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Refractory Coeliac Disease: Diagnosis, Treatment, and Emerging Therapies

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ABSTRACT

Introduction: Coeliac disease (CD) is a chronic immune-mediated disorder triggered by gluten ingestion in genetically predisposed individuals, primarily affecting the small intestine and leading to villous atrophy, malabsorption, and systemic complications. While traditionally considered a gastrointestinal condition, CD is now recognized as a multisystem disorder with neurological, musculoskeletal, endocrine, and cardiovascular implications. Despite advancements in diagnostic tools, the disease remains underdiagnosed, often due to its diverse clinical presentations, ranging from classic gastrointestinal symptoms to atypical manifestations such as anemia, osteoporosis, and chronic fatigue.

The global prevalence of CD is approximately 1%, with increasing incidence attributed to improved screening and potential environmental triggers. Diagnosis involves serological testing, histological confirmation via duodenal biopsy, and, in select cases, HLA genotyping. Lifelong adherence to a strict gluten-free diet (GFD) remains the only effective treatment, but dietary compliance challenges and persistent symptoms in some patients necessitate further evaluation for refractory CD or alternative conditions.

Emerging research focuses on novel therapeutic approaches, including gluten detoxification, intestinal barrier modulation, and immune-based therapies. The gut microbiome's role in CD pathogenesis is also gaining attention, offering potential new avenues for treatment. As research progresses, there is a growing need for earlier diagnosis, individualized management strategies, and alternative therapies beyond dietary restriction to improve patient outcomes and long-term quality of life.

Materials and Methods: A systematic review was conducted using PubMed, Scopus, and Web of Science to identify studies on coeliac disease published between 2000 and 2023. The search focused on key topics such as gluten intolerance, immune-mediated enteropathy, refractory coeliac disease, and systemic complications. Inclusion criteria comprised original research, systematic reviews, meta-analyses, and clinical guidelines addressing immunological mechanisms, diagnosis, treatment strategies, and extra-intestinal manifestations. Particular emphasis was placed on studies exploring refractory cases and emerging therapies beyond the gluten-free diet.

Results: Coeliac disease (CD) is a complex immune-mediated disorder driven by gluten ingestion in genetically predisposed individuals, leading to chronic intestinal inflammation and systemic complications. While classic gastrointestinal symptoms such as diarrhea and malabsorption are common, many patients present with extra-intestinal manifestations, including anemia, osteoporosis, neurological impairments, and autoimmune comorbidities. Diagnosis relies on serological testing, duodenal biopsy, and, in select cases, genetic

screening. The gluten-free diet (GFD) remains the primary treatment, but adherence challenges, nutritional deficiencies, and persistent symptoms necessitate further evaluation. Emerging therapies targeting immune modulation, gut microbiota, and intestinal permeability are under investigation, offering potential alternatives for patients with refractory CD. Despite advances in understanding and managing CD, continued research is needed to optimize early detection, improve treatment adherence, and develop novel therapeutic interventions.

Conclusions:. Coeliac disease is a complex immune-mediated disorder with both gastrointestinal and systemic implications. While the gluten-free diet remains the mainstay of treatment, challenges in adherence and persistent symptoms highlight the need for alternative therapies. Advances in diagnosis, immune modulation, and gut microbiome research offer promising directions for improving patient outcomes. Early detection and individualized management strategies remain crucial in mitigating long-term complications and enhancing quality of life.

Keywords: coeliac disease, gluten intolerance, gluten free diet, nutrient malabsorption, gut microbiome

INTRODUCTION

Coeliac disease (CD) is a chronic immune-mediated disorder triggered by gluten ingestion in genetically predisposed individuals. It primarily affects the small intestine, leading to villous atrophy, malabsorption, and a wide spectrum of clinical manifestations [1,2]. The disease is driven by an aberrant immune response to gluten peptides, particularly in individuals carrying HLA-DQ2 and HLA-DQ8 genetic markers [3]. Historically considered a gastrointestinal disorder, coeliac disease is now recognized as a systemic condition with both

intestinal and extra-intestinal manifestations, including neurological, endocrine, musculoskeletal, and cardiovascular complications [4,5]. Despite advances in diagnostic techniques and increasing disease awareness, coeliac disease remains underdiagnosed, with many individuals experiencing prolonged diagnostic delays [6,7].

The global prevalence of coeliac disease is estimated at approximately 1%, though significant geographic variation exists [8]. The increasing incidence has been attributed to improved screening practices, dietary changes, and potential environmental triggers affecting immune tolerance [9,10]. Coeliac disease can present at any age, with symptoms ranging from classic gastrointestinal complaints, such as diarrhea, bloating, and weight loss, to atypical presentations, including anemia, osteoporosis, chronic fatigue, and neurological disorders [11,12]. The heterogeneity of clinical manifestations often complicates diagnosis, necessitating a combination of serological testing, histological assessment via duodenal biopsy, and, in select cases, HLA genotyping to confirm susceptibility [13,14].

Currently, the only established treatment for coeliac disease is lifelong adherence to a strict gluten-free diet (GFD) [15]. While this approach effectively alleviates symptoms and promotes mucosal healing in most patients, challenges related to dietary compliance, persistent symptoms, and ongoing intestinal inflammation are common [16,17]. Non-responsive coeliac disease, which affects a subset of patients despite adherence to a GFD, presents a significant clinical challenge, often requiring further evaluation for alternative causes of symptoms or refractory disease [18,19]. Additionally, the long-term consequences of untreated or undiagnosed coeliac disease include an increased risk of osteoporosis, infertility, neurological complications, and, in rare cases, enteropathy-associated T-cell lymphoma (EATL) [20,21].

Recent research has focused on expanding treatment options beyond dietary management, with novel therapeutic strategies targeting gluten detoxification, intestinal barrier integrity, and immune modulation currently under investigation [22]. The role of the gut microbiome in coeliac disease pathogenesis has also gained attention, suggesting potential avenues for microbiota-targeted interventions [23]. As research continues to evolve, there is a growing need for early diagnosis, individualized management strategies, and the development of non-dietary therapeutic options to improve patient outcomes [1-3]. This review explores the pathophysiology, risk factors, clinical presentation, and management strategies for coeliac disease, with a focus on emerging diagnostic tools and novel therapeutic approaches.

MATERIALS AND METHODS

A systematic search was conducted using electronic databases, including PubMed, Scopus, and Web of Science, to identify relevant studies published between 2000 and 2023. Search terms included “coeliac disease,” “gluten intolerance,” “immune-mediated enteropathy,” “gluten-free diet,” “refractory coeliac disease,” and “systemic consequences of coeliac disease.”

Inclusion criteria encompassed original research articles, systematic reviews, meta-analyses, and clinical guidelines that focused on the immunological mechanisms, diagnostic criteria, treatment approaches, and extra-

intestinal manifestations of coeliac disease [3,4]. Priority was given to studies providing evidence-based insights into non-responsive and refractory cases, as well as those exploring emerging therapeutic interventions beyond the gluten-free diet [5,6].

RESULTS

Coeliac disease (CD) is a chronic immune-mediated disorder triggered by gluten ingestion in genetically predisposed individuals, resulting in small intestinal damage and a broad spectrum of systemic manifestations [7,8]. It arises from a complex interplay of genetic susceptibility, environmental factors, and immune dysregulation [9]. Nearly all affected individuals carry the HLA-DQ2 or HLA-DQ8 haplotypes, which facilitate the presentation of gluten-derived peptides to T cells, initiating an inflammatory cascade [10]. However, genetic predisposition alone is insufficient for disease onset, as additional environmental triggers such as early-life gluten exposure, intestinal infections, and gut microbiota imbalances contribute to immune activation. The loss of tolerance to gluten leads to an abnormal immune response involving tissue transglutaminase (TG2), which modifies gliadin peptides, enhancing their immunogenicity. This results in chronic inflammation, villous atrophy, and increased intestinal permeability, further exacerbating the disease process [11,12].

The clinical presentation of CD varies widely, complicating diagnosis and often leading to delays in recognition [13]. While classic cases manifest with gastrointestinal symptoms such as chronic diarrhea, abdominal pain, weight loss, and malabsorption, many patients present with extra-intestinal symptoms, including iron-deficiency anemia, osteoporosis, chronic fatigue, neurological dysfunction, and reproductive disorders [14,15]. The disease can also remain asymptomatic, only becoming apparent following serological screening or the development of complications. Given this heterogeneity, a combination of serological, histological, and genetic tests is required for an accurate diagnosis. Tissue transglutaminase (TG2) and anti-endomysial antibodies are highly sensitive and specific markers for CD, but a definitive diagnosis typically requires histological confirmation through duodenal biopsy, which reveals villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. In cases where serological markers are negative but symptoms persist, HLA genotyping and a gluten-free diet (GFD) trial may provide diagnostic clarity [16-18].

Beyond intestinal involvement, CD has far-reaching systemic consequences. Neurological complications, including gluten ataxia, peripheral neuropathy, and cognitive impairment, have been documented, suggesting a link between gluten exposure and neuroinflammation [19]. Additionally, prolonged intestinal malabsorption leads to metabolic bone disease, increasing the risk of osteopenia and osteoporosis due to deficiencies in calcium, vitamin D, and other micronutrients. Autoimmune comorbidities, particularly type 1 diabetes, autoimmune thyroiditis, and primary biliary cholangitis, frequently coexist with CD, highlighting shared immunopathogenic mechanisms. There is also emerging evidence that chronic inflammation in untreated CD may contribute to

cardiovascular risk factors such as endothelial dysfunction and an increased propensity for atherosclerosis. Furthermore, persistent villous atrophy despite dietary adherence has been associated with an elevated risk of malignancies, including enteropathy-associated T-cell lymphoma (EATL), emphasizing the need for regular long-term monitoring [1-5, 22].

The primary treatment for CD remains strict lifelong adherence to a GFD, which is effective in resolving symptoms and promoting intestinal healing in most patients. However, dietary compliance is often challenging due to the risk of inadvertent gluten exposure, the social burden of dietary restrictions, and persistent symptoms in some individuals despite apparent adherence. Non-responsive CD, characterized by ongoing symptoms and mucosal damage despite following a GFD, requires further evaluation to rule out hidden gluten intake, concurrent disorders such as irritable bowel syndrome, or the development of refractory CD [5-8]. Refractory CD type I is managed conservatively, whereas type II, marked by clonal expansion of aberrant intraepithelial lymphocytes, carries a risk of progression to lymphoma and may necessitate immunosuppressive therapy or novel targeted treatments. Given the limitations of dietary management, research into alternative therapeutic approaches is rapidly advancing. Enzyme therapy aims to degrade immunogenic gluten peptides before they reach the small intestine, reducing their ability to trigger an immune response. Immunomodulatory therapies targeting HLA-DQ2-mediated antigen presentation, TG2 activity, and pro-inflammatory cytokines are being explored as potential disease-modifying treatments. Additionally, tight junction regulators, such as larazotide acetate, seek to restore intestinal barrier function and reduce gluten-induced permeability [10-13]. The gut microbiome's role in CD pathogenesis is increasingly recognized, with studies suggesting that microbiota-targeted interventions such as probiotics and fecal microbiota transplantation may modulate immune responses and influence disease progression.

Despite significant advances in understanding CD, challenges remain in optimizing diagnostic accuracy, improving patient adherence to dietary therapy, and developing effective non-dietary treatments. Many patients continue to experience persistent symptoms, requiring ongoing dietary education, nutritional support, and individualized treatment approaches. Future research should focus on refining biomarkers for early detection, investigating microbiome-targeted therapies, and advancing pharmacological interventions that may eventually provide alternatives to the restrictive GFD. Long-term follow-up remains essential for monitoring disease progression, assessing nutritional status, and preventing complications, ensuring that patients achieve optimal health outcomes while managing this chronic condition [18-22].

Emerging therapeutic approaches beyond dietary management are currently under investigation, with several strategies showing promise. Enzyme therapy aims to break down gluten peptides before they trigger an immune response, potentially reducing the impact of inadvertent gluten exposure. Tight junction regulators such as larazotide acetate seek to restore intestinal barrier integrity, reducing inflammation and permeability. Immunomodulatory treatments targeting TG2 activity, gliadin-specific T cells, or inflammatory cytokines could help reprogram immune responses and reduce disease progression. Additionally, studies on gut microbiota modulation through probiotics and fecal microbiota transplantation are being explored as potential adjunct

therapies. However, these interventions are still in experimental stages, and further research is needed to establish their long-term safety and efficacy. Despite significant advances in understanding CD, many challenges remain in optimizing diagnosis, improving dietary adherence, and developing alternative treatments. Delayed diagnosis often leads to prolonged symptom duration and an increased risk of complications [4-10]. Long-term follow-up is crucial to monitor disease progression, ensure nutritional adequacy, and assess comorbidities such as osteoporosis, neurological deficits, and autoimmune disorders. For some patients, persistent symptoms despite a strict GFD highlight the need for better therapeutic options beyond dietary restriction. Future research should focus on refining biomarkers for early detection, personalizing treatment strategies, and advancing pharmacological interventions that may eventually provide alternatives to the restrictive GFD. Continued investigation into the immunological mechanisms underlying CD will help pave the way for novel disease-modifying therapies, ultimately improving patient outcomes and quality of life.

CONCLUSIONS

Coeliac disease (CD) is a chronic immune-mediated disorder triggered by gluten ingestion in genetically predisposed individuals, leading to intestinal inflammation, villous atrophy, and nutrient malabsorption [1,2]. While traditionally considered a gastrointestinal condition, its extra-intestinal manifestations—including anemia, osteoporosis, neurological disorders, and autoimmune comorbidities—highlight its systemic nature. The variability in clinical presentation often results in diagnostic delays, increasing the risk of long-term complications [5].

Diagnosis relies on serological testing, histological examination, and, in select cases, genetic screening. Although a strict gluten-free diet (GFD) remains the mainstay of treatment, adherence challenges and persistent symptoms in some patients underscore the need for additional therapeutic approaches. Refractory CD requires further evaluation and, in some cases, immunosuppressive therapy [8-10].

Given the disease's broad impact, a multidisciplinary approach is essential for monitoring nutritional status, preventing complications, and improving long-term outcomes. Ongoing research into enzyme therapy, gut microbiota modulation, and immunotherapy offers promising alternatives to dietary restriction. Future advancements in early detection and targeted treatments will be key to enhancing patient care and quality of life [6].

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