Review Article

Celiac Disease with Systemic Extraintestinal Manifestations: Pathophysiological Mechanisms, Comprehensive Diagnostic Approach, and Integrated Therapeutic Management

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Abstract

Celiac disease is a chronic immune-mediated disorder triggered by gluten ingestion in genetically predisposed individuals, particularly those carrying HLA-DQ2 or HLA-DQ8 haplotypes. Although traditionally considered a gastrointestinal condition, it is now recognized as a systemic disease with a broad spectrum of extraintestinal manifestations. Gluten exposure induces deamidation of gliadin

peptides by tissue transglutaminase, facilitating antigen presentation to CD4-positive T lymphocytes and initiating a proinflammatory cascade. This immune activation leads to villous atrophy, autoantibody production, and increased intestinal permeability, allowing inflammatory mediators to enter the systemic circulation and contribute to distant organ involvement. Extraintestinal manifestations are diverse and may include iron deficiency anemia, osteoporosis, dermatitis herpetiformis, neurological disorders such as ataxia and neuropathy, hepatic abnormalities, endocrine diseases including type 1 diabetes and autoimmune thyroiditis, and reproductive complications. These systemic features may occur in the absence of gastrointestinal symptoms, contributing to underdiagnosis and delayed treatment. Diagnosis relies on a structured approach that includes serologic testing with immunoglobulin A anti–tissue transglutaminase antibodies, confirmation by duodenal biopsy, and selective genetic testing in equivocal cases. A strict gluten-free diet remains the cornerstone of therapy, preventing ongoing immune activation and promoting mucosal healing. Comprehensive management also requires correction of nutritional deficiencies, monitoring of adherence, and multidisciplinary follow-up. Refractory disease and the risk of enteropathy-associated T-cell lymphoma underscore the importance of vigilant surveillance. Emerging therapies targeting gluten degradation, intestinal permeability, and immune modulation offer promising future directions in personalized management.

Key words

HLA-DQ2, Iron deficiency anemia, Dermatitis herpetiformis, Gluten ataxia, Enteropathy-associated T-cell lymphoma, Intestinal permeability.

Introduction

Celiac disease affects approximately 1% of the global population; however, despite its relatively high prevalence, it remains significantly underdiagnosed due to its heterogeneous clinical presentations, which include asymptomatic individuals and patients with atypical manifestations [1, 2]. This diagnostic gap has been conceptualized through the “celiac iceberg” metaphor, which illustrates the substantial proportion of unrecognized cases beneath the surface of clinically apparent disease. Epidemiological data indicate that seroprevalence exceeds 1% worldwide, while biopsy-confirmed cases surpass 0.5%, underscoring the magnitude of underdiagnosis at a global level [3].

Historically regarded as a pediatric disorder characterized predominantly by malabsorptive gastrointestinal symptoms, celiac disease is now recognized as a systemic condition with a broad and diverse clinical spectrum. Increasing evidence supports a shift from the classical presentation toward non-classical and extraintestinal phenotypes, including neuropsychiatric disorders, dermatologic conditions, and endocrinological abnormalities [4, 5]. Importantly, extraintestinal manifestations may occur in the absence of overt gastrointestinal complaints, thereby complicating clinical suspicion and contributing further to underrecognition and delayed diagnosis [6].

The clinical relevance of these systemic manifestations is substantial. Neurological involvement, such as ataxia and peripheral neuropathy, has been documented and may show improvement following adherence to a gluten-free diet (GFD), highlighting the importance of timely identification [6]. In addition to neurological features, patients may present with liver dysfunction, dermatologic disorders, and alterations in bone health. These complications can become severe if celiac disease is not diagnosed and appropriately managed at an early stage [1, 5].

Given the multisystem nature of the disease, a multidisciplinary and integrative approach is essential for optimal patient care. Collaboration among gastroenterologists, neurologists, dermatologists, and dietitians facilitates comprehensive evaluation and targeted management, particularly in individuals presenting with extraintestinal manifestations [5]. Early diagnosis followed by strict implementation of a gluten-free diet remains the cornerstone of therapy and is critical to preventing irreversible complications and improving long-term clinical outcomes [1, 7].

The objective of this review is to examine celiac disease with systemic extraintestinal manifestations, highlighting its underdiagnosis and the importance of an integrated diagnostic and therapeutic approach.

Methodology

The present study was designed as a structured narrative review aimed at critically integrating recent evidence on celiac disease with systemic extraintestinal manifestations, with particular emphasis on patterns of underdiagnosis, the evolving spectrum of non-classical presentations, and clinically oriented diagnostic and therapeutic strategies. The objective was to synthesize advances in immunopathogenesis, clinical phenotyping, diagnostic assessment in patients with minimal or absent gastrointestinal symptoms, complication recognition, and multidisciplinary management, from a clinically oriented and translational perspective. This review was not conducted as a systematic review; therefore, formal PRISMA flow diagrams or quantitative meta-analytic techniques were not applied. Instead, the methodological approach prioritized conceptual integration, clinical applicability, and interpretative depth to provide a coherent and updated overview of extraintestinal celiac disease.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, selected for their broad coverage of gastroenterology, internal medicine, immunology, and translational research. Peer-reviewed articles published between January 2020 and December 2025 in English or Spanish were considered eligible. The search strategy combined Medical Subject Headings and free-text terms using Boolean operators, including: (“celiac disease” OR “coeliac disease”) AND (“extraintestinal” OR “systemic manifestations” OR “atypical presentation” OR “non-classical”) AND (“diagnosis” OR “serology” OR “tissue transglutaminase” OR “endomysial antibodies” OR “duodenal biopsy” OR “HLA-DQ2” OR “HLA-DQ8”) AND (“gluten-free diet” OR “treatment” OR “nutritional deficiencies” OR “multidisciplinary management” OR “follow-up” OR “refractory celiac disease”). Manual screening of reference lists from relevant publications was performed to identify additional pertinent studies. Titles and abstracts were initially screened for relevance, followed by full-text assessment when necessary. Studies were excluded if they were non–peer-reviewed, lacked sufficient methodological detail, duplicated previously published data, or did not directly address diagnostic pathways, extraintestinal phenotypes, clinical outcomes, or therapeutic management of celiac disease.

Selected studies were analyzed using a qualitative and integrative framework. Priority was given to clinical practice guidelines and consensus statements, randomized and non-randomized interventional studies evaluating dietary and adjunctive strategies, large observational cohorts, and translational investigations addressing immune mechanisms and organ-specific manifestations. Extracted variables included study design, population characteristics, definition and type of extraintestinal manifestations, diagnostic approach (serological testing, histopathology, genetic testing), intervention type (gluten-free

diet implementation, supplementation strategies, management of complications), follow-up duration, and outcomes such as symptom resolution, serologic normalization, nutritional recovery, and complication prevention. The synthesis was organized into thematic domains encompassing epidemiology and underdiagnosis, immunopathogenesis of systemic involvement, clinical phenotypes of extraintestinal disease, diagnostic algorithms for non-classical presentations, therapeutic strategies and monitoring of adherence, management of complications, refractory disease, and multidisciplinary models of care.

Artificial intelligence–based tools were employed exclusively to assist in literature organization, thematic clustering, and structural refinement of the manuscript. Critical evaluation of the evidence, verification of data sources, and final interpretation were conducted independently by the authors, ensuring methodological rigor and academic oversight throughout the development of the review.

Immunopathogenesis and Mechanisms of Systemic Involvement

Genetic susceptibility represents a central component in the pathogenesis of celiac disease. The presence of HLA-DQ2 and HLA-DQ8 haplotypes constitutes a major genetic factor, as these molecules present deamidated gluten peptides to CD4-positive T cells, thereby initiating the immune response [8, 9]. Nevertheless, not all individuals carrying these haplotypes develop celiac disease, indicating that additional genetic and environmental factors are required for disease expression. In this context, genome-wide association studies have identified supplementary non-HLA genetic loci that contribute to susceptibility, although their impact accounts for a smaller proportion of the overall genetic risk when compared with HLA-related genes [10].

Within this genetically predisposed background, gluten exposure triggers a complex immune activation process. Tissue transglutaminase modifies gliadin peptides through deamidation, enhancing their binding affinity to HLA-DQ2 and HLA-DQ8 molecules and thereby facilitating T cell activation [9]. Once presented, these modified gluten peptides are recognized by CD4-positive T lymphocytes in the lamina propria, which initiates a cascade of immune responses that includes the activation of CD8-positive T cells and B cells [11, 12]. The resulting T cell activation promotes the release of pro-inflammatory cytokines, sustaining chronic intestinal inflammation and contributing directly to mucosal damage [9].

Concomitantly, the interaction between gluten-specific T cells and B cells drives the production of disease-specific autoantibodies, particularly anti–tissue transglutaminase and anti-endomysial antibodies, which constitute a hallmark of celiac disease [13]. Beyond their diagnostic relevance, these autoantibodies may participate in systemic involvement through mechanisms such as molecular mimicry and cross-reactivity with antigens expressed in extraintestinal tissues, potentially explaining several systemic manifestations [14].

Moreover, gluten exposure has been associated with disruption of intestinal tight junctions, leading to increased epithelial permeability and facilitating the passage of inflammatory mediators into the systemic circulation. This enhanced permeability promotes the translocation of immune mediators beyond the intestinal compartment, thereby contributing to inflammation in distant organs [14]. As a result, the systemic immune response may extend to various tissues, providing a mechanistic basis for extraintestinal symptoms, including neurological and dermatological manifestations [15].

Spectrum of Extraintestinal Manifestations

Celiac disease is associated with a broad spectrum of extraintestinal manifestations that reflect its systemic nature and the consequences of chronic inflammation and malabsorption. Among the hematologic manifestations, iron deficiency anemia represents one of the most prevalent findings. It is frequently refractory to oral iron supplementation due to impaired absorption in the damaged duodenum. The reported prevalence of iron deficiency anemia in individuals with celiac disease ranges from 12% to 82%, depending on the study population, and although it typically improves with adherence to a gluten-free diet, normalization of iron stores may require up to two years [16, 17]. In addition to iron deficiency, folate and vitamin B12 deficiencies are also common because of malabsorption, contributing not only to anemia but also to other systemic symptoms. Furthermore, functional hyposplenism has been described in celiac disease, leading to reduced splenic function and an increased risk of infections and other hematologic complications [1].

Skeletal and metabolic complications constitute another major extraintestinal domain. Celiac disease is associated with decreased bone mineral density, resulting in osteopenia and osteoporosis. This reduction in bone mass is related to impaired absorption of calcium and vitamin D, as well as the effects of chronic inflammation. Studies have demonstrated a higher prevalence of osteopenia and osteoporosis in patients with celiac disease compared with healthy controls. Alterations in the calcium–vitamin D axis further contribute to compromised bone health and increased fracture risk, even though patients with celiac disease often report higher rates of vitamin D and calcium supplementation [17].

Dermatologic involvement also reflects the systemic immune dysregulation characteristic of the disease. Dermatitis herpetiformis represents a specific cutaneous manifestation, characterized by pruritic, blistering skin lesions and strongly associated with celiac disease. In addition, immune-mediated conditions such as alopecia areata and chronic urticaria have been linked to celiac disease, further underscoring its multisystem impact [1].

Neurological and psychiatric manifestations are increasingly recognized and may significantly affect quality of life. Gluten ataxia and peripheral neuropathy are among the most frequently reported neurological complications, and symptoms often show improvement with strict adherence to a gluten-free diet [18]. Cognitive impairment and mood disorders, including anxiety and depression, have also been associated with celiac disease, with evidence suggesting potential improvement following dietary management [1, 19].

Hepatic involvement represents another important extraintestinal expression. Celiac disease may present with isolated hypertransaminasemia and may overlap with autoimmune hepatitis, both of which can improve after initiation of a gluten-free diet. Additionally, an association between celiac disease and non-alcoholic fatty liver disease has been described, possibly related to shared metabolic pathways [1].

Endocrine and autoimmune associations further highlight the systemic character of celiac disease. It frequently coexists with other autoimmune disorders, particularly type 1 diabetes mellitus and autoimmune thyroid disease, which necessitates appropriate screening strategies in affected individuals. Primary ovarian insufficiency has also been identified as a potential endocrine manifestation. Reproductive health may be adversely affected. Celiac disease has been linked to unexplained infertility and recurrent pregnancy loss, representing significant clinical concern. Delayed puberty has also been reported in adolescents with celiac disease and

may improve following appropriate dietary management [1, 20].

Diagnostic Strategy in Patients with Extraintestinal Presentations

Clinical suspicion of celiac disease is essential in patients presenting with isolated systemic findings, particularly when gastrointestinal symptoms are absent. Individuals with unexplained neurological manifestations, dermatological conditions, or endocrine disorders should be considered for screening, especially if they belong to high-risk groups such as those with concomitant autoimmune diseases or a family history of celiac disease [1, 21]. In this context, appropriate risk stratification plays a central role. Screening is specifically recommended for individuals with autoimmune disorders, first-degree relatives of patients with celiac disease, and those with associated conditions including type 1 diabetes, Down syndrome, and unexplained abnormalities in liver enzymes [21].

Once clinical suspicion is established, serologic testing constitutes the first step in the diagnostic evaluation. Immunoglobulin A anti–tissue transglutaminase is the preferred initial test due to its high sensitivity and specificity, particularly when antibody levels reach or exceed ten times the upper limit of normal [22, 23]. For confirmation, anti-endomysial antibodies may be employed; however, recent guidelines indicate that high-titer anti–tissue transglutaminase immunoglobulin A levels may be sufficient to establish the diagnosis without additional anti-endomysia testing [22, 24]. Concurrent measurement of total immunoglobulin A is crucial to exclude selective immunoglobulin A deficiency, which may result in false-negative serologic findings. In such cases, immunoglobulin G-based assays should be considered to ensure diagnostic accuracy [25].

Histopathological confirmation remains the gold standard for diagnosis. Duodenal biopsy is recommended, with at least four specimens obtained from the second portion of the duodenum to optimize diagnostic yield [22]. The Marsh–Oberhuber classification system is used to evaluate the degree of villous atrophy and to correlate histologic findings with clinical and systemic involvement [23]. Notably, the severity of histological alterations often parallels the extent of systemic manifestations, reinforcing the importance of comprehensive histopathological assessment [26].

Genetic testing for HLA-DQ2 and HLA-DQ8 alleles may be particularly useful in equivocal cases. Although the presence of these alleles is not diagnostic in isolation, their absence makes celiac disease unlikely, thereby providing significant exclusion value in patients with ambiguous serologic or histologic results [22]. Careful consideration of differential diagnoses is required to avoid misclassification. Non-celiac gluten sensitivity may mimic celiac disease clinically but lacks the autoimmune component and villous atrophy characteristic of the condition [7]. Other disorders that should be considered include irritable bowel syndrome, inflammatory bowel disease, and primary hematologic or endocrine diseases, as these conditions may present with systemic symptoms like those observed in celiac disease [21].

Integrated Therapeutic Management

The strict gluten-free diet constitutes the cornerstone of celiac disease management, as gluten ingestion directly triggers the autoimmune response responsible for intestinal damage and systemic manifestations in genetically predisposed individuals [7, 27]. From a pathophysiological perspective, continued exposure to gluten perpetuates villous atrophy and malabsorption, thereby promoting nutritional deficiencies and contributing to extraintestinal complications. Consequently, sustained adherence to a gluten-free diet is essential to prevent ongoing mucosal injury and its systemic consequences [28].

Effective implementation of this dietary intervention requires comprehensive nutritional counseling and structured patient education. Patients must clearly understand the rationale for lifelong gluten avoidance and acquire practical skills to incorporate the diet into daily life [29]. Education should include detailed guidance on identifying gluten-containing foods, interpreting product labels, and recognizing hidden sources of gluten, as well as understanding the risks associated with cross-contamination [30]. Avoidance of cross-contamination is particularly critical, since even minimal amounts of gluten may trigger symptoms and immune activation. Therefore, patients should receive specific instructions on preventing contamination in household kitchens, restaurants, and social environments [28].

Monitoring adherence to the gluten-free diet is equally important. Serologic testing for celiac-specific antibodies provides an objective measure of dietary compliance and disease activity, while patient-reported adherence offers complementary clinical insight [30]. Regular follow-up with healthcare professionals, including dietitians, supports sustained compliance, allows identification of dietary challenges, and facilitates early correction of potential lapses [29].

Given that malabsorption frequently leads to nutritional deficiencies, correction of these deficits represents a fundamental component of management. Iron, folate, and vitamin B12 deficiencies are common and require targeted supplementation to restore normal hematologic parameters and prevent anemia. In addition, impaired absorption of calcium and vitamin D places patients at increased risk of osteoporosis; therefore, supplementation and appropriate dietary adjustments are necessary to preserve bone health. Regular bone density assessments are recommended to evaluate fracture risk and guide therapeutic decisions [27].

Management of systemic complications must be individualized according to organ involvement. Osteoporosis should be addressed with calcium and vitamin D supplementation, and when indicated, pharmacological interventions may be considered [27]. Neurological manifestations, including gluten ataxia, often require a multidisciplinary strategy involving neurologists and dietitians to optimize outcomes [31]. In cases where psychiatric symptoms are present, psychological support and appropriate mental health interventions are necessary to improve overall well-being [32]. Patients with concurrent endocrine disorders, such as type 1 diabetes, may benefit from coordinated co-management with endocrinologists to ensure integrated care [33].

Long-term follow-up remains a critical element of comprehensive care. Serial serologic testing allows ongoing monitoring of antibody levels and dietary adherence. Continuous clinical reassessment is essential to evaluate the resolution or persistence of systemic manifestations and to adjust management strategies accordingly. Repeat duodenal biopsy may be indicated in cases of non-responsive disease or when symptoms persist despite strict adherence to a gluten-free diet [33]. Ultimately, sustained longitudinal follow-up enables assessment of long-term health outcomes and quality of life, ensuring that the multisystem aspects of celiac disease are addressed in a comprehensive and coordinated manner [2].

Refractory Celiac Disease and Malignant Complications

Refractory celiac disease is defined by the persistence or recurrence of malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet, and it is classified into two distinct subtypes based on the phenotype of intraepithelial lymphocytes. Refractory celiac disease type I is characterized by a polyclonal expansion of intraepithelial lymphocytes with a normal immunophenotype. Although its precise etiology remains unclear, it

has been proposed that gluten-independent autoimmune mechanisms may contribute to its pathogenesis [33, 34]. In contrast, refractory celiac disease type II is defined by a clonal proliferation of aberrant intraepithelial lymphocytes and is considered a low-grade lymphoproliferative disorder. Due to its biological behavior and malignant potential, it is often described as "cryptic" enteropathy-associated T-cell lymphoma, reflecting its propensity to progress to overt lymphoma [33, 35].

The risk of progression to enteropathy-associated T-cell lymphoma is particularly significant in refractory celiac disease type II. This lymphoma is rare but highly aggressive and is associated with a poor prognosis. Genetic alterations, especially involving the JAK-STAT signaling pathway, have been implicated in its pathogenesis and may contribute to uncontrolled lymphocytic proliferation [35, 36]. Clinically, enteropathy-associated T-cell lymphoma carries a high mortality rate, with median overall survival often limited to only a few months, and outcomes are especially unfavorable in advanced stages of the disease [36, 37].

In response to the malignant potential of refractory disease, advanced immunomodulatory therapies are being explored. Novel treatments targeting immune pathways, including the JAK-STAT axis, have emerged as potential strategies. Among these, targeted agents such as brentuximab vedotin have shown promise in the management of enteropathy-associated T-cell lymphoma [14, 38]. Current therapeutic approaches differ according to subtype. Refractory celiac disease type I may respond to corticosteroids such as budesonide, whereas type II generally requires more aggressive treatment due to its higher risk of malignant transformation [33, 34].

Prognosis varies substantially between the two forms. Refractory celiac disease type I is associated with a comparatively favorable outcome, while type II frequently progresses to enteropathy-associated T-cell lymphoma. The detection of clonal intraepithelial lymphocytes and the presence of specific genetic mutations in type II disease serve as indicators of poor prognosis [34, 35]. Given these risks, vigilant surveillance and close monitoring are essential. Early identification of malignant transformation is critical, and serum markers such as chromogranin A and β2-microglobulin may assist in recognizing patients at increased risk of refractoriness and lymphoma development [39].

Multidisciplinary Care Model

The management of celiac disease requires the coordinated involvement of multiple medical specialists, reflecting its multisystem nature. Gastroenterologists play a central role in diagnosis and overall management, particularly in evaluating gastrointestinal manifestations, confirming the diagnosis, and monitoring adherence to a gluten-free diet [5, 40]. Endocrinologists contribute to the management of associated endocrine disorders, such as type 1 diabetes, which frequently coexists with celiac disease and requires integrated care to optimize metabolic control [32]. Neurologists are essential in addressing neurological complications, including neuropathy and ataxia, which may arise as extraintestinal manifestations [5]. Dermatologists are involved in the treatment of cutaneous conditions such as dermatitis herpetiformis, a characteristic extraintestinal presentation, while hematologists manage anemia and other hematologic abnormalities related to malabsorption [41].

Nutritional specialists and dietitians play a pivotal role in long-term disease control, given that the gluten-free diet remains the cornerstone of therapy. Through structured nutritional management, dietitians educate patients on dietary restrictions, ensure nutritional adequacy, and support sustained adherence to the gluten-free diet. Dietitian-led clinics have demonstrated

the capacity to facilitate timely diagnosis and optimize nutritional care, while also reducing the need for repeated gastroenterology appointments and improving patient satisfaction [29, 42].

Psychological and psychosocial support further complement this multidisciplinary approach. Adherence to a lifelong gluten-free diet can impose significant emotional and social challenges, making psychological interventions an important component of care. Targeted support may alleviate psychological burden and enhance quality of life [29]. A patient-centered model that integrates psychological care has been associated with improved adherence and overall well-being [40].

Long-term management strategies benefit from structured multidisciplinary programs specifically dedicated to celiac disease. Such programs, which integrate various specialists, have been associated with improvements in quality-of-care metrics and clinical outcomes, including symptom resolution and favorable serological responses [40]. Regular follow-up is essential to evaluate adherence to the gluten-free diet, monitor antibody levels, assess nutritional status, and manage complications. In addition, effective communication and a well-planned transition from pediatric to adult care are critical to maintaining continuity of management and addressing the evolving clinical needs of patients across the lifespan [32, 42].

Emerging Therapies and Future Directions

Emerging therapeutic strategies in celiac disease aim to complement or potentially transcend the traditional gluten-free diet by targeting specific mechanisms involved in disease pathogenesis. Among these approaches, enzyme therapies designed to degrade gluten before it elicits an immune response have gained particular attention. These therapies utilize gluten-specific peptidases capable of breaking down immunogenic gluten peptides, especially those rich in proline and glutamine residues that are resistant to normal gastrointestinal digestion [43]. By reducing the burden of intact immunogenic fragments, these enzymes seek to limit downstream immune activation. ALV003, a combination of two proteases, has demonstrated promising results in clinical trials, showing a reduction in gluten-induced mucosal damage when administered alongside a gluten-free diet [44].

Another investigational strategy involves tight junction modulators, which target the increased intestinal permeability characteristic of celiac disease. Disruption of tight junction integrity facilitates the passage of gluten peptides into the lamina propria, where they initiate immune activation. Larazotide acetate is a tight junction modulator that has shown efficacy in reducing both symptoms and intestinal permeability in patients with celiac disease [45]. By preventing the paracellular uptake of gluten peptides, such agents may attenuate immune activation associated with gluten exposure [44].

Immunotherapy-based approaches represent an additional avenue of investigation, focusing on modulating the immune response or inducing tolerance to gluten. Strategies under evaluation include the use of nanoparticles to deliver gluten antigens in a manner that promotes immune tolerance rather than inflammation [46]. Furthermore, a bispecific antibody targeting HLA-DQ2.5–gluten peptide complexes has been developed to block gluten-specific T cell activation, a central mechanism in the pathogenesis of celiac disease [47].

Parallel to therapeutic innovation, biomarker development is crucial for identifying patients who may benefit from specific interventions and for monitoring treatment efficacy. Current diagnostic and monitoring tools rely primarily on serologic testing and duodenal biopsy; however, these methods have recognized limitations. Ongoing research seeks to establish less invasive

biomarkers, including peripheral blood cell profiles and cytokine markers, which may provide real-time information on disease activity and therapeutic response [48].

Within this evolving landscape, precision medicine perspectives are increasingly relevant. Personalized management in celiac disease involves tailoring therapeutic strategies according to individual genetic and immunological characteristics. Stratification based on HLA-DQ2 or HLA-DQ8 status may help optimize treatment efficacy while minimizing adverse effects [49]. Moreover, the development of targeted therapies directed at specific pathogenic pathways, such as transglutaminase 2 inhibitors, reflects a broader movement toward individualized and mechanism-based treatment approaches [50].

Conclusions

Celiac disease is a genetically predisposed, immune-mediated systemic disorder in which HLA-DQ2 and HLA-DQ8 haplotypes enable gluten-driven T cell activation, autoantibody production, and chronic inflammation. The resulting immune dysregulation and increased intestinal permeability explain its wide spectrum of extraintestinal manifestations, highlighting that celiac disease extends beyond the gastrointestinal tract and may present with isolated systemic findings.

Diagnosis requires an integrated approach combining serology, histopathology, and selective genetic testing, while strict adherence to a gluten-free diet remains the cornerstone of therapy. Long-term multidisciplinary management is essential to correct nutritional deficiencies, address systemic complications, monitor for refractory disease, and reduce the risk of malignant transformation, with emerging targeted therapies offering future therapeutic potential.

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