Mol Diag Ther 2008; 12 (5): 289-298
1177-1062/08/0005-0289/$48.00/0

Celiac Disease

Risk Assessment, Diagnosis, and Monitoring

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Contents

Abstract

Celiac disease is an autoimmune disorder occurring in genetically susceptible individuals, triggered by gluten and related prolamins. Well identified haplotypes in the human leukocyte antigen (HLA) class II region (either DQ2 [*DQA*0501-DQB*0201*] or DQ8 [*DQA*0301-DQB1*0302*]) confer a large part of the genetic susceptibility to celiac disease.

Celiac disease originates as a result of a combined action involving both adaptive and innate immunity. The adaptive immune response to gluten has been well described, with the identification of specific peptide sequences demonstrating HLA-DQ2 or -DQ8 restrictive binding motifs across various gluten proteins. As for innate immunity, through specific natural killer receptors expressed on their surface, intra-epithelial lymphocytes recognize nonclassical major histocompatibility complex (MHC)-I molecules such as MICA, which are induced on the surface of enterocytes by stress and inflammation, and this interaction leads to their activation to become lymphokine-activated killing cells.

Four possible presentations of celiac disease are recognized: (i) typical, characterized mostly by gastrointestinal signs and symptoms; (ii) atypical or extraintestinal, where gastrointestinal signs/symptoms are minimal or absent and a number of other manifestations are present; (iii) silent, where the small intestinal mucosa is

damaged and celiac disease autoimmunity can be detected by serology, but there are no symptoms; and, finally, (iv) latent, where individuals possess genetic compatibility with celiac disease and may also show positive autoimmune serology, that have a normal mucosa morphology and may or may not be symptomatic.

The diagnosis of celiac disease still rests on the demonstration of changes in the histology of the small intestinal mucosa. The classic celiac lesion occurs in the proximal small intestine with histologic changes of villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytosis. Currently, serological screening tests are utilized primarily to identify those individuals in need of a diagnostic endoscopic biopsy. The serum levels of immunoglobulin (Ig)A anti-tissue transglutaminase (or TG2) are the first choice in screening for celiac disease, displaying the highest levels of sensitivity (up to 98%) and specificity (around 96%). Anti-endomysium antibodies-IgA (EMA), on the other hand, have close to 100% specificity and a sensitivity of greater than 90%. The interplay between gliadin peptides and TG2 is responsible for the generation of novel antigenic epitopes, the TG2-generated deamidated gliadin peptides. Such peptides represent much more celiac disease-specific epitopes than native peptides, and deamidated gliadin antibodies (DGP) have shown promising results as serological markers for celiac disease. Serology has also been employed in monitoring the response to a gluten-free diet.

Despite the gluten-free diet being so effective, there is a growing demand for alternative treatment options. In the future, new forms of treatment may include the use of gluten-degrading enzymes to be ingested with meals, the development of alternative, gluten-free grains by genetic modification, the use of substrates regulating intestinal permeability to prevent gluten entry across the epithelium, and, finally, the availability of different forms of immunotherapy.

Celiac disease is an autoimmune disorder occurring in genetically susceptible individuals, triggered by gluten and related prolamins. It primarily affects the small intestine, where it progressively leads to the flattening of the small intestinal mucosa. The three cereals that contain gluten, and are thereby toxic for celiac patients, are wheat, rye, and barley.[1]

Well identified haplotypes in the human leukocyte antigen (HLA) class II region (expressing either the molecule DQ2 or DQ8) confer a large part of the genetic susceptibility to celiac disease. The antigen-presenting cells (APC) of the intestinal mucosa carry the heterodimer DQ2 (about 95% of all patients with celiac disease) or the heterodimer DQ8 (the remaining 5%).

1. Epidemiology

The recent availability of sensitive and specific serologic tests has now made it possible to assess the true prevalence of celiac disease, as such tests are able to detect cases with the typical mucosal changes that are minimally symptomatic, or even asymptomatic. We have therefore learned from screening studies that celiac disease has a very high prevalence, occurring in almost 1% of the general population throughout Europe and North America.[2]

The prevalence of celiac disease in other parts of the world has been less studied; however, data are available from Latin America, North Africa, the Near and Middle East, and Northwest India. In all of these areas celiac disease has been reported, and where prevalence data were sought, they do not differ significantly from that given for Europe and North America. Thus, it is fair to assume that celiac disease constitutes one of the most common genetically induced chronic diseases. However, celiac disease is considered extremely rare or non-existent in people with African, Chinese, or Japanese ancestry, where the prevalence of the HLA serotypes DQ2 and DQ8 is negligible.

In addition to gluten, other factors are important, such as the modalities of gluten weaning, the duration of breast feeding, and the occurrence of repeated intestinal infections. In fact, studies show that if gluten is begun in the first 3 months of life, the risk of developing celiac disease is significantly higher;[3] also, a high intake of gluten at weaning seems to be associated with an increased risk.[4] As for breast feeding, infants who are breast-fed at the time of gluten introduction and beyond are less likely to develop celiac disease later in life.[5] Finally, there is evidence that repeated rotavirus infections are more frequent in children later who later go on to develop 'celiac disease autoimmunity' than in matched controls,[6] thus suggesting that such infections may set the stage for later development of celiac disease.

2. Pathogenesis

Celiac disease originates as a result of a combined action involving both branches of immunity: adaptive and innate.

2.1 Adaptive Immunity

The adaptive immune response to gluten has been well described with the identification of specific peptide sequences demonstrating HLA-DQ2 or -DQ8 restrictive binding motifs across various gluten proteins.[7] HLA-DQ2 heterodimers on APC discerningly bind gluten peptides, presenting them to CD4+ gluten-specific T cells. Though the DQ2 binding register recognizes specific sequences, there is no single pathogenic motif. Generally, these epitopes are rich in proline and contain the negatively charged deamidated glutamine (thus, glutamic acid) residues.

The gluten-specific CD4+ T cells of the lamina propria express α/β T-cell receptors TCRs and can be isolated and cultivated *in vitro*.[8] These T cells demonstrate recognition of specific peptides presented through the interaction with DQ2 or DQ8 molecules, and induce proliferation and triggering of a T_h1 cytokine response, primarily with the release of interferon-γ.[9] In addition, this interaction mediates autoreactive B-cell activation and the production of autoantibodies to tissue transglutaminase (TG2).

2.1.1 Role of Transglutaminase (TG2)

Localized on the cell surface and in the extracellular matrix with a wide range of biologic activities, the enzyme tissue TG2 catalyzes the covalent and irreversible cross-linking of proteins, resulting in the formation of an isopeptidyl bond through deamidation. Stored intracellularly, TG2 is released during cellular injury and plays an important role in stabilizing the scaffold of connective tissues. Interestingly, TG2 is involved in the formation of active transforming growth factor-β (TGFβ) by the cross-linking of the TGFβ-binding protein,[10] and in knockout models demonstrates an impaired capacity of macrophage engulfment of apoptotic cells, leading to an abnormal inflammatory response. In addition to these enzymatic activities, TG2 is necessary for the attachment and motility of fibroblasts and monocytes via interactions with integrins and fibronectin. It can therefore be understood how disruption of this function may lead to impaired migration of fibroblasts and epithelial cells.

In the extracellular environment, TG2 plays a role in tissue matrix assembly, cell adhesion, and wound healing.[11] In celiac mucosa, TG2 expression is upregulated in the subepithelial lamina propria. Enzymatically, TG2 has a high avidity for prolamins and possesses the ability for deamidation, which transforms neutral glutamine residues into negatively charged glutamic acid. As mentioned, the introduction of these negatively charged residues into gluten peptides at specific positions favors their interaction with basic amino acids located in the anchor positions of the HLA-DQ2/DQ8 molecules, subsequently enhancing peptide binding and T-cell stimulation. Through this specific anti-gluten response, stimulated CD4+ T cells are able to induce B-lymphocyte differentiation into plasma cells capable of producing specific anti-gliadin and anti-TG2 antibodies.[12,13] Selective deamidation of conformationally intact B-cell epitopes greatly increases their antigenicity, giving birth to the newer deamidated gliadin peptide antibodies.

2.1.2 The Role of TG2 Autoantibodies

Primarily, the target antigen is the Ca^{2+} activated form of TG2.[10] Recent studies using fluorescently labeled monoclonal antibodies to immunoglobulin (Ig)A and TG2 have demonstrated co-localization along the subepithelial region of even normal-appearing intestinal biopsies prior to positive serology and overt epithelial cell damage,[14] suggesting that local autoantibody deposition may be an early phase of disease process. However, the exact role of these TG2 autoantibodies in the pathogenesis of celiac disease still remains unclear.

A particularly interesting observation is the reversal of celiac disease-associated severe liver disease once the patient is on a gluten-free diet. In patients with dermatitis herpetiformis, the presence of antibodies to both TG2 and TG3, a transglutaminase uniquely expressed in the dermal papillae of patients with dermatitis herpetiformis, suggests similarities in the mechanism of immune activation occurring within the gastrointestinal tract. And although the steps leading to autoantibody formation in celiac disease are not understood, it is known that production of IgA antibodies is dependent on T-cell facilitation of isotype switching of autoreactive B cells. However, the higher incidence of celiac disease seen among individuals who are IgA deficient is intriguing: this finding questions the real importance of specific autoantibody response (an IgA response) in disease progression.

2.2 Innate Immunity

Through screening protocols, a fairly large subset of individuals have been identified who, despite the serological presence of TG2 autoantibodies, have histologically normal mucosa and, thus, are referred to as potential celiac cases. The lack of an effector response and epithelial destruction in this subset of patients suggests that they may lack an event or events leading to the activation of cytotoxic intraepithelial CD8+ TCRα/β T lymphocytes (IEL). These IEL play an important role in the destruction of epithelial cells, and their mechanism of activation relies on innate immune responses in the epithelial compartment. Through specific natural killer receptors (NKR) expressed on their surface, IEL recognize nonclassical major histocompatibility complex (MHC)-I mole-

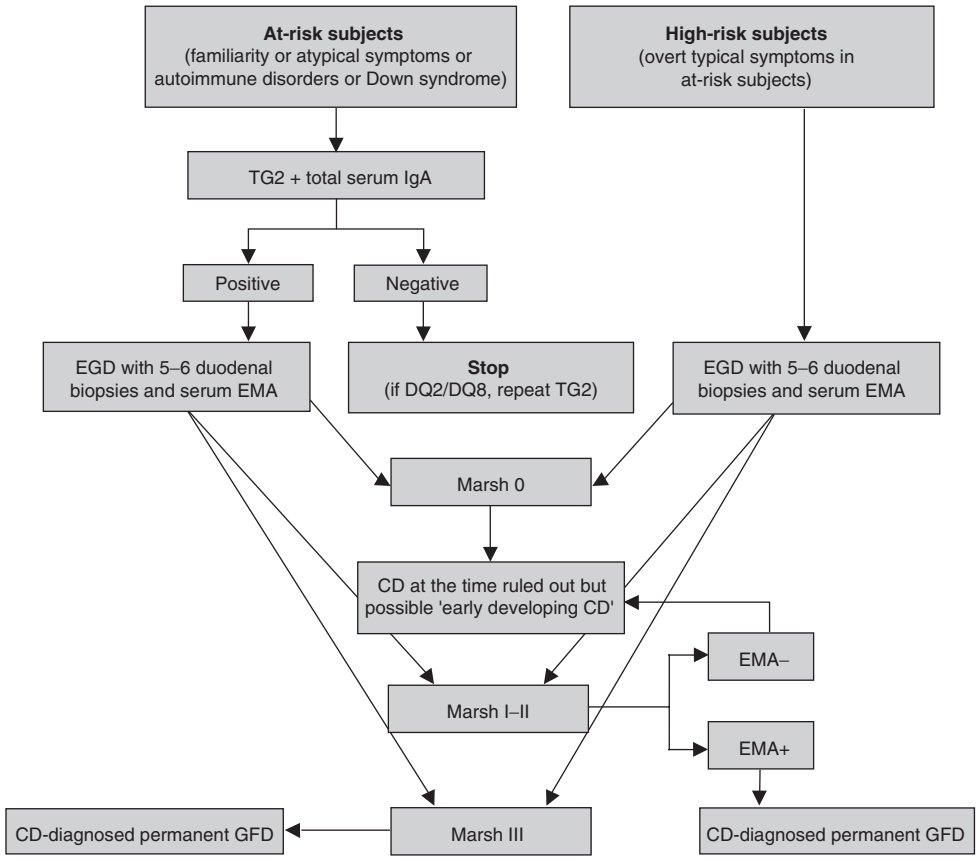

Fig. 1. Proposed diagnostic algorithm for celiac disease (CD). **DQ2/DQ8** = human leukocyte antigen DQ2 or DQ8 serotypes; **EGD** = esophagogastroduodenoscopy; **EMA** = endomysium antibodies-IgA; **GFD** = gluten-free diet; **Ig** = immunoglobulin; **Marsh** = Marsh classification score for CD; **TG2** = tissue transglutaminase.

cules, such as MICA, induced on the surface of enterocytes by stress and inflammation. This interaction leads to the activation of these armed effector IEL to become lymphokine-activated killing cells, and effect epithelial cell death in a TCR-independent manner.[15] This killing is particularly enhanced through the innate cytokine, interleukin (IL)-15, expressed highly in celiac mucosa,[16] expanding CD8+ IEL activation and upregulating the expression of MICA on intestinal epithelial cells.

3. Diagnosis

As celiac disease can present in many forms (and even be asymptomatic), we give a very succinct description of its clinical presentations in order to clarify under what circumstances the diagnostic process should be initiated (see figure 1).

Patients with celiac disease may present with four possible groupings of symptoms[1] (see table I):

- Typical: characterized mostly by gastrointestinal signs and symptoms.
- Atypical or extraintestinal: gastrointestinal signs/symptoms are minimal or absent. Various extraintestinal manifestations are present (see table II).
- Silent: the small intestinal mucosa is damaged and celiac disease autoimmunity can be detected by serology, but there are no symptoms. Table III lists groups of patients who are at increased risk of having celiac disease, mostly of the silent form.
- Latent: mucosa morphology is normal. These individuals have genetic compatibility with celiac disease and may also show positive autoimmune serology and may be entirely asymptomatic or present with varying degrees of signs and symptoms.[17] Full-blown celiac disease may ensue at a later time. For an expanded presentation of the clinical manifestations and associated conditions see Guandalini.[18]

3.1 Pathology

The diagnosis of celiac disease still rests on the demonstration of changes in the histology of the small intestinal mucosa. The classic celiac lesion occurs in the proximal small intestine, with

Table I. The four presentations of celiac disease

Type	Presentation
Typical	Predominant gastrointestinal signs/symptoms
	Vomiting
	Anorexia
	Constipation
	Diarrhea
	Failure to thrive
	Recurrent abdominal pain
Atypical or extraintestinal	Gastrointestinal signs/symptoms are minimal or absent. Most common signs/symptoms of extraintestinal celiac disease are reported in table II
Silent	No signs/symptoms. Gluten-dependent duodenal mucosa changes are typical of celiac disease
Latent	Signs/symptoms may or may not be present. Duodenal mucosa normal. Gluten-dependent changes with or without symptoms appear later in time

histologic changes of villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytosis. Three distinctive and progressive histological stages have been described, as classified by Marsh.[19] In detail, the histologic changes of celiac disease are classified as follows:

- type 0 or 'preinfiltrative' stage (normal);
- type 1 or 'infiltrative' lesion (increased intraepithelial lymphocytes);
- type 2 or 'hyperplastic' lesion (type 1 + hyperplastic crypts);
- type 3 or 'destructive' lesion (type 2 + villous atrophy of progressively more severe degrees, denominated as 3a, 3b, and 3c).

Despite growing evidence that celiac disease can be identified early, when serology is clearly positive and with changes of the intestinal mucosa still in their early phases (i.e. Marsh I or II), current 'official' guidelines[20] still call for the documentation of Marsh III changes before a diagnosis of celiac disease can be made. Clearly, this is an area in evolution, and it is likely that new diagnostic criteria will have to be generated.

3.2 Role of Antibodies in the Clinical Assessment of Celiac Disease

Currently, serologic screening tests are primarily utilized to identify those individuals in need of a diagnostic endoscopic biopsy (table IV). Serology is also important in monitoring clinical response to a gluten-free diet. The evolution of celiac serology has led to the recognition of more specific target antibodies, while the improvement of technical approaches has resulted in increasingly more consistent and reliable assays. Screening in large population studies has also identified a wide range of presentations and manifestations of celiac disease in the population, and has brought new insights into this largely undiagnosed condition.

The first of these serologic assays to be developed utilized the antigliadin antibodies (AGA) discovered in the 1960s;[21] however, these food protein antibodies were later superseded by the 1984 discovery[22] of IgA to endomysial antigen (EMA), which is localized to the perivascular connective tissue that lines smooth muscle bundles. In 1997, the target antigen was found to be the TG2 enzyme,[23] recognized to be the major antigenic target for the previously described endomysial antibodies. The presence of antibodies to gluten and TG2 is strictly dependent on dietary exposure to gluten. The EMA antibody test, although essentially as accurate as TG2, being an immunofluorescence assay, is observer dependent; in addition, it carries elevated costs. Based on the current evidence and practical considerations, including accuracy, reliability, and cost, measurement of IgA antibody to human recombinant TG2 is the chosen standard for initial diagnostic testing.[20]

In celiac disease, both IgA and IgG isotypes of anti-TG2 are present, although IgA antibodies demonstrate the highest disease

Table II. Extraintestinal manifestations of celiac disease

Dermatitis herpetiformis
Permanent enamel hypoplasia
Iron-deficient anemia resistant to oral iron supplements
Short stature, delayed puberty
Chronic hepatitis with hypertransaminasemia
Arthritis
Osteopenia/osteoporosis
Epilepsy with occipital calcifications
Primary ataxia, white-matter focal lesions
Psychiatric disorders

Table III. Groups that are at risk of having silent celiac disease

Condition	Approximate prevalence of celiac disease (%)
Tyepe 1 diabetes mellitus	8–10
Thyroiditis	3–5
Sjögren syndrome and other connective tissue diseases	3–4
Down syndrome	10–12
Williams syndrome	5
Turner syndrome	5
First-degree relatives of celiac patients	8–10

specificity. Thus, IgA-TG2 is generally acknowledged as the first choice in screening for celiac disease, displaying the highest levels of sensitivity (up to 98%). Despite this, IgA-TG2 is not a perfect test. Its specificity is not great, particularly for mildly increased antibody titers, and the sensitivity decreases in those with minimal degrees of mucosal damage.[24,25] In these situations, IgA-EMA are utilized in conjunction with intestinal biopsy to confirm the diagnosis. Though EMA-IgA testing has close to 100% specificity and a sensitivity of greater than 90%, this test has some drawbacks, such as low reproducibility and, as mentioned, high interobserver variability.

Clinical studies have estimated a 10- to 20-fold increased risk of celiac disease in patients with selective IgA deficiency.[26] This represents a special challenge in this group, since the specific IgA class antibodies (AGA, TG2, EMA) are not produced in patients with celiac disease. IgG anti-TG2 and IgG EMA have shown variable sensitivity and typically high specificity;[27,28] however, IgG anti-deamidated gliadin peptide (DGP) antibodies have shown promise, with one study showing a sensitivity of 84.4% and specificity of 98.5%.[29]

3.3 Deamidated Gliadin Peptide Antibodies

The interplay between gliadin peptides and TG2 is responsible for the generation of novel antigenic epitopes, the TG2-generated DGPs; therefore, such peptides represent much more celiac disease-specific epitopes than native peptides. Patients with celiac disease develop antibodies against these peptides that can, thus, be measured in the serum as markers of celiac disease. Currently, DGPs are showing promise as serologic markers and are being studied both for monitoring the treatment course and as a potential screening tool for celiac disease.[30] Table IV lists in detail the serologic markers of celiac disease and their sensitivities and specificities.

3.4 Role of Genetic Analysis in the Diagnosis of Celiac Disease

Genetics plays a key role in the multifactorial pathogenesis of celiac disease. Familial aggregation is seen with 5–15% of patients with celiac disease, and a striking 83–86% concordance rate is noted among monozygotic twin pairs.[31] HLA-linked genes on chromosome 6p21 (*CELIAC1* region) provide a significant proportion of the genetic risk for celiac diseases and the role of HLA-DQ2 and -DQ8 is crucial in the pathogenic recognition of gluten peptides. In particular, the CD4+ gluten-specific T cells in celiac lamina propria is restricted by the DQ2 or DQ8 molecules on APC. However, as much as 40% of the population have either HLA-DQ2 or -DQ8 serotypes, and yet they do not develop celiac disease. It is estimated that only about 50% of the genetic load is accounted for by these HLA genes.[32] Thus, the significant role of non-HLA genes as contributors to the development of disease is generally accepted; however, population-based linkage studies have so far failed to identify any clear associations.[33-35] Through a genome-wide association study, a recent paper[36] identified a

Table IV. Serological studies for the diagnosis and clinical follow-up of celiac disease

Serologic marker	Assay type	Substrate	Sensitivity (%)	Specificity (%)
IgA-AGA	ELISA	Human	73–96	80–95
	ELISA	Human	40–73	77–87
IgA-EMA	Indirect IF	Monkey esophagus	80–97	97–100
	Indirect IF	Monkey esophagus	39–100	98–100
IgA-TG2	ELISA	Human recombinant	85–95	95–96
	ELISA	Human recombinant	68–100	80–100
IgA-DGP	ELISA	Human	84–98	90–94
	ELISA	Human	84–97	99–100

AGA = antigliadin antibodies; **DGP** = deamidated gliadin peptide antibodies; **ELISA** = enzyme-linked immunosorbent assay; **EMA** = endomysium antibodies-IgA; **IF** = immunoflurescence; **Ig** = immunoglobulin; **TG2** = tissue transglutaminase.

region on 4q27 that contains the *IL2* and *IL21* genes; it is estimated that this region explains less than 1% of the increased familial risk for celiac disease, suggesting that additional genes remain to be identified.

The HLA-DQ molecules are heterodimers consisting of an α and β chain. Specifically, it is the combination of alleles encoding the α chain DQA1*05 and β chain DQB1*02 of the HLA-DQ2 heterodimer that are associated in more than 90% of celiac disease in a given population, whereas the remaining carry DQ8 haplotypes. In an European registry, 947 of 1008 patients had the classical HLA haplotypes; however, 61 of 1008 patients with celiac disease did not have either the DQ2 nor DQ8 heterodimers, and 57 were found to encode half the DQ2 heterodimer.[37,38]

In a more recent report,[39] seven more susceptibility loci were identified through population-based genetics evaluation.

These studies in genetic susceptibility highlight the important role of genetic testing in the diagnosis of celiac disease. In the clinical setting, HLA typing is primarily relevant for the testing of susceptibility to celiac disease, particularly among family members, given that the absence of HLA-DQ2 or -DQ8 (and DQ2 heterodimer) excludes the possibility of celiac disease. Thus, the test can and should be employed only as a tool, when negative, to rule out the possibility of such diagnosis (negative predictive value 100%), while when it is positive its predictive value is negligible, at less than 3%.

4. Treatment and Monitoring

Once the diagnosis of celiac disease has been confirmed, patients need to follow a strict gluten-free diet. Total lifelong avoidance of gluten ingestion is the cornerstone of treatment for celiac disease. Although a 'zero tolerance' policy is recommended, it is known that sensitivity to ingested gluten varies greatly amongst patients. A recent meta-analysis[40] estimated, from all published data, that gluten in amounts less than 10 mg/day is safe to consume in all cases, while amounts larger than 100 mg/day are likely to result in the majority of patients exhibiting some signs of immune reactivation and/or symptoms. It may be worth remembering that a typical Western diet contains an average of 156 g of wheat (i.e. about 40 g of gluten) a day. Wheat, rye, and barley are the grains containing the immunogenic peptides. When patients with symptomatic celiac disease adhere to a gluten-free diet, they can typically be expected to resolve their gastrointestinal symptoms within a few weeks, showing additional normalization of nutritional measures, improved growth in height and weight (if children), and normalization of hematologic and biochemical parameters. Furthermore, treatment with a gluten-free diet reverses the decrease in bone mineralization and risk for fractures. Symptomatic patients treated with a gluten-free diet also improve in their sense of physical and psychological well-being, as documented by a recent quality of life study.[41]

For a long time, oats were considered toxic and their elimination from the diet was recommended. However, during the past decade or so, a growing body of scientific evidence obtained from *in vitro* studies and clinical investigations, particularly in adults but also more recently in children, has allowed us to conclude that oats are indeed totally safe for the vast majority of patients with celiac disease.[42] Despite this conclusion, the cross-contamination of oats by gluten is still a concern because of uncontrolled harvesting and milling procedures, and the potential for lines of manufacturing employed in wheat-based flours also being used in the preparation of oat-based foods.

Serology has been employed in monitoring the response to a gluten-free diet. The percentage of negative serology increases over the course of a such a diet; the first antibody to disappear, between 6 and 12 months after exclusion of gluten, is IgA-AGA. This is followed by the disappearance of IgA-TG2 and, later, IgA-EMA.[43] Although the normalization of EMA or TG2 does not necessarily guarantee good dietary compliance or mucosal recovery,[44] it is generally not necessary to perform other biopsies in order to better assess dietary response, except in selected cases when the symptomatic response is unclear. In adults, there is evidence that even after adhering to a gluten-free diet the mucosa may not completely recover.[45] Although the pathophysiology of such persistent inflammation is currently unclear, follow-up bioptic controls may be indicated in cases where the response to the diet is not unequivocal.

Refractory celiac sprue is defined as symptomatic severe enteritis that does not respond to a strict gluten-free diet even after 6 months, and is not accounted for by other causes of enteropathy or overt intestinal lymphoma. Patients with refractory celiac sprue are often elderly and have a poor nutritional status because of chronic malabsorption and protein losing enteropathy. Approximately 75% of such patients have an aberrant clonal intraepithelial T-cell population, a condition referred to as enteropathy-associated intestinal T-cell lymphoma. Serologic studies are often negative in this rare condition, but patients with refractory celiac sprue occasionally respond to immunosuppressive agents. Patients with refractory sprue may require treatment with corticosteroids and other immunosuppressants, including azathioprine or ciclosporin, or even total parenteral nutrition. A program of total parenteral nutrition allows the correction of nutritional problems,

while antibiotics and pancreatic enzyme supplements help correct the digestive and absorptive capacity of the gut.

5. Newer Forms of Therapy

Despite the gluten-free diet being so effective, there is a growing demand for alternative treatment options. This stems in part from the current lifestyle were eating out is an important part of social life (thus posing a constant risk for celiac patients) and the rare but serious occurrence of refractory sprue, where the diet fails to resolve the intestinal damage.

5.1 Gluten-Degrading Enzymes

Several approaches have recently been taken to develop alternative treatments. One is based on the use of bacterial prolyl-endopeptidases to promote the complete digestion of cereal proteins and, thus, destroy immunodominant T-cell epitopes. Khosla et al.[46] investigated the use of such enzyme therapy for the luminal digestion of dietary gluten in patients with celiac disease.

Prolyl-endopeptidase enzymes are attractive drug candidates for the oral treatment of celiac sprue because of the ability to accelerate gluten digestion in the gastrointestinal tract. In biopsy studies, very high concentrations of prolyl-endopeptidases have been shown to reduce the amount of immunostimulatory gliadin peptides (both innate immune and T-cell activating) reaching the mucosa.[46]

5.2 Modified Grains

Grains that have little or no content of immunogenic sequences and that allow reasonable baking quality are under development for dietary consumption. Potentially, these grains can be developed either through the selective breeding of early wheat species or using small interfering RNA (siRNA) technology to mutate or silence immunostimulatory sequences. The possibility of producing 'gluten-free' wheat would offer celiac patients options for a nutritionally balanced diet, and if used among the general population it may offset the rise in the incidence of celiac disease. On the other hand, one needs to be aware of the theoretical risk of contamination of such new grains with natural wheat, something that currently available techniques to detect even minimal amounts of gliadin-derived peptides[47] may not be able to assess.

5.3 Blocking Gluten Entry across the Intestinal Epithelium

Elucidation of disease pathogenesis has created opportunities for novel therapeutic approaches to celiac disease. Previous studies have demonstrated increased lactulose/mannitol ratios resulting from the increased permeability of the small bowel in patients with celiac disease. Thus, some of the newer therapeutic approaches have been focusing on the prevention and protection of the 'leaky gut'. The use of the zonulin inhibitor larazotide (AT-1001) to correct intestinal barrier defects has already been successfully explored in an animal model of autoimmunity.[48] More recently, larazotide has been tested in an inpatient, double-blind, randomized, placebo-controlled human clinical trial to determine its safety, tolerability, and preliminary efficacy.[49] No increase in adverse events were reported among patients exposed to larazotide compared with placebo. Following acute gluten exposure, a 70% increase in intestinal permeability was detected in the placebo group, whereas no changes were seen in the larazotide group. Furthermore, after exposure to small amounts of gluten, interferon-γ levels increased in 4 of 7 patients in the placebo group but in only 4 of 14 patients in the larazotide group. Gastrointestinal symptoms were significantly less frequent among patients of the larazotide group.[49] However, one should remain cognizant of the fact that the entry of toxic gliadin peptides across the intestinal barrier does not exclusively occur through the paracellular route, and that transcellular penetration may still be ongoing even when the paracellular route is effectively blocked.

5.4 Immunotherapy

IL-15 is a cytokine that has been shown to be a central innate mediator of gluten-specific effects in celiac disease, making IL-15 neutralizing agents promising as potential therapeutic candidates. Two such compounds are in clinical trials; a humanized anti-IL-15 antibody, HuMax-IL-15, is in phase II trials for rheumatoid arthritis[50] and possibly other inflammatory conditions; and an IL-15/Fc chimeric protein, CRB-15,[51] is in preclinical testing. Earlier studies suggest that HuMax-IL-15 has acceptable adverse effects and might, therefore, be a candidate for testing in patients with celiac disease. Recent phase I studies[52] demonstrated the potential for the disruption of IL-15 by the monoclonal antibody Mikβ1, which targets CD122, the β-subunit shared by the IL-2 and IL-15 receptors.

It was recently reported that alemtuzumab,[53] a monoclonal antibody targeting CD52, was utilized in a patient with refractory celiac sprue with an aberrant TCRγδ population of IEL in order to prevent progression to enteropathy-associated intestinal T-cell lymphoma.

6. Conclusion

Celiac disease is a fascinating and still not fully understood condition, and it is clearly not the straightforward malabsorption syndrome it was regarded as for many decades.

Diagnosis has been made simpler on one hand by improved accuracy of serological tests, and an intelligent use of the information on the genetic component. Finally, recent developments are offering new clues as to its pathogenesis and, for the first time new treatment options, in addition to the gluten-free diet, are beginning to appear.

Acknowledgments

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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