dietary gluten feeding pattern in biopsy-confirmed celiac disease by age 3 (65). Breast-feeding practice and pattern also did not seem to negatively or positively influence the development of celiac disease in these studies. Similarly, late gluten feeding at 12 months versus six months of age also did not affect degrees of autoimmunity or biopsy-proven disease development at age 5 (64). Children with high risk HLA genotypes were more likely to develop celiac disease by age 10, suggesting that genetic predisposition was the more important predictor, whereas infant dietary pattern played no significant role (64). Interestingly, a Finnish study reported a disproportionally high incidence of celiac disease in Finland compared with other European countries, suggesting that unknown environmental factors may be the missing puzzle pieces (66).

A recent Canadian study identified pivotal roles played by duodenal microbes, such as *Pseudomonas aeruginosa* and *Lactobacillus* species, in celiac disease pathogenesis. Regulation of the immunogenicity of the gluten peptides is exerted on the

intestinal mucosal level by various microbial proteases that selectively cleave the peptides into difference polymers, which process may heighten or lessen their immunogenicity. Using the mouse model for celiac disease, a study linked bacterial dysbiosis to the pathogenesis of celiac disease (67).

Viral agents such as rotavirus are also implicated in the early pathogenesis of celiac disease (68). Rotavirus was reported to disrupt the intestinal mucosa and promote immunity response to dietary antigens. Rotavirus is a common cause of viral gastroenteritis in children. A prospective study followed 1931 genetically susceptible infants after birth and used rotavirus antibody titers to estimate the frequency of rotavirus infection. Rotavirus titers predicted the risk of celiac disease in these children (69).

New Therapies

The mainstay treatment of CeD is a strict GFD without wheat, rye, barley, or their byproducts. Oats are naturally gluten free, except contaminated oats, which may contain trace gluten. Moderate oats consumption was not associated with the development of celiac disease or adverse effects, as reported by one randomized controlled study; therefore, oats are considered a gluten-free alternative (70).

There are a few pharmacological therapies to treat celiac disease. This paper limits the discussion to randomized, controlled human studies (Table 3) (71). One approach is to restore intestinal permeability using a zonulin inhibitor such as larazotide acetate (72). Larazotide reduced in vitro tight

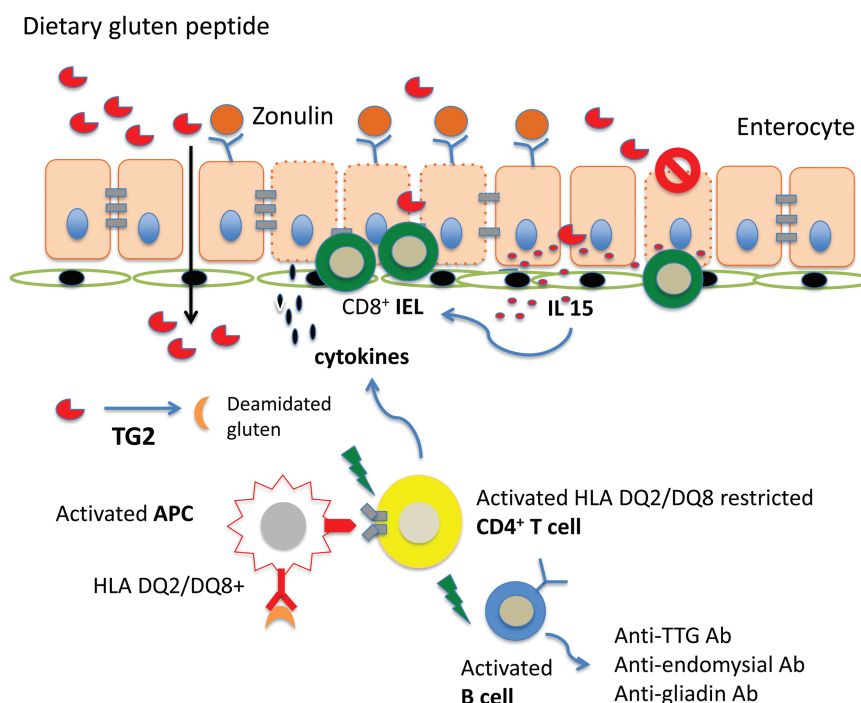


Figure 1. Classic view on the pathogenesis of celiac disease. Dietary gluten peptides increase epithelial permeability by activating zonulin signaling pathway, allowing gluten peptides to cross the epithelial barrier. Tissue transglutaminase 2 (TG2) deamidates gluten peptides, making them more attractive to HLA DQ2/DQ8 positive antigen presenting cells (APC). Activated APC turns on HLA DQ2/DQ8 restricted CD4+ T cell, which in turn produces cytokines to attract CD8+ intraepithelial lymphocytes (IEL) to attack the intestinal mucosa, resulting in tissue inflammation, enterocyte apoptosis, and villous atrophy. B cells are activated by CD4+ T cells to produce auto-immunity antibodies, including TTG antibodies, endomysial antibodies and gliadin antibodies. The role of interleukin 15 (IL 15) is essential in celiac disease pathogenesis. IL 15 promotes pro-inflammatory T cell response, cytolysis, and prolongs IEL survival.

Table 3. New pharmacological therapies in celiac disease

	Mechanism of Action	Studies	Results
Nexvax2	Vaccine to restore tolerance to gluten; modify pathogenic T-cell response	Phase I trial	Well tolerated in healthy volunteers
Larazotide acetate	Zonulin inhibitor and tight junction regulator peptide	Randomized controlled trials (RCT)	Reduction of gluten induced antibody formation against tTG; reduction of GI symptoms
Latiglutinas	Prolyl endopeptidase	Phase II trial	No improvement in villous height to depth ratio; no difference in clinical symptoms

junction disassembly and blocked translocation of gliadin polymers (73). In randomized, double-blinded, placebo-controlled clinical trials, larazotide arm had gluten-induced antibody formation against tissue transglutaminase and diminished gastrointestinal symptoms, even after a gluten challenge (72, 74). The study demonstrated that larazotide at 0.5 mg per day was beneficial in reducing gastrointestinal symptoms in persistently symptomatic patients despite GFD (75).

Another approach is to enhance gluten detoxification and digestion at the intraluminal phase. In a phase II study, oral recombinant, gluten-specific proteases (AVL003) attenuated gluten-induced mucosal injury compared with placebo in celiac disease patients after six weeks of daily gluten challenge; although there was no difference in symptom severity between the treatment and control groups (76). However, in a 2013 study with a small number of CeD patients taking *Aspergillus niger* prolyl endopeptidase, there was neither improvement in Marsh score nor changes in auto-antibody titer in the short term (77). It remains to be determined whether intraluminal proteases are efficacious adjunctive therapy in patients on GFD.

Nexvax2[®], a vaccination designed to restore tolerance to gluten molecules by modifying the T-cell response, underwent phase I clinical trials (78). In this three-week trial, weekly injection of Nexvax2[®] was well tolerated in healthy volunteers. This vaccination targets genetically susceptible HLA-DQ2 populations.

A few studies further explored the roles of gut microbiota as modulators of immune response in patients with celiac disease. One study randomized 22 patients with active CeD to supplemental *Bifidobacterium infantis* versus placebo; patients on *Bifidobacterium infantis* had lower scores on the gastrointestinal symptom rating scale and lower auto-antibody titers (79). Another study used experimental hookworm in 12 patients undergoing gluten challenge and found GI symptoms were lower in the hookworm arm after 52 weeks, and their Marsh scores did not progress despite the escalation of gluten exposure (79, 80).

Refractory celiac disease continues to be difficult to treat. Immunosuppressants, such as systemic glucocorticoids, azathioprine, 6-mercaptopurine, budesonide and cladribine, have shown various degrees of satisfactory clinical responses (43, 81–83).

GFD Challenges, Economic Burden and Health Care Costs

Like other autoimmune diseases, CeD has a considerable economical and patient-perceived disease burden (19, 84). The benefits of GFD are improvement in symptoms, nutritional status, body composition and bone mineral density within the first year of treatment (61, 85). Although improvement in serology and mucosal healing may take years to achieve (85), a recent study showed that GFD significantly altered the gut microbiome composition and function of microbial pathways, which could also mediate early alleviation of gastrointestinal symptoms (86).

Uncontrolled celiac disease has serious health consequences and can generate more than 20 systemic disorders from osteoporosis and infertility to neurological sequela and lymphoproliferative disorders (28, 87). Undiagnosed CeD is associated with an increased all-cause mortality compared with those who are seronegative (88). Causes of poor CeD control may be noncompliance to GFD, unintentional gluten ingestion, or lack of response to GFD. In Europe and the United States, the threshold of gluten-free foods is up to 20 parts per million of gluten (ppm) established by the FDA (19, 89). Strict GFD poses unique challenges for those trying to adhere to it (90). Up to 50% of patients with CeD reported gluten intake during the GFD period either intentionally or unintentionally (90). Given that gluten is ubiquitous in foods, environment and medical products, unrecognized gluten ingestion is a common cause of lack of clinical response in patients with celiac disease (90). The economic burden associated with CeD is comparable to other autoimmune conditions. When comparing ulcerative colitis to CeD in the United States, the average annual direct cost in CeD patients is higher, with excess medical costs associated with hospitalization and emergency room visits (84). Celiac disease patients in partial remission have the highest total mean all-cause costs and all-cause medical costs (91). From a patient's perspective, CeD patients are more likely to report a higher treatment burden than patients with hypertension or gastro-esophageal reflux disease, and the perceived disease burden is similar to individuals with congestive heart failure and end-stage renal disease (92). Barriers to adherence to a gluten-free diet may

also be the access to gluten-free foods and the high costs associated with gluten-free foods above that of regular foods (84).

In Canada, patients certified with celiac disease by their physicians are eligible for financial subsidies from the federal government in the form of income tax reduction under medical expenses to reimburse the incremental costs of gluten-free foods incurred in the previous year (93). However, this approach has several limitations. It is not a real-time financial subsidy that mirrors a person's day-to-day need for gluten-free (GF) products. It also disadvantages low-income families and their children with celiac disease, as tax-reduction provides little financial gain to them. Furthermore, additional costs for food transportation, gasoline or shipping fees for GF products are not covered, forcing patients to pay out of their pockets, something that many low income families cannot afford. Alternatives such as monthly allowances and strict food provision for patients with celiac disease are modelled in countries like Italy, Argentina and Spain (93). Another plausible model is practiced in New Zealand, the Republic of Ireland, and parts of the United Kingdom, where a price subsidy exists and where certain gluten-free products fall under physician prescriptions that are then covered by medical health insurance (93).

In summary, celiac disease has transformed from being a regional pediatric disease in the first half of the 20th century to a global disease affecting all ages—especially adults 40 to 60 years of age—in this millennium. It is clear that celiac disease is more prevalent than once thought. With the advances in the understanding of disease pathogenesis and disease genetics, the treatment of celiac disease has evolved beyond the dietary restriction of gluten-containing foods toward potentially new adjunctive therapies that could modify disease severity and lead to improved long-term outcomes. Celiac disease is rapidly moving forward in daily practice and is entering the mainstream of gastroenterology.

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