International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	COELIAC DISEASE: A COMPREHENSIVE LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5475
RECEIVED	26 February 2026
ACCEPTED	08 May 2026
PUBLISHED	14 May 2026
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COELIAC DISEASE: A COMPREHENSIVE LITERATURE REVIEW

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ABSTRACT

Introduction and purpose: Celiac disease is a chronic, autoimmune, and gluten-dependent disorder that, in genetically predisposed individuals, leads to inflammation of the intestinal mucosa and villous atrophy. This results in the malabsorption of micro- and macroelements, subsequently leading to various complications. It is estimated to affect approximately 1% of the population. Due to oligosymptomatic presentations, many cases remain undiagnosed; however, untreated disease can lead to serious complications ranging from anemia to gastrointestinal malignancies. This review paper summarizes the epidemiology, diagnostics, clinical presentation, and treatment of the disease, while also discussing potential new methods for treatment and monitoring.

Description of the State of Knowledge: Gluten molecules entering the gastrointestinal tract are rich in glutamine, which is converted by tissue transglutaminase (tTG) into glutamic acid. This acid has a high affinity for HLA-DQ2/DQ8 antigens on antigen-presenting cells. These cells stimulate CD4+ T lymphocytes, which produce pro-inflammatory cytokines and activate B lymphocytes to produce specific antibodies: anti-endomysial (EMA), anti-deamidated gliadin peptides (DGP), and anti-tissue transglutaminase (tTG). Under the influence of IL-15, intraepithelial CD8+ lymphocytes destroy the intestinal villi. These mechanisms lead to gastrointestinal symptoms such as abdominal pain, diarrhea, and bloating, as well as extraintestinal manifestations including anemia, skin lesions, and neurological, psychiatric, or gynecological disorders. Currently, the primary treatment is a strict gluten-free diet. As many cases remain undiagnosed or are detected late, new diagnostic and therapeutic methods are actively being researched.

Conclusion: Our understanding of celiac disease is constantly expanding, and new diagnostic tools are being developed. While a restrictive diet is effective in many cases, it remains burdensome and can decrease the patient's quality of life. Further research into novel therapeutic and diagnostic approaches is essential to improve the detection rate, particularly in cases with an atypical clinical course.

KEYWORDS

Gluten, Transglutaminase, Dermatitis Herpetiformis, Endomysium, T-cell Lymphoma

CITATION

Szymon Targosz, Karol Józef Szkarłat, Maksymilian Szklarski, Jędrzej Sztajura, Ewa Maraszewska, Michał Stachel, Weronika Szymacha, Aleksandra Płecka, Karol Zimnicki, Alicja Stępień. (2026) Coeliac Disease: A Comprehensive Literature Review. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5475

Introduction

Celiac disease is an autoimmune disorder predisposed by the presence of HLA-DQ2/DQ8 alleles and the ingestion of gluten found in cereal grains [5]. It is estimated to affect approximately 1% of the population, and the rate of diagnosis is increasing due to modern and more accessible diagnostic tools [2]. If left untreated, it can cause numerous gastrointestinal symptoms—such as diarrhea, abdominal pain, and bloating—as well as systemic manifestations, including anemia, growth impairment in children, and dermatological or skeletal changes [1]. These symptoms result from chronic inflammation of the small intestinal mucosa, which leads to villous atrophy and nutrient malabsorption. Currently, the standard treatment consists of a strict gluten-free diet (GFD) that excludes gluten-containing grains [2]. Long-term adherence to such a diet is associated with a risk of nutritional deficiencies and the consumption of products that are low in fiber but high in simple sugars and saturated fatty acids, which may predispose patients to metabolic syndrome [21]. Furthermore, trace amounts of gluten may be present in food, causing persistent intestinal inflammation despite dietary compliance, leading to further villous destruction [8]. This review paper summarizes the epidemiology, pathophysiology, and clinical presentation of the disease, as well as the latest guidelines for its diagnosis and treatment. Despite increased medical awareness, a deeper understanding of its pathogenesis, and modern diagnostic methods, celiac disease often remains undiagnosed or is detected late [28]. The prevalence of paucisymptomatic forms and the challenges of maintaining a rigorous diet have encouraged researchers to seek alternative methods for diagnosis, treatment, and monitoring [31]. Consequently, this work also includes information on novel markers investigated in recent years for disease monitoring, as well as potential

therapeutic interventions. These methods are based, among others, on the administration of substances that degrade gluten in the gastrointestinal tract into non-immunogenic forms, the inhibition of tissue transglutaminase (an enzyme that plays a key role in the pathogenesis of the disease), and the suppression of inflammatory interleukins.

Methodology

This literature review on coeliac disease utilized articles published between 2008 and 2025, sourced from the PubMed database. This review focused mainly on studies addressing the pathophysiology, clinical presentation, diagnosis and treatment. A total of 31 articles were analyzed to provide a comprehensive synthesis of current knowledge.

Epidemiology

Approximately 1% of the global population is affected by celiac disease (CeD), with variations depending on the geographic region. Many cases remain undiagnosed due to a heterogeneous clinical presentation that often does not immediately suggest the condition. While the disease is diagnosed more frequently in females (with a reported female-to-male ratio of 2:1) the overall biological occurrence is considered similar between genders. In Europe, the prevalence of CeD is distributed as follows: Northern Europe (1.60%), Eastern Europe (0.98%), Southern Europe (0.69%), and Western Europe (0.60%) [1,2]. The highest prevalence has been observed in the Saharawi population of North Africa, reaching approximately 5.6%. In contrast, significantly lower incidence rates are reported in East Asia, particularly in Japan. This lower frequency is attributed to both a lower prevalence of the HLA-DQ2/DQ8 alleles within the population and a lower overall intake of gluten in the traditional diet [20].

Pathophysiology

The onset of celiac disease is determined by genetic predisposition, specifically within the HLA-DQ2.5 system (present in over 90% of patients [3]), as well as the HLA-DQ2.2 or HLA-DQ8 systems [3,5]. The HLA system accounts for 35–40% of the genetic risk for developing the disease, while the remainder is attributed to other regions of the genome [3,4]. Gluten found in grains such as wheat, rye, and barley constitutes a water-insoluble protein mass [4]. It contains high amounts of proline and glutamine, which exhibit resistance to the action of digestive enzymes. Tissue transglutaminase (TG2) acts on these amino acids through deamidation, resulting in the conversion of glutamine into glutamic acid. This process creates a strong negative charge that increases the affinity for HLA-DQ molecules found on antigen-presenting cells (APCs). In the lamina propria of the intestinal mucosa, deamidated peptides are presented to CD4+ T lymphocytes. In response, these lymphocytes begin to proliferate and produce pro-inflammatory cytokines, such as IFN-γ and IL-21. B lymphocytes possessing receptors specific for TG2 capture TG2-glutamic acid complexes, digest them, and present them to T lymphocytes. Plasma cells then produce characteristic antibodies, including TG2 autoantibodies and antibodies against deamidated gluten peptides (DGP) [5]. DGP strongly stimulates the T-lymphocyte response within the mucosa of the small intestine [4]. IL-15, produced by dendritic cells, macrophages, and enterocytes, strongly stimulates the survival and proliferation of intraepithelial lymphocytes (IELs), which belong to the CD8+, αβ, and γδ populations. Under the influence of inflammatory factors, enterocytes produce MICA/B and HLA-E molecules, which affect the intraepithelial lymphocytes. By recognizing these molecules through NK receptors, these lymphocytes destroy living enterocytes, and the body compensatorily forces cell proliferation in the crypts. This leads to crypt hyperplasia with simultaneous villous atrophy [5]. The consequence of this state is the loss of the intestinal absorptive surface and a decrease in the concentration of digestive enzymes, resulting in malabsorption syndrome, diarrhea, abdominal pain, and weight loss [4]. Portions of the gluten peptide are also absorbed into the circulation and even appear in the urine. Following exposure to gluten, plasma levels of cytokines and chemokines increase within just 2–4 hours, among which the rise in IL-2 appears to be the most rapid [3].

Clinical forms

Classical form- symptoms are primarily gastrointestinal. It is more frequently diagnosed in children. Common manifestations include diarrhea, loss of appetite, abdominal bloating, and growth retardation. In older children and adults, symptoms such as constipation, abdominal pain, diarrhea, and weight loss are more dominant. In adults, this form most closely resembles irritable bowel syndrome [1].

Non-classical form – significantly more common than the classical form [6]. It may occur independently or alongside intestinal symptoms [1]; however, more than 50% of diagnosed patients do not report daily diarrhea. Milder complaints include reflux, constipation, dyspepsia, abdominal pain, and bloating. Many patients do not experience weight loss, and some may even present with overweight or obesity [6]. The extraintestinal symptoms occurring in this form include:

- microcytic anemia due to iron deficiency or chronic disease in approximately 40%, while macrocytic anemia from B12 or folic acid deficiency occurs less frequently [1];
- dermatitis herpetiformis – itchy vesicles and papules that typically appear on the elbows, knees, and buttocks [23];
- osteopenia or osteoporosis in about 70% of patients due to the malabsorption of calcium and vitamin D [1];
- neurological and psychiatric symptoms – headaches, numbness [1], chronic fatigue, epilepsy [6], anxiety, and depression [1];
- in children – short stature, enamel hypoplasia [6], and aphthous ulcers in approximately 20% of undiagnosed cases;
- elevated liver transaminase levels due to increased intestinal permeability, which allows bacterial antigens to reach the liver [1];
- reproductive system issues – late menarche, recurrent miscarriages, early menopause, and reduced semen quality [1].

Subclinical form – clinical symptoms or changes are at the threshold of clinical diagnosis. Such patients are identified through screening programs, and their well-being improves after the introduction of a gluten-free diet [1].

Potential form – anti-tTG and EMA antibodies, as well as HLA-DQ2/DQ8 alleles, are present in the blood, but the intestinal mucosa remains normal or shows only minor inflammatory changes. This form may be asymptomatic or present with mild symptoms [1].

Seronegative form – rare, occurring in 2-3% of cases. The patient lacks specific antibodies, but villous atrophy and malabsorption syndrome are present. Improvement is observed after starting the diet, and genetic testing confirms the presence of HLA-DQ2/DQ8. This form requires the exclusion of other conditions that can cause mucosal damage, such as parasitic infections, Crohn's disease, or drug-induced injury [1,30].

Non-responsive form – gastrointestinal symptoms do not subside after more than 12 months on a gluten-free diet [1].

Slow-responder form – affects 7-30% of adults with celiac disease who, despite following a strict gluten-free diet for at least 6-12 months, continue to experience symptoms or show abnormalities in laboratory tests [4].

Refractory Celiac Disease (RCD) – a very rare and dangerous form (approximately 1-1.5% of all cases) characterized by malabsorption syndrome and persistent villous atrophy lasting more than 12 months despite dietary adherence [1]. It is divided into RCD-I, where the percentage of abnormal intraepithelial lymphocytes (IELs) is less than 20%, and RCD-II, where the percentage of abnormal cells exceeds 20% [4]. The latter is associated with a high risk of developing enteropathy-associated T-cell lymphoma (EATL) [1].

Ultra-short form – intestinal mucosal damage is limited to the duodenal bulb. It presents with mild symptoms and less frequent nutritional deficiencies [4].

Associated conditions

Celiac disease screening should be performed in the following conditions due to their co-occurrence:

- Endocrine and autoimmune diseases: Type 1 diabetes, Hashimoto's disease, Graves' disease, and Sjögren's syndrome [7,27].
- Gastrointestinal diseases: Irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), microscopic colitis (MC), and autoimmune atrophic gastritis [7].
- Liver, pancreas, and spleen diseases: Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) [27], unexplained elevation of liver enzymes, idiopathic pancreatitis, hyposplenism, and asplenia [7].
- Skin and oral diseases: dermatitis herpetiformis, recurrent aphthous ulcers, and dental enamel defects [7].
- Gynecological disorders: delayed menarche, premature menopause [7], recurrent miscarriages, and difficulty conceiving [29].
- Neurological disorders: unexplained epilepsy and peripheral neuropathy [7,27].
- Genetic syndromes: Down syndrome, Turner syndrome, and Williams syndrome [7,27].
- Other conditions: IgA nephropathy, selective IgA deficiency (IgAD), and chronic fatigue syndrome [7].

Additionally, screening should be ordered for first-degree relatives of patients already diagnosed with celiac disease [7].

Diagnostic

Blood tests – The initial and primary diagnostic tool is the assessment of tissue transglutaminase antibodies in the IgA class (IgA tTG). It is essential that the patient remains on a gluten-containing diet prior to testing. Total IgA levels should also be evaluated, as antibody results may be falsely low due to selective IgA deficiency. If IgA levels are low, the diagnosis relies on IgG anti-tTG or IgG anti-deamidated gliadin peptide (DGP) antibodies [19]. Currently, the routine use of anti-endomysial antibodies (IgA EMA) as an initial screen is not recommended; instead, they serve as a supplementary test in clinically ambiguous cases [2]. A diagnosis based solely on laboratory results can be made in adults under 45 years of age only when IgA anti-tTG levels are ≥ 10x ULN in two separate blood samples [2,28]. HLA-DQ2 and HLA-DQ8 testing carries a strong negative predictive value and is utilized only in inconclusive cases or as a tool to determine whether screening can be discontinued in high-risk individuals, such as those with type 1 diabetes [19].

Histopathological examination – To confirm the diagnosis, a biopsy consisting of four specimens from the descending part of the duodenum and two additional specimens from the duodenal bulb is necessary. These specimens are evaluated using the modified Marsh scale:

0 – Normal duodenal mucosal architecture.

I – Infiltrative changes: an increased count of intraepithelial lymphocytes (IELs).

II – Hyperplastic changes: lymphocytic infiltration accompanied by intestinal crypt hyperplasia.

III – Villous atrophy. The modified scale divides this stage into three subcategories:

- 3A – Partial villous atrophy.
- 3B – Subtotal villous atrophy.
- 3C – Total villous atrophy.

A definitive diagnosis can be established when positive serology is accompanied by Marsh II or Marsh III changes. In cases of Marsh I, patients with positive serological results and the presence of HLA-DQ2/DQ8 antigens are classified as having potential celiac disease [2].

Gluten challenge – In patients who have already excluded gluten from their diet, HLA-DQ2 and HLA-DQ8 genotyping should be performed first. If the result is negative, celiac disease can be ruled out, and the patient should not be subjected to a gluten challenge. If the result is positive, it is recommended to consume a minimum of 3 grams of gluten daily for a period of 6 weeks [2].

Treatment

The only recommended and most effective treatment for celiac disease is a rigorous, lifelong gluten-free diet (GFD). Products naturally containing gluten specifically wheat, barley, rye, triticale, and oats must be completely eliminated. The diet must be strictly followed [2]. Trace amounts found even on countertops, cabinets, and kitchen appliances shared with individuals consuming gluten can sustain inflammation and cause further villous destruction. Adherence to the diet alleviates symptoms of malabsorption syndrome and improves bone mineral density. In 95% of children with celiac disease who adhere to the diet, the architecture of the small intestinal mucosa regenerates within two years. In adults, the process is significantly slower; mucosal recovery is observed in only 34% of patients after 2 years and in 66% after 5 years [8].

Research into New Treatment Methods

The current method of treatment involves avoiding the causative factor, namely gluten-containing foods [2]. Over time, such therapy can become burdensome and difficult to maintain. For these reasons, research is being conducted on pharmacological treatment methods for this chronic disease:

The use of enzymes that degrade digestion-resistant immunogenic gluten peptides within the gastrointestinal lumen, known as glutenases. The primary enzymes under investigation include:

- Latiglutenase (IMGX003) – consists of two enzymes (Hordeum vulgare endoprotease B2 and Sphingomonas capsulata prolyl endopeptidase), which are taken in liquid form during meals. It acts exclusively in the stomach by degrading and neutralizing immunogenic gluten peptides. Studies of gluten immunogenic peptides (GIP) in urine showed that the drug degraded approximately 95% of ingested gluten. The drug demonstrated efficacy in protecting the small intestinal mucosa; in the study group, the increase in the number of intraepithelial lymphocytes (IELs) was nearly three times lower than in the placebo group [9].
- Zamaglutenase (TAK-062) – an oral, computationally designed enzyme based on an enzyme from the bacterium Alicyclobacillus sendaiensis. It exhibits strong activity in the acidic pH of the stomach. Its mechanism of action involves the rapid digestion of gluten in the stomach to prevent it from reaching the intestine and triggering an immune response. In vitro and in the stomachs of patients, the drug degraded 97–99% of ingested gluten within 10–35 minutes. Additionally, the use of proton pump inhibitors (PPIs) seven days prior to the study did not affect enzyme activity in some subjects, suggesting that this drug could be an effective therapeutic option for individuals using acid-suppressing medications. The drug also proved to be safe and well-tolerated, with studies showing it is not absorbed into the bloodstream [10].
- AN-PEP – a prolyl endopeptidase derived from the fungus Aspergillus niger. While this enzyme effectively degrades gluten in vitro, its in vivo degradation proved insufficient in clinical studies [11].

Inhibition of tissue transglutaminase (TG2), the enzyme responsible for the deamidation of glutamine in the gluten molecule, which creates forms that strongly stimulate lymphocytes:

- ZED1227 (TAK-227) – acts through permanent, irreversible binding to the active site of the enzyme. The drug acts almost exclusively on TG2 present on the surface of the intestinal mucosa and does not block similar enzymes, thereby avoiding significant side effects. Phase 2a trials demonstrated that it protects against damage to the duodenal mucosa [12].

Biological and immunomodulating treatments:

- TEV-53408 – a monoclonal antibody designed to neutralize IL-15. Phase 1 studies showed that single doses are safe and well-tolerated, with potential side effects being mild to moderate and transient. Additionally, it was shown to effectively lower free IL-15 levels in the serum and reduce the number of NK cells [13].
- Amlitelimab (anti-OX40) – an IgG4 monoclonal antibody that blocks the interaction between OX40 and its ligand on antigen-presenting cells (APCs) [14].

Inducing immune tolerance to gluten – these methods aim to train the immune system to ignore gluten:

- TAK-101 (TIMP-GLIA) – negatively charged nanoparticles containing gliadin. Phase 1 and 2 studies demonstrated that this drug reduces the number of gluten-reactive T cells by 88% and prevents villous atrophy. Furthermore, the drug did not show any treatment-emergent adverse events (TEAEs) [15].
- KAN-101 – a gliadin peptide conjugate that targets antigens to the liver to promote immune tolerance pathways. In a study conducted on 41 adult patients, the drug proved to be safe and well-tolerated. Side effects were limited to mild nausea, vomiting, and diarrhea. The drug is cleared rapidly from the bloodstream and does not accumulate. Additionally, it demonstrated the ability to inhibit the IL-2 response, which plays a key role in the inflammatory reaction in celiac disease patients [16].

Monitoring

Currently used methods for assessing dietary adherence and improvements in intestinal mucosal morphology are tTg-IgA and EMA antibodies; however, these have poor sensitivity and are not suitable for evaluation in patients with IgA deficiency. Follow-up biopsy is also crucial, but the invasiveness of this method makes the procedure burdensome. For these reasons, additional markers are being sought to help evaluate the effectiveness of the diet. Recently investigated potential biomarkers include:

- Gluten Immunogenic Peptides (GIP) – these are fragments of undigested gluten excreted in feces and urine. They exhibit high sensitivity but persist in the body for a very short duration: 4 to 24 hours in urine and approximately 3 days in feces [24].
- Intestinal Fatty Acid-Binding Protein (I-FABP) – characterized by high sensitivity. In patients subjected to a gluten challenge, blood levels of this marker rise sharply and then decrease within 14 days of

returning to a strict diet. Among subjects who transitioned to a gluten-free diet, I-FABP levels completely normalized in 82% of cases within 26 weeks [25].

- MicroRNAs – these control gene expression and play a key role in regulating the immune system. Specifically involved in the pathogenesis of celiac disease are miR-155, which promotes inflammatory responses and increases significantly, and miR-15b, which acts as a "brake" for the immune system. In addition to being a potential marker for monitoring treatment, microRNA may serve as a potential target for biological therapy in the future [26].

Complications

Untreated celiac disease can lead to a wide variety of complications, such as osteoporosis and osteopenia, delayed puberty, recurrent miscarriages, pregnancy complications, and neurological disorders including neuropathies and ataxia [17]. Psychiatric disorders, such as anxiety, depression, and eating disorders, may also occur [22]. Furthermore, a gluten-free diet is often low in fiber and minerals while being high in simple sugars and fats, which can negatively affect the metabolic profile of patients [21]. The most severe complication is enteropathy-associated T-cell lymphoma (EATL) [17]. This is a rare but highly aggressive non-Hodgkin lymphoma that most frequently develops as a consequence of long-term, refractory celiac disease. The median survival rate is 10 months, and in the majority of patients, the disease is detected at stage IV [18]. The overall risk of death in individuals with celiac disease, even for those adhering to a gluten-free diet, is 1.2–2 times higher than in the general population [20].

Conclusions

In recent years, the recognition of celiac disease has been steadily increasing; however, it remains insufficient due to the frequent occurrence of non-specific clinical presentations. The current gold standard of treatment a gluten-free diet is proving inadequate due to the difficulty of avoiding hidden sources of gluten and its ineffectiveness in cases of refractory celiac disease (RCD). Consequently, there is an ongoing need for further research into the disease's pathomechanism, which is not yet fully elucidated. Particular attention is required to explain the low genetic penetrance of HLA-DQ2/DQ8 haplotypes, as well as the environmental, microbial, or epigenetic factors determining the varied age of disease onset. The objective of future research should be the development of pharmacological interventions that could replace the aforementioned strict dietary regimen, thereby enhancing patients' quality of life.

Disclosure

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All authors have read and agreed with the published version of the manuscript

Funding Statement: The study did not receive any special funding

Conflict of Interests: The authors declare no conflict of interest

Declaration of the use of generative ai-assisted technologies in the writing process: During the preparation of this work, the authors used Google Gemini to improve language and readability. The authors subsequently reviewed and edited the content; they take full responsibility of the published work.

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