

Celiac Disease



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Abstract

Introduction and Definition: Celiac Disease (CD) is an autoimmune disorder affecting the small intestine, triggered by an abnormal immune response to gluten, a protein found in wheat, barley, and rye. Although its roots date back to the 2nd century AD, the condition was first identified by English physician Samuel Gee in 1888, who hypothesized dietary changes as beneficial. Today, the National Institute of Diabetes and Digestive and Kidney Diseases defines CD as "*a chronic digestive and immune disorder that damages the small intestine*". CD affects about 1% of the global population, yet about 80% of cases go undiagnosed. This significant underdiagnosis highlights the need for greater awareness and research, as delayed diagnosis can cause complications and reduce quality of life.

Causes: Gluten consumption in individuals carrying the HLA-DQ2 and HLA-DQ8 genetic alleles causes inflammation in the small intestine, leading to villous atrophy (damage to nutrient-absorbing villi). Beyond genetics, environmental factors such as early-life gluten exposure, gastrointestinal infections, frequent early-life illnesses, and microbiome (digestive bacteria) changes may contribute to disease onset in some cases.

Symptoms and Diagnosis: CD symptoms vary widely, ranging from digestive issues like diarrhea and bloating to nutrient malabsorption problems like anemia, as well as systemic effects including osteoporosis, mental health issues, and reproductive problems. Timely diagnosis can prevent complications and often begins with blood tests to detect elevated levels of antibodies, followed by biopsies of the small intestine to confirm villous atrophy.

Treatment and Management: The only current treatment for CD is a lifelong gluten-free diet, essential for healing the small intestine and alleviating symptoms. While vitamin and mineral supplements may help manage deficiencies, they do not heal the intestine. Effective management involves educating patients about CD, providing regular medical monitoring, and offering support for the social and emotional challenges associated with the condition.

Current Research: Ongoing research explores enzyme therapies, vaccines, and microbiome-targeted treatments to supplement the gluten-free diet. Latiglutenase, a combination of enzymes that break down gluten, shows promise in reducing intestinal damage and symptoms from accidental gluten exposure, a common issue for patients. It is being considered as a possible additional therapy for CD.

Keywords: celiac disease; gastroenterology; autoimmune disease; gluten; small intestine

Introduction and Definition

Celiac disease (CD) is a chronic autoimmune disorder that affects the small intestine, triggered by the ingestion of gluten—a protein found in wheat, barley, and rye. In genetically predisposed individuals, gluten consumption leads to an immune-mediated inflammatory response, resulting in damage to the intestinal lining and impaired nutrient absorption. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) defines CD as "*a chronic digestive and immune disorder that damages the small intestine*" [1].

Historically, the earliest known description of a condition resembling CD dates back to the 2nd century AD,

when the Greek physician Aretaeus of Cappadocia documented a malabsorptive disorder causing chronic diarrhea and weight loss. The term "Celiac" originates from the Greek word "*koiliakos*", meaning "abdominal." In 1888, English physician Samuel Gee provided a more detailed account of the disease and suggested that dietary modifications could alleviate symptoms. However, it wasn't until the mid-20th century that the connection between gluten and celiac disease was established, leading to the implementation of gluten-free diets as the primary treatment [2].

Epidemiological studies indicate that CD affects approximately 1.4% of the global population. Despite its

prevalence, a significant number of cases remain undiagnosed or misdiagnosed, with estimates suggesting that up to 83% of Americans with CD are unaware of their condition. This underdiagnosis underscores the necessity for increased awareness, improved diagnostic strategies, and further research to enhance patient outcomes and quality of life [3].

Body

Causes

Celiac disease (CD) is a complex autoimmune disorder resulting from an interplay between genetic predisposition and environmental factors.

HLA Gene Variants

A significant genetic component of CD involves specific human leukocyte antigen (HLA) gene variants, which increase susceptibility to the condition, but do not cause it directly. An individual with these variants is more likely to develop the condition [5]. Approximately 95% of individuals with CD possess the HLA-DQ2.5 variant, while most of the remaining 5% carry HLA-DQ8 [5]. The HLA-DQ2.5 variant is more strongly associated with CD than HLA-DQ8, due to its greater affinity for binding gluten peptides and presenting them to T cells. This explains its presence in the vast majority of CD patients. The immune responses triggered by the variants also differ in strength: HLA-DQ2.5 carrying individuals may experience stronger and more rapid immune activation than those with HLA-DQ8. The pathways of the immune response are largely similar, however [23]. The immune system of individuals with the HLA variants responds differently to gluten than individuals without these variants. The ingestion of gluten, a protein found in wheat, barley, and rye, is the primary trigger of CD [1]. In the small intestine, gluten peptides bind to the HLA molecules on the surface of antigen-presenting cells, rather than being broken down as typical. This activates T cells, which recognize the gluten fragments as foreign invaders and employ the adaptive immune response. The T cells release pro-inflammatory cytokines and initiate an inappropriate immune response leading to intestinal inflammation and villous atrophy. Villous atrophy is damage to the finger-like villi that line the walls of the small intestine, responsible for maximizing surface area to absorb essential nutrients [21]. The inheritance pattern of HLA variants is complex and first-degree relatives of individuals with CD carry a significantly higher lifetime risk of developing the condition. [22]. About 30% of the general population carries HLA-DQ2.5 or HLA-DQ8, yet only approximately 3% of these individuals develop CD [1], indicating that these genetic factors are not solely sufficient for disease manifestation [5]. Other genetic factors that affect the body's immune system regulation and intestinal permeability increase risk of CD as well. In fact, scientists have identified 40 non-HLA gene variants that contribute

to CD risk [24]. Celiac disease was once thought to primarily affect white Europeans but is now recognized as widespread worldwide, with underdiagnosis in regions like Africa, Asia, and South America. The global distribution of CD aligns with migratory wheat consumption of mankind [22].

In addition to genetic factors, environmental factors also play a crucial role in the development of CD. Studies have explored the impact of the timing of gluten introduction in infancy on the risk of developing CD. Research suggests that both early (before 17 weeks of age) and late (after 26 weeks of age) introduction of gluten may influence the likelihood of disease onset, though findings remain inconclusive [6]. Additionally, gastrointestinal infections during early life have been associated with an increased risk of CD, as such infections may disrupt the gut microbiome and trigger immune responses in genetically susceptible individuals [7]. The gut microbiome is a diverse community of organisms in the digestive tract, which plays a crucial role in an immune system regulation. Pathogenic gastrointestinal infections can cause shifts in the composition of the gut microbiome, leading to a loss of protective bacteria that maintain the intestinal barrier and regulate immune responses. This imbalance makes the immune system more prone to inflammatory responses caused by antigens such as gluten. The intestinal lining may also become more permeable, allowing large gluten fragments to pass through and enter the immune system, triggering an immune response in genetically predisposed individuals [8]. The immune responses triggered by the complex interplay between the genetic and environmental factors of CD give rise to specific symptoms, which are essential for diagnosing the disease.

Symptoms

Celiac disease (CD) manifests through a range of gastrointestinal and extra-intestinal symptoms, making a comprehensive diagnostic approach necessary. Common digestive manifestations of CD include chronic diarrhea, abdominal pain, bloating, and, in some cases, constipation. Patients with CD may also experience steatorrhea, which refers to fatty and foul-smelling stools due to malabsorption of dietary fats [9]. In children, key symptoms may include poor weight gain, decreased appetite, irritability, diarrhea, abdominal distension, vomiting, and constipation [9]. Gastrointestinal symptoms are a result of malabsorption in the small intestine due to villous atrophy [9].

Beyond the digestive tract, CD can present with extraintestinal systemic manifestations. Patients often present nutrient deficiencies: malabsorption may result in deficiencies of iron, folate, vitamin B12, vitamin D, and calcium, potentially leading to anemia and osteoporosis [9]. Individuals with CD may also experience peripheral neuropathy (nerve damage causing weakness or numbness), ataxia (loss of coordination), headaches, depression, and anxiety [9]. A major manifestation of CD is its association

with infertility and recurrent miscarriages likely due to nutrient deficiencies and chronic inflammation. Children may develop dental enamel defects, short stature, and delayed puberty due to CD [9].

Some individuals with celiac disease are asymptomatic, meaning they do not exhibit common symptoms such as diarrhea, bloating, or stomach pain, yet they still develop villous atrophy [4]. Given the diverse ways that CD presents itself, a comprehensive diagnostic approach is important to confirm the disease.

Diagnosis

Accurate diagnosis of CD involves a combination of serological tests (blood tests for antibody levels) and histological examinations (microscopic examination of gastrointestinal tissue). Serological testing is the first step in diagnosis which allows detection of elevated levels of specific antibodies produced in response to gluten exposure. The tissue transglutaminase immunoglobulin A (tTG-IgA) test is a highly sensitive and specific test for CD, with over 90% sensitivity and specificity, making it highly accurate for detecting CD in those who have a high degree of intestinal damage [18]. Tissue transglutaminase (tTG) is an enzyme in human tissues, central to the development of CD by modifying gluten peptides. The modified gluten triggers the adaptive immune response, recruiting T cells, inflammatory cytokines and other immune cells to the inflammation site. tTG also becomes an autoantigen and the immune system employs anti-tTG antibodies to attack it. High levels of tTG-IgA antibodies indicate presence of CD since the immune system is reacting to gluten by attacking the enzyme tTG [19]. Although IgA deficiency is rare in the general population, it affects 2-3% of individuals with celiac disease, potentially leading to diagnostic inaccuracies. These patients undergo IgG testing, which can yield unreliable results when IgA is present but provides conclusive findings in its absence [18].

If serological testing suggests the possibility of CD, histological examinations are done. Confirmatory diagnosis requires an upper gastrointestinal (GI) endoscopy with biopsy of the duodenal mucosa (lining of the duodenum, a part of the small intestine) [18]. In this procedure, tissue samples from the small intestine are collected to assess for intestinal damage caused by gluten consumption. Histopathological findings typically show villous atrophy (flattening of the finger-like projections in the intestine), crypt hyperplasia (elongation of grooves between villi), and an increased density of immune cells along the intestinal lining [20]. In some individuals, when an upper GI endoscopy is not feasible, CD can be diagnosed based on strongly positive tTG-IgA results [18].

Additionally, genetic testing for HLA-DQ2.5 and HLA-DQ8 may help rule out the possibility of CD. Those who do not carry these genetic variants are very unlikely to develop CD [18].

It is crucial that patients continue consuming gluten during the diagnostic processes to ensure the accuracy of serological and histological assessments [10]. Early and precise diagnosis facilitates timely intervention, mitigating potential complications and enhancing the quality of life for individuals with CD [11].

Treatment and Management

CD is a chronic autoimmune disorder and unlike other conditions that can be managed with medication, it has no pharmacological treatment.

Gluten Free Diet

The primary treatment for CD is strict adherence to a lifelong gluten free diet (GFD), which is essential for healing the small intestine and alleviating symptoms [1]. A GFD is void of grains in which gluten occurs naturally; these include all types of wheat, barley, rye, and triticale (a wheat and rye hybrid). It is important to make sure that no cross-contact occurs between gluten containing and gluten free food, as even small amounts could damage the intestinal lining [1]. Eliminating gluten from the diet allows intestinal villi to recover from villous atrophy and significantly improve nutrient absorption and overall health. While a GFD alleviates many of the intestinal and extraintestinal symptoms described in the symptoms section above, some may need additional help to treat [1]. For example, vitamin and mineral supplements play a supportive role in managing celiac disease by addressing specific nutrient deficiencies resulting from malabsorption [1]. It is important to educate patients about how to follow a GFD; this education covers identifying gluten-containing foods, understanding food labels, and strategies to avoid cross-contamination [1]. Regular medical follow-ups are essential to monitor adherence to the GFD, assess symptom resolution, and detect potential complications.

Effective management of CD encompasses comprehensive patient education, regular medical monitoring, and support for social and emotional challenges associated with the condition. Follow-ups may include further serological tests and in some cases, additional biopsies [1]. The tTG-IgA levels should return back to normal after adherence to a GFD, however if there is no sign of improvement, there could be potential complications. Often, accidental gluten consumption may be occurring, however other health problems such as irritable bowel syndrome, lactose intolerance, etc. may be a cause [1]. A rare complication is Refractory CD, where symptoms and villous atrophy relapse even after strict adherence to a GFD [1]. Many additional conditions could accompany CD, such as Type 1 Diabetes, Hashimoto's Thyroiditis, T-cell Lymphoma, etc [11].

Addressing the social and emotional aspects is also vital, as living with CD can lead to feelings of isolation or anxiety, particularly in social settings involving food. Providing mental health support and connecting patients

with support groups can significantly enhance their quality of life [12]. While the GFD remains the cornerstone of CD treatment, ongoing research is exploring additional therapies to complement this approach and offer further options for disease management.

Current Research

Ongoing research is exploring enzyme therapies, vaccines, and microbiome-targeted treatments to enhance CD management and supplement the GFD, which remains the primary treatment for CD. Latiglutenase is an oral enzyme therapy designed to degrade gluten in the gastrointestinal tract and reduce the effects of accidental gluten ingestion in individuals with CD. Clinical studies have proven that latiglutenase can reduce gluten levels by over 90% compared to a placebo, indicating its potential to decrease villous atrophy and associated symptoms [13]. Another enzyme therapy is Transglutaminase 2 Inhibitors which inhibits an enzyme involved in the immune response to gluten, providing similar results of Latiglutenase as a supplementary treatment to the GFD [14]. Ongoing research in immune modulation includes developing vaccines and immunotherapies to induce immune tolerance to gluten and prevent the autoimmune response characteristic of CD [15]. Further research is being done on microbiome-targeted treatments by investigating the role of gut microbiota in CD, in order to develop prebiotics and probiotics or microbiome-modifying therapies that could support intestinal health and regulate immune responses [16]. Another promising drug under early-stage clinical trials is IMU-856 which promotes regeneration of villi in the small intestine, helping enhance nutrient absorption and reduce intestinal damage [17]. While all these treatments are promising for the future of CD, they are currently under development and investigation and not yet approved for clinical use. Currently, a GFD is the only treatment to CD.

List of Abbreviations

CD: Celiac Disease
GFD: Gluten Free Diet
GI: gastrointestinal
tTG: tissue transglutaminase

Conflicts of Interest

The author has been diagnosed with Celiac Disease, which informs their perspective on this topic. However, all efforts have been made to ensure accuracy and objectivity in this article.

Authors' Contributions

IKK: made contributions to: the conception and design of the article; acquisition, interpretation, and analysis of information; drafted and revised the article critically; gave final approval of the version to be published; agrees to be accountable for all aspects of the work.

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