Celiac Disease: A Comprehensive Review on Diagnosis, Management, and Future Directions

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Abstract: Celiac disease is a prevalent autoimmune inflammatory enteropathy affecting the small intestine. This comprehensive review discusses the disease's etiology, diagnosis, management, and future research directions. The article emphasizes the importance of early detection and lifelong adherence to a gluten - free diet for successful management and highlights the need for further research on dietary treatment options.

Keywords: celiac disease, autoimmune, gluten, diagnosis, management, gluten - free diet, future research

1. Introduction

1.1 Definition

Celiac disease (CD) is an autoimmune inflammatory enteropathy that primarily affects the small intestine and may also exhibit systemic symptoms. The ingestion of gluten - containing foods such as wheat, barley, rye, and spelt triggers the onset of this condition. ¹, ² The confirmation of the diagnosis in patients who are positive for HLA - DQ2/8 involves the demonstration of serum autoantibodies against endomysium (EMA) or tissue transglutaminase (tTG). Additionally, a characteristic histological picture in the duodenum, which includes inflammatory infiltrate, crypt hyperplasia, and villous atrophy, is observed. Finally, remission of clinical and serologic findings is achieved through adherence to a gluten - free diet. Individuals diagnosed with CD may exhibit symptoms such as diarrhea and impaired growth, while others may remain asymptomatic. ¹, ³, ⁴

1.2 Epidemiology

CD can potentially present clinically at any age in an individual's lifespan. The condition is diagnosed with comparable frequency in both adult and pediatric populations, with a current trend towards a higher incidence among school - aged individuals as opposed to those in the preschool age range. ¹, ⁵ The incidence rate of CD among the general populace ranges from 0.5% to 1%. The actual occurrence, identification, and categorization of a particular condition have increased upward trend during the last two decades. Individuals with autoimmune disorders such as type 1 diabetes exhibit a higher incidence rate. Individuals with a familial relationship with CD patients have a 10% chance of developing the condition. ⁶, ⁷

The findings of a systematic review of the worldwide prevalence of CD revealed a seroprevalence rate of 1.4% and 0.7% by histology findings. ⁵ The prevalence rates varied across different continents, ranging from 1.3% (South America, based on 11 studies) to 1.8% (Asia, based on 20 studies). This might overestimate the true prevalence of CD, given the imperfect specificity of CD serologies. This study also found 0.7% biopsy - diagnosed CD, which varied by continent and location. Because not all serology - positive CD patients undergo comprehensive endoscopic assessment, biopsy - proven CD may be underestimated. Another study found a 0.5% to 1.0% prevalence among Americans, Europeans, Australians, North Africans, Middle Easterners, Indians, and maybe northern Chinese (depending on HLA - DQ2 and DQ8). Finland, Mexico, and North African Sahrawi youngsters have a 2%–5% prevalence. ¹, ⁵, ⁸

1.3 Pathogenesis

CD is caused by a strong immune reaction to gluten that damages the small intestine and causes malabsorption and autoimmune disease. Gliadin, a gluten - derived peptide, damages the small intestine. Local inflammation causes tiny intestinal villi destruction. ⁵, ⁶ Destroying the gut surface causes malabsorption and impaired function. The digestive system is directly affected by nutrient absorption, but other physiological systems are indirectly affected. ¹, ⁵, ⁹

CD is a well - defined disorder of the immune system. Individuals impacted by this condition possess a genetic inclination, specifically HLA - DQ2 or HLA - DQ8. The precipitating factor is well - defined as gluten, and these individuals exhibit a heightened sensitivity to particular autoantibodies that target the naturally occurring human enzyme known as tissue transglutaminase (tTG). ¹, ⁸, ¹⁰ The autoantigen tTG is known to have an essential part in the pathogenesis of CD. Its function involves enhancing the immunogenicity of gluten peptides that are already immunogenic through a chemical process called deamidation, which occurs in the small intestine. ¹, ⁸

The alcohol - soluble portion of wheat protein, gluten, is ingested daily (10–20 g). Some gluten peptides are taken up by the small - intestine epithelium by gastrointestinal enzymes. They stimulate gluten - specific T cells on the antigen - presenting cells of people with HLA - DQ2 or HLA - DQ8 (approximately 90% and 10% of CD patients, respectively). ¹, ⁶, ⁸ In this process, an enzyme and autoantigen tTG deamidate a neutral glutamine residue to an acidic glutamic acid residue, thereby facilitating the binding of gluten peptides to HLA - DQ2 or HLA - DQ8 and...
enhancing the inflammatory T - cell response. Intestinal epithelial and dendritic cells produce IL - 15, which stimulates intraepithelial lymphocytes. Other cytokines involved in the typical immune response of CD include IFN, TNF - a, IL - 8, IL - 18, and IL - 21. The cytotoxic effects of activated T cells in the lamina propria and epithelium include apoptosis of enterocytes, atrophic remodeling of the mucosa, and malabsorption. 1, 4, 11

Recent studies have demonstrated that amylose - trypsin inhibitors (ATI), a type of resistance protein in wheat, rye, and barley, can stimulate the innate immune system in individuals with CD and non - celiac wheat intolerance. 1, 12 The prevalence of HLA - DQ2 or - DQ8 in the general population ranges from 30% to 40%, with additional genetic predispositions identified in recent years that have a smaller impact (approximately 3 - 4% overall compared to 50% for HLA - DQ2/8). Consequently, other factors such as early and extensive gluten exposure, gastrointestinal infections, and medication use are now considered potential precipitating factors for CD. 1, 8, 13

1.4 Clinical presentation and diagnosis

The classic manifestations of CD are rarely seen in both adult and pediatric populations. The nomenclature "celiac sprue" is attributed to the presence of prevalent indications such as fatigue and gastrointestinal distress, specifically diarrhea. 1 Additional gastrointestinal symptoms include abdominal distension, discomfort or pain, emesis, and constipation. During childhood’s developmental stage, the failure to thrive holds significant historical value, whereas, in the adult stage, the corresponding manifestation would be unexplained loss of body weight. 1, 6 A majority of the diagnosed cases exhibit oligosymptomatic or clinically atypical characteristics. These characteristics are often linked with various medical conditions such as anemia, osteoporosis, musculoskeletal and neurological disorders, endocrinopathies, or skin diseases. The latent or potential CD, which includes asymptomatic and oligosymptomatic forms with or without the typical pathological findings of CD in the small - intestine mucosa, is primarily identified through serological screening tests. 1, 6, 14

The clinical presentation of CD may be dominated by extraintestinal manifestations, which may overshadow intestinal symptoms. However, timely and accurate diagnosis followed by adherence to a gluten - free diet (GFD) may improve these manifestations. 1, 6, 7 In addition to gastrointestinal manifestations, various symptoms associated with this condition have been reported. These include joint pain, mood disturbances such as depression, recurrent aphthous ulcers in the oral cavity, iron deficiency anemia, ataxia, chronic headaches, coagulopathy resulting from impaired absorption of vitamin K, delayed onset of menarche, osteoporosis, and neurological symptoms such as muscle weakness, paresthesias, seizures, and ataxia. 1, 4, 15 Certain obstetric complications, including preterm labor, growth restriction, and stillbirth, are prevalent among women who have not received treatment for CD. Duhring’s dermatitis herpetiformis is a dermatological disorder that arises from gluten intolerance. Like enteropathy, it typically positively responds to eliminating gluten from the individual’s diet. 1, 6, 16

1.5 Serologic

The initial step in a diagnostic procedure typically involves the administration of serological examinations. The two tested antibodies are anti - tissue transglutaminase antibodies, which are quantitatively measured through enzyme - linked immunosorbent assay (ELISA), and anti - endomysial antibodies. 1, 5, 6 Serologic antibody tests are recommended for individuals who are suspected of having CD or are known to be at risk for the condition. It is recommended that patients consume food containing gluten for a minimum of several days or weeks prior to undergoing a serologic antibody test, such as a small - intestine biopsy. This is due to the fact that serum antibodies have a half - life of approximately 30 to 60 days. 1, 5, 6

ELISA blood testing for IgA anti - tissue transglutaminase antibodies (tTGA) is the best serological method. These antibodies have a sensitivity of 97%, a specificity of 96%, and an accuracy of 98%. IgA anti - endomysial (IgA EMA) antibodies are used as a confirmatory test in tTGA positive cases owing to their greater specificity (approximately 100% versus 91% of tTGA). In 2% - 10% of individuals with IgA deficiency and CD, tTG - IgG testing is appropriate. IgA deficiency causes false negatives. IgA EMA has the highest specificity (nearly 100%), sensitivity (94%), and diagnostic accuracy (97%). 1, 6 EMA is costly, difficult, operator - dependent, and yields only qualitative results. The most specific serological test is the anti - EMA IgA test, which should be performed to confirm a low anti - tTG level. Anti - tTG and anti - EMA IgG have limited sensitivity. Indirect subjective immunofluorescence detects EMA regularly. IgA deficiency and older children might potentially make these antibodies erroneously negative. Intestinal infections, chronic liver illness, congestive heart failure, and hypergammaglobulinemia might cause false positives. All serologically positive individuals should have upper endoscopy with duodenal biopsies. Negative serological testing and substantial clinical suspicion warrant endoscopy. 1, 5, 13

1.6 Histology

Endoscopy intestinal biopsy is the gold standard for adult CD diagnosis. Endoscopy generally shows extensive abnormalities in the proximal small intestine, such as scalloping of duodenal folds, mosaic mucosal pattern, and mucosal atrophy. CD histology evaluates villous atrophy, crypt hyperplasia, enterocyte height, and inflammatory infiltrates in small - intestine mucosal biopsies. 1, 6 Histologic assessment according to the Marsh classification requires at least four biopsies from the four quadrants of the descending duodenum and one or two from the bulb. Mucosal lesions frequently have a mosaic pattern (“patchy lesions”) rather than covering the full surface. Marsh III a – c lesions (partial to complete villi loss) are typical. 1, 6, 17, 18 CD diagnosis is also confirmed when crypt hyperplasia is observed alongside a minimum of 25 intraepithelial lymphocytes per 100 enterocytes in the absence of villous atrophy, commonly known as a Marsh II lesion. This confirmation is contingent

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Upon the detection of autoantibodies, the Marsh I lesion, characterized by the isolated proliferation of intraepithelial lymphocytes with a minimum count of 25 per 100 epithelial cells, is an unspcific observation that exhibits a positive predictive value of approximately 15%. The utility of immunohistochemical techniques, specifically the deposition of mucosal IgA - TG2, remains a topic of ongoing discussion. Table 1 shows Marsh Categorization of celiac disease histology.

Table 1: Marsh categorization of histlogic findings in celiac disease

<table>
<thead>
<tr>
<th>Marsh 0</th>
<th>Normal mucosal architecture without significant intraepithelial lymphocytic infiltration.</th>
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<tbody>
<tr>
<td>Marsh I</td>
<td>Lymphocytic enteritis: Normal mucosal architecture with marked infiltration of villous epithelium by lymphocytes; arbitrarily defined marked as more than 25 lymphocytes per 100 enterocytes</td>
</tr>
<tr>
<td>Marsh II</td>
<td>Lymphocytic enteritis with crypt hyperplasia: intraepithelial lymphocytosis and elongation and branching of crypts in which there is an increased proliferation of epithelial cells</td>
</tr>
<tr>
<td>Marsh III</td>
<td>Intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy. There are 3 distinct stages of villous atrophy</td>
</tr>
<tr>
<td>Marsh IIIA</td>
<td>In partial villous atrophy, the villi are blunted and shortened. Arbitrarily, samples are classified as partial villous atrophy if the villus - crypt ratio is less than 1:1</td>
</tr>
<tr>
<td>Marsh IIIB</td>
<td>In subtotal villous atrophy, villi are clearly atrophic but still recognizable.</td>
</tr>
<tr>
<td>Marsh IIIC</td>
<td>In total villous atrophy, villi are rudimentary or absent, and the mucosa resembles colonic mucosa.</td>
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The duodenal biopsy and serologic testing for CD should be done at the same time when the patient is symptomatic, and a gluten - free diet should not be started until after the biopsy. Normal mucosal histology rules out CD, although visual examination cannot show Marsh II lesions. Because CD is so prevalent, biopsies should always be collected during gastroduodenoscopy. Tissue samples should be tangentially implanted for histological processing and accurately examined using the Marsh criteria (unfortunately, this is generally not done). A gluten - free diet does not need endoscopic documentation of histological remission in patients who achieve clinical and serological remission. Capsule endoscopy may help identify atypcal or distant small - intestine involvement in difficult instances like refractory CD.

1.7 Genetic Analyses

HLA testing should not be conducted routinely in all cases of CD; it is only necessary when the diagnosis is questioned. Human leukocyte antigen (HLA) is a useful diagnostic test. Certain HLA genotypes have been found to be significantly linked to CD. Diagnostic procedures can incorporate HLA testing. Joint BSPGHAN and Celiac UK guidelines published in 2013 indicate, for instance, that positive serological tests with positive HLA typing in the presence of typical symptoms may be accepted as diagnostic confirmation without needing a biopsy.

1.8 The screening of persons at risk

This group involves asymptomatic people at risk with an underlying genetic or autoimmune illness and those with an oligosymptomatic clinical picture indicative of CD. tTG - IgA testing should be done every two or three years for HLA - DQ2/8 carriers. After a CD diagnosis, genetic counseling and testing of first - degree relatives for the HLA - DQ2/8 genotype or anti - tTG antibodies are advised. According to a comprehensive Italian study conducted on individuals with CD, it was observed that nearly 30% of the participants also exhibited symptoms of autoimmune disorders, including but not limited to type 1 diabetes, autoimmune thyroiditis (Hashimoto’s disease, Graves’ disease), and autoimmunity hepatitis. Therefore, the presence of CD serves as a basis for conducting additional autoimmune diagnostic examinations. This is because CD exhibits a shared fundamental genetic susceptibility with other autoimmune disorders, namely HLA - DQ2 or HLA - DQ8, which are linked to HLA - DR3 and HLA - DR4.

2. Management

2.1 Life - long gluten - free diet

Primary therapy for CD is a gluten - free diet for life. It affects people's life and is hard to sustain. The mucosal injury heals in 1 - 2 years and clinical recovery occurs within weeks. A GFD prohibits wheat (and its gluten - containing derivatives bulgur, couscous, and seitan), rye, and barley. Oats are difficult to eliminate. Avenin, a gluten - related peptide, is found in oats. Fiber in oats might cause symptoms too. Therefore, oat consumption should not exceed 50-60 g/day and patients should be clinically and serologically monitored. In serious illness, avoid oats. Gluten may cause mucosal atrophy in as low as 1/100th of a piece of bread (50 mg). <20 ppm of gluten (6 mg/day) is gluten - free. Patients should be mindful of nondietary gluten sources including toothpaste and lipstick. CD patients may have brush border lactase insufficiency due to surface epithelial cell destruction, hence milk and dairy products should be avoided during therapy. All patients should take a gluten - free multivitamin since vitamin B insufficiency is frequent following a GFD.

Early diagnosis and therapy are crucial in pediatric CD, since growth retardation, poor dentition, and osteoporosis may be permanent. Observational studies show that prolonged nursing and progressively introducing gluten in the first year of life may minimize the incidence of CD in childhood. In fact, in terms of dietary restriction, GFD is unsuccessful in the subset of individuals afflicted with refractory CD (RCD). After 1 year on GFD and eliminating alternative reasons for villous atrophy or malignancy, 1.5% of CD patients develop RCD, characterized as clinical malabsorption and villous atrophy. Inadvertent gluten consumption is the major cause of chronic villous atrophy. RCD type 2 has a greater fatality rate than RCD type 1 due to its more severe malnutrition and increased likelihood of lymphoma. Corticosteroids and immunosuppressants like azathioprine or cyclosporin may relieve clinical symptoms in most individuals with these variants of the illness. However, viable therapies for both
forms of RCD have not yet been developed. These medicines may increase the risk of T - cell lymphoma, thus they should be used with cautiously, especially in RCD type 2 patients. Recently, anti - T cell nucleoside analogues Chlormidine and Pentostatine and stem cell transplantation have been employed with moderate effectiveness. 3, 8, 13

Current endeavors are being made to establish efficacious pharmacotherapy to provide support for individuals who adhere to a rigorous gluten - free diet. This is because patient compliance with GFD is frequently suboptimal, particularly in patients with few symptoms, and some individuals may experience adverse reactions to minute amounts of gluten, as low as 50 mg per day, equivalent to a single noodle. Various methods for drug treatment are available, such as 3, 8, 13:

1) Gluten - degrading enzymes
Enzyme supplementation with bacterial prolyl - endopeptidase from diverse microbes has been suggested to expedite gluten breakdown in the gastrointestinal system and eliminate T cell epitopes. Gluten peptides may be cleaved by proline - specific prolyl - endopeptidase. Two therapeutic candidates, ALV003 and AN - PEP (Aspergillus niger prolyl - endopeptidase), are in clinical development. In a stomach - compatible pH, AN - PEP destroys gluten peptides. Thus, this enzyme may be acceptable for oral supplementation. 5, 8

2) Blocking gluten entry across the intestinal epithelium
The larazotide (AT - 1001) zonulin inhibitor has been shown to effectively address deficiencies in the intestinal barrier. An animal model has been investigated. AT - 1001 is presently the most extensively researched pharmacological agent for the treatment of CD, having undergone phase II clinical trials [104]. AT - 1001 - treated patients had an improved symptom score, a diminished autoantibody response and pro - inflammatory production, and decreased urinary nitrate excretion compared to placebo - treated patients. 5, 8

3) Rho/Rho kinase inhibition
The present study has elucidated that the augmentation in intestinal permeability is contingent upon Rho kinase (ROCK) activity. In addition to its role in regulating tight junction structure and function, Rho - associated coiled - coil - containing protein kinase (ROCK) has been identified as a key regulator of axon growth. The drug has the potential to determine the efficacy of ROCK inhibition in mitigating the gluten - induced elevation of intestinal permeability in this cohort of individuals. 5, 8

4) Immunotherapy and vaccines
IL - 15 monoclonal antibodies (AMG 714) are being tested in gluten challenge and RCD type II patients in phase 2 research, although further safety studies are required to obtain and compete for the license. IL - 15 blocking antibodies may trigger intra - epithelial lymphocyte death in human IL - 15 transgenic mice intestinal epithelium. Finally, gliadin peptide desensitization by vaccination (Nexvax2) is another treatment option for CD patients. The experiment cleared phase I despite substantial adverse effects including vomiting and abdominal discomfort. If vaccines work, CD might be cured. 5, 8

3. Prognosis
The prognosis is favorable for patients who have received the correct diagnosis and treatment. Relapses are prevalent with gluten - free diets. Enteropathy - associated T - cell lymphoma (EATL) and small intestinal cancer are more common in long - term untreated individuals. EATL survival is 11% after five years. There are still many unsolved questions about the danger of acquiring other cancers. 5, 8, 6

CD patients had a 20% higher death rate, especially in young people in the first two years after diagnosis. CD sufferers die younger even 10 years after diagnosis. The mortality rate is likely affected by age of diagnosis, severity of presentation, GFD adherence, gluten consumption, and related diseases. CD patients are 5 times more likely to die from infections, especially sepsis. Miscarriages, congenital birth abnormalities, small height, and ruin to thrive in children might happen in pregnant women. 5, 6, 8

4. Conclusions
Celiac disease is a prevalent condition that requires early detection and lifelong management. Adherence to a gluten - free diet is currently the most effective treatment, but further research is needed to explore non - dietary treatment options. This review provides a comprehensive overview of the disease, its diagnosis, and management, highlighting the need for future research.

References


