STRZAŁKOWSKA, Paulina, HOBOT, Maciej, GRABSKI, Wojciech, SZAJ, Dominika, RACZKOWSKA, Michalina and MAZUR, Aleksandra. Coeliac disease as a systemic disorder - current state of knowledge. Quality in Sport. 2025;46:66576. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.46.66576
https://apcz.umk.pl/QS/article/view/66576

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). **© The Authors 2025.**
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The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 12.11.2025. Revised: 16.11.2025. Accepted: 16.11.2025. Published: 24.11.2025.

Coeliac disease as a systemic disorder - current state of knowledge

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ABSTRACT

Coeliac disease is a chronic autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals, primarily those carrying the HLA-DQ2 and HLA-DQ8 alleles. Although it was previously considered a condition limited to the gastrointestinal tract, it is now recognized as a systemic disease. In addition to classical intestinal symptoms (diarrhea, abdominal pain, malabsorption), coeliac disease can cause extraintestinal manifestations affecting the musculoskeletal, neurological, endocrine, dermatological, and hepatic systems. If left untreated, it is associated with an increased risk of malignancies, including enteropathy-associated T-cell lymphoma (EATL) and adenocarcinoma of the small intestine. The cornerstone of treatment remains a strict gluten-free diet, which alleviates symptoms and reduces the risk of complications. The aim of this review is to present the current state of knowledge regarding the systemic manifestations of coeliac disease, the underlying pathogenic mechanisms, and the impact of treatment on disease course and quality of life. Emphasis is placed on the importance of early diagnosis and individualized patient management.

Keywords: coeliac disease, gluten-free diet, extraintestinal manifestations, HLA-DQ2/DQ8, enteropathy-associated T-cell lymphoma, quality of life

INTRODUCTION

Coeliac disease is a chronic systemic autoimmune disorder triggered by the ingestion of gluten - a protein found in wheat, rye, and barley - in genetically predisposed individuals [1,2]. For many decades, it was primarily considered a gastrointestinal disorder characterized by chronic diarrhea, abdominal pain, and malabsorption leading to nutritional deficiencies and malnutrition [3]. However, advances in diagnostics and pathogenesis research have led modern medicine to recognize coeliac disease as a systemic condition with symptoms potentially affecting nearly every organ system in the body [3,4].

Current epidemiological data indicate that coeliac disease affects approximately 1% of the general population, although the true prevalence may be significantly higher due to a large number of asymptomatic or oligosymptomatic cases [2,5]. Increasingly, atypical forms are observed, in which extraintestinal manifestations predominate, such as neurological disorders, dermatological diseases, osteoporosis, and concomitant autoimmune conditions [4,6].

The underlying mechanism of coeliac disease is an abnormal immune response to gluten, mediated by the presence of specific human leukocyte antigen (HLA) molecules HLA-DQ2 and HLA-DQ8 [1,7]. Chronic inflammation results in damage to the small intestinal mucosa and generalized immune activation, leading to a wide range of systemic manifestations [4,8]. Untreated or poorly controlled coeliac disease is also associated with an increased risk of serious complications, including malignancies such as enteropathy-associated T-cell lymphoma (EATL) and adenocarcinoma of the small intestine [9–11].

In recent years, there has been growing emphasis on adopting a holistic approach to patients with coeliac disease - not only considering gastrointestinal symptoms but also metabolic, neurological, dermatological, endocrine disturbances, and psychosocial burden [3,6,8]. Only a comprehensive diagnostic and therapeutic strategy effectively reduces the risk of long-term complications and improves patients' quality of life [12].

The aim of this review is to present the current state of knowledge on coeliac disease as a systemic disorder. The immunopathogenetic mechanisms, diverse clinical manifestations (both intestinal and extraintestinal), diagnostic methods, the role of a gluten-free diet, and the impact of the disease on patient functioning will be discussed. Special emphasis is placed on systemic

complications, including the increased risk of malignancies, which represent a significant clinical and societal challenge.

PATHOGENESIS AND SYSTEMIC MECHANISMS

Coeliac disease develops as a result of an abnormal immune response to gluten in genetically predisposed individuals. Gluten is a heterogeneous mixture of plant proteins, among which the gliadin fraction plays a particularly pathogenic role [3,4]. Tissue transglutaminase (tTG) catalyzes the deamidation of gliadin peptides, significantly increasing their immunogenicity and enabling their presentation by HLA-DQ2 and HLA-DQ8 molecules on antigen-presenting cells [1,4].

The presence of HLA-DQ2 and HLA-DQ8 haplotypes is detected in over 95% of patients with coeliac disease, making them necessary but not sufficient conditions for disease development [1,7]. Following antigen presentation, CD4+ T lymphocytes become activated and induce the secretion of various proinflammatory cytokines such as interferon gamma (IFN-γ), interleukin-15 (IL-15), and other mediators [4,8]. These processes result in villous atrophy, crypt hyperplasia, and mucosal remodeling, leading to a significant reduction in absorptive surface area [3,4].

A crucial component of the systemic mechanisms of the disease is the translocation of cytokines and autoantibodies (including anti-tTG antibodies) into the systemic circulation [4,8]. It has been shown that these autoantibodies can deposit in the skin and blood vessels, contributing to distant manifestations such as dermatitis herpetiformis, gluten ataxia, and peripheral neuropathies [4,6].

Moreover, chronic activation of the immune system promotes the development of other autoimmune diseases, including type 1 diabetes, autoimmune thyroiditis (Hashimoto's disease), autoimmune hepatitis, and rheumatoid arthritis [3,4,7]. Studies have demonstrated that polyautoimmunity is particularly frequent in patients diagnosed with coeliac disease during adulthood [7].

Increasing attention is also being paid to the gut microbiota as a potential modulator of the immune response. Dysbiosis may enhance intestinal permeability, facilitating exposure of the immune system to gluten peptides and amplifying inflammatory responses [4,8]. It remains unclear whether microbiota alterations are a primary etiological factor or a secondary effect of mucosal damage—this is the subject of ongoing prospective research.

In summary, the pathogenesis of coeliac disease is a complex, multifactorial process in which interplay among genetic, environmental, and immunological factors plays a key role. Understanding these mechanisms is critical for assessing the risk of systemic complications and planning personalized treatment strategies.

INTESTINAL AND EXTRA-INTESTINAL MANIFESTATIONS - SYSTEMS OVERVIEW

Classic symptoms of coeliac disease arise from damage to the small intestinal mucosa, leading to malabsorption. The most common manifestations include chronic diarrhea, bloating, abdominal pain, and weight loss [3,4]. Reduced absorptive surface results in deficiencies of protein, iron, folic acid, fat-soluble vitamins (A, D, E, K), and disturbances in calcium-phosphorus metabolism [3,4,8]. These symptoms predominantly affect children, causing growth retardation and delayed puberty [3]. In adults, the disease often presents with oligosymptomatic or atypical features, which delays diagnosis and increases the risk of complications [4].

Currently, subclinical forms of coeliac disease with minimal or absent intestinal symptoms are increasingly recognized. In such cases, extraintestinal manifestations predominate, posing diagnostic challenges and requiring high clinical vigilance [4,15].

In the musculoskeletal system, osteopenia and osteoporosis are frequently observed, affecting up to 75% of untreated patients [3,4,8]. Calcium and vitamin D deficiencies, along with chronic inflammation, contribute to increased bone fragility and chronic bone and joint pain, which may be the initial symptom in adults [4].

Neurological manifestations include peripheral neuropathies, gluten ataxia, and epilepsy [3,6,8,13]. Peripheral neuropathies occur in approximately 10–20% of patients, presenting with paresthesias, limb numbness, and muscle weakness [13]. Gluten ataxia, defined as a chronic cerebellar syndrome associated with antigliadin antibodies, affects about 6% of patients [13]. In children, a syndrome of epilepsy with occipital calcifications (“celiac epilepsy”) may occur [3,13].

Coeliac disease commonly coexists with autoimmune disorders such as type 1 diabetes and autoimmune thyroiditis (Hashimoto’s disease) [3,4,7]. Additionally, hormonal disturbances including irregular menstruation, premature menopause, and infertility have been reported

[4,14]. Untreated coeliac disease has been shown to reduce ovarian reserve and negatively impact spermatogenesis [14].

Dermatologically, dermatitis herpetiformis, characterized by IgA deposits against tissue transglutaminase, is observed in 10–20% of patients [3,6]. Lesions typically localize to the elbows, knees, buttocks, and scalp [6].

The liver and biliary tract may also be involved. Approximately 40% of patients exhibit transient mild elevation of aminotransferases ("celiac hepatitis") [4,8]. Untreated coeliac disease increases the risk of autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis [3,4].

Cardiovascular involvement includes increased risk of atherosclerosis, cardiomyopathy, and heart failure [3,8,15]. These risks are linked to chronic inflammation, vitamin deficiencies, metabolic disturbances, and endothelial dysfunction [15].

Extraintestinal symptoms, particularly neurological, endocrine, and dermatological, significantly affect patients' quality of life, as confirmed by studies using questionnaires and assessments of psychological well-being [6,15].

LATE COMPLICATIONS, INCLUDING MALIGNANCIES

Untreated or poorly controlled coeliac disease is associated with an increased risk of serious complications, including malignancies of the gastrointestinal tract and beyond. The most severe, although relatively rare, complication is enteropathy-associated T-cell lymphoma (EATL) [3,4,9]. EATL develops in approximately 0.5-1% of patients with long-standing untreated coeliac disease and is linked to very poor prognosis [9,17]. The highest risk of EATL occurs in patients with refractory coeliac disease, particularly type II, characterized by persistent mucosal damage despite adherence to a gluten-free diet [9,16].

Beyond EATL, patients with coeliac disease also have an increased risk of non-Hodgkin lymphomas located outside the gastrointestinal tract, including lymphomas of lymph nodes and the spleen [10,15,17]. This phenomenon is related to chronic immune system activation, continuous T-cell stimulation, and impaired control of cellular proliferation [4,9,16].

Another significant concern is the increased incidence of small bowel adenocarcinoma, which, although rare in the general population, occurs 10-20 times more frequently in individuals with

coeliac disease [4,15,17]. The risk of this malignancy is especially elevated in patients with long undiagnosed disease or poor adherence to a gluten-free diet [9,16].

Some studies have also reported a higher risk of pharyngeal and esophageal cancers in patients with untreated coeliac disease [3,4]. Chronic inflammation, immune dysregulation, and increased exposure of the mucosa to dietary and reflux carcinogens are believed to contribute to this elevated risk.

Other cancers that may have an increased incidence in coeliac patients include hepatocellular carcinoma, pancreatic cancer, and certain skin malignancies [3,4,15,17]. Although data on these neoplasms are less definitive, chronic inflammation, micronutrient deficiencies, and autoimmune mechanisms are thought to play roles in their development [4,15].

Strict adherence to a gluten-free diet is crucial in reducing the risk of malignancies. It has been demonstrated that patients who rigorously follow the diet for many years have significantly lower risks of lymphomas and adenocarcinomas compared to those who do not comply with dietary recommendations [3,4,9,15,16]. Gluten-free diet promotes mucosal healing, decreases chronic immune stimulation, and normalizes inflammatory markers, thereby reducing cancer risk and improving prognosis.

Early detection of malignant complications requires regular serological monitoring and, in selected cases, repeated endoscopic evaluations with histopathological assessment [9,15,16]. Close surveillance, especially in high-risk groups such as patients with refractory coeliac disease, constitutes a critical component of long-term care.

DIAGNOSIS OF SYSTEMIC MANIFESTATIONS OF COELIAC DISEASE

Diagnosis of coeliac disease primarily relies on identifying the immune response to gluten and histopathological assessment of the small intestinal mucosa. The standard initial step involves serological testing for antibodies, including IgA-class anti-tissue transglutaminase (tTG-IgA) and anti-endomysial antibodies (EmA), both characterized by high sensitivity and specificity [3,4]. Meta-analyses have demonstrated that EmA exhibits specificity up to 99%, although tTG-IgA remains a more practical screening test due to its wider availability and lower cost [18]. In cases of IgA deficiency, present in approximately 2–3% of coeliac patients, IgG-class antibodies against deamidated gliadin peptides (DGP-IgG) should be measured [3,18].

Confirmation of diagnosis is achieved via small intestinal biopsy, typically obtained from the duodenal bulb and more distal parts, revealing villous atrophy, crypt hyperplasia, and lymphocytic infiltration [3,4,16]. According to the 2020 ESPGHAN guidelines, in children with very high tTG-IgA levels (≥10 times the upper limit of normal) and positive EmA, coeliac disease diagnosis may be established without intestinal biopsy [12].

Genetic testing for the presence of HLA-DQ2 and HLA-DQ8 haplotypes, found in over 95% of patients with coeliac disease, serves as an adjunctive tool. While their presence is not sufficient for diagnosis, their absence effectively excludes it [1,4,16].

Diagnosing extraintestinal manifestations poses a significant clinical challenge and requires individualized evaluation. These manifestations may be the initial or sole symptoms of coeliac disease, particularly in adults [3,4]. For bone disorders such as osteopenia or osteoporosis, assessment of calcium-phosphorus metabolism, vitamin D levels, and bone densitometry is recommended [3,4].

Neurological symptoms, including peripheral neuropathies and gluten ataxia, necessitate differential diagnosis from idiopathic neuropathies, diabetic polyneuropathy, vitamin B12 deficiency, demyelinating diseases, and systemic lupus erythematosus (SLE) [4,13,16]. Diagnostic aids include nerve conduction studies, brain MRI, and autoantibody testing [13].

Dermatological diagnosis, especially for suspected dermatitis herpetiformis, is based on direct immunofluorescence of skin biopsy, revealing granular IgA deposits in dermal papillae [6]. For endocrine disturbances such as menstrual irregularities, premature menopause, or infertility, hormonal profiling, pelvic ultrasound, and gynecological or andrological consultations are indicated [4,14].

Given the multisystemic and nonspecific nature of coeliac disease manifestations, differential diagnosis encompasses a broad range of autoimmune and metabolic disorders including SLE, autoimmune hepatitis, Hashimoto’s thyroiditis, Sjögren’s syndrome, and inflammatory bowel diseases [4,15,16].

TREATMENT AND THE IMPACT OF A GLUTEN-FREE DIET ON SYSTEMIC MANIFESTATIONS

The cornerstone of coeliac disease treatment is a strict, lifelong gluten-free diet, which remains the gold standard therapeutic approach [3,4,16]. Gluten elimination leads to regeneration of the

small intestinal mucosa, reduction of lymphocytic infiltration, and restoration of normal villous architecture [3,4]. In most cases, adherence to the diet results in significant alleviation of intestinal symptoms, improved nutrient absorption, and normalization of nutritional parameters.

The gluten-free diet also exerts a substantial impact on extraintestinal manifestations. In patients with osteopenia and osteoporosis, it improves calcium and vitamin D absorption, which can increase bone mineral density and reduce fracture risk [3,4]. Neurological symptoms such as gluten ataxia and peripheral neuropathies improve in some patients, especially when treatment is initiated early [13,18]. However, in advanced neurological damage, changes may be irreversible, highlighting the importance of prompt diagnosis [13].

Adherence to a gluten-free diet also reduces the risk of coeliac-associated malignancies, such as enteropathy-associated T-cell lymphoma (EATL) and small bowel adenocarcinoma [3,4,9,17]. It has been demonstrated that patients who strictly follow the diet for many years have significantly lower cancer-related complication risks compared to those who do not adhere to dietary recommendations [3,9].

Despite the effectiveness of the gluten-free diet, treatment faces significant challenges. Approximately 2-5% of patients develop refractory coeliac disease, characterized by persistent symptoms and villous atrophy despite adherence to the diet for at least 12 months [9,16]. Type II refractory disease is particularly difficult to treat and is associated with a risk of progression to T-cell lymphoma [9]. In such cases, immunosuppressive therapy or corticosteroids may be required [9,16].

Treatment can be further complicated by coexisting autoimmune diseases such as type 1 diabetes, Hashimoto's thyroiditis, or autoimmune hepatitis [3,4,7], which require simultaneous monitoring and often modification of overall management.

In recent years, there has been growing interest in adjunctive therapeutic approaches to complement the gluten-free diet. These include gluten-degrading enzymes (e.g., latiglutenase), zonulin inhibitors, and immunomodulatory vaccines (e.g., Nexvax2), aimed at inducing immunological tolerance to gluten [19]. Although none of these have yet been approved as standard therapy, phase III clinical trials are ongoing and offer hope for future treatment strategies, especially for patients with refractory disease [19].

An essential component of therapy is dietary education, which helps patients understand gluten elimination principles and learn to interpret food labels [3,4]. Studies show that clinical dietitian support improves dietary adherence, nutritional status, and overall quality of life [4,18]. Psychological support is also crucial, particularly given the long-term nature of the restrictive diet and associated social and emotional challenges [6].

For some patients, the gluten-free diet is associated with feelings of social exclusion, anxiety about accidental gluten ingestion, and reduced quality of life [6,15]. Therefore, a comprehensive treatment approach should address not only dietary but also psychological and social support.

In summary, the gluten-free diet remains the fundamental and most effective treatment for coeliac disease and prevention of systemic complications. Early treatment initiation and multidisciplinary care enable symptom reduction, improved nutritional status, and decreased risk of late complications, including malignancies.

COELIAC DISEASE AND QUALITY OF LIFE

Due to its chronic and systemic nature, coeliac disease significantly impacts patients' quality of life. Beyond classical gastrointestinal symptoms, numerous extraintestinal manifestations - including bone, neurological, and endocrine disorders - place additional physical and psychological burdens on affected individuals [3,4,6]. Chronic fatigue, joint and muscle pain, neuropathies, and secondary hormonal disturbances can impair daily functioning, limit occupational and social activities, and negatively influence overall well-being [4,6].

Adherence to a strict gluten-free diet, although fundamental to treatment and improving general health, presents numerous challenges. Patients must constantly monitor the ingredients of consumed products and avoid gluten contamination at home, restaurants, and during travel [3,6,18]. Fear of accidental gluten ingestion can lead to heightened vigilance and even anxiety-related behaviors, often referred to as "gluten anxiety" [6,15].

Social consequences of the gluten-free diet are also significant. Participation in social gatherings, dining out, or traveling often involves feelings of exclusion, embarrassment, or uncertainty. Many patients avoid such situations, which may result in social isolation and reduced interpersonal relationships [6,15].

A meta-analysis encompassing 18 studies found that despite improved quality of life following the initiation of a gluten-free diet, patients with coeliac disease still report lower levels of social

and emotional satisfaction compared to the general population [20]. To more accurately assess the quality of life in coeliac patients, specialized tools such as the Celiac Disease Quality of Life Questionnaire (CD-QoL) are increasingly utilized, addressing dietary, emotional, and social aspects [20].

Economic challenges also represent an additional burden due to the need to purchase specialized gluten-free products, which are often more expensive and less accessible than conventional alternatives [3,4].

The importance of dietary and psychological education in improving patients' quality of life is emphasized. Training led by qualified dietitians helps patients better understand the diet and cope with daily nutritional challenges [4,18]. Psychological support facilitates adaptation to living with a chronic illness, reduces anxiety, and supports motivation for dietary adherence [6]. Support groups, as well as family and workplace environments, play crucial roles in easing daily functioning and minimizing feelings of exclusion [6,15].

SUMMARY

Coeliac disease is an autoimmune disorder with a distinctly systemic nature, extending far beyond classic gastrointestinal symptoms. Advances in diagnostics and improved understanding of its pathogenesis have established that coeliac disease can manifest in virtually every organ system, leading to bone, neurological, dermatological, endocrine, and hepatic symptoms, as well as serious oncological complications [3,4,9].

Effective treatment and improved patient prognosis require an individualized and multidisciplinary approach. Collaboration among gastroenterologists, neurologists, endocrinologists, dermatologists, rheumatologists, and clinical dietitians facilitates not only accurate diagnosis but also monitoring of systemic manifestations and treatment efficacy [4,16].

Early serological and histopathological diagnosis, combined with HLA haplotype determination, enables prompt initiation of a gluten-free diet, which remains the gold standard of therapy. Adherence to the diet promotes mucosal healing, reduces extraintestinal symptoms, improves quality of life, and lowers the risk of complications, including malignancies [3,4,9,17].

An equally important element of comprehensive patient care is addressing the disease's impact on quality of life, encompassing psychological, social, and economic aspects, which necessitate appropriate psychological and dietary support [4,6,15,20]. Patient and family education plays a

key role in enhancing disease understanding, increasing motivation for dietary compliance, and minimizing the risk of inadvertent gluten exposure [4,6].

Despite significant progress, further research is needed on the autoimmune mechanisms underlying coeliac disease and the development of novel therapies that could complement or serve as alternatives to the gluten-free diet, particularly in refractory cases [19]. Equally important is a better understanding of factors influencing cancer risk and the development of effective strategies for monitoring high-risk patients [9,17].

In conclusion, coeliac disease should be regarded as a multisystem chronic condition requiring comprehensive, individualized treatment and ongoing specialist care. Continued advances in diagnostics, therapy, and multidisciplinary management offer hope for improved long-term outcomes and quality of life for patients worldwide.

Disclosure

Author's Contribution

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

Funding Statement: The study did not receive special funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Nor applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: The authors report no conflict of interests.

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