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Celiac Disease as an Underlying Cause of Multisystemic Symptoms: Consequences of Delayed Diagnosis - A Literature Review

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Abstract

Introduction and purpose

Celiac disease (CD) is an autoimmune disorder that develops in genetically predisposed individuals in response to gluten intake. The overall prevalence of CD is approximately 0.75% in the general population, making it a condition frequently encountered in everyday clinical practice. CD impacts multiple organ systems. This paper describes its influence on, among others, the skin and mucous membranes, hematological parameters, bone health, reproductive function, and neuropsychiatric status. This review aims to summarize current evidence on the extraintestinal manifestations of this condition and highlight the importance of early recognition of these diverse symptoms.

A brief description of the state of knowledge

A comprehensive literature review was conducted using PubMed and MDPI databases. The analysis included original articles, reviews, and meta-analyses related to extraintestinal symptoms of CD, with emphasis on publications from the last ten years. The findings suggest that such symptoms are common and frequently non-specific, which frequently contributes to

diagnostic delays. Many of them may occur before gastrointestinal symptoms or appear as isolated signs, leading to underdiagnosis and untreated disease.

Summary

Many extraintestinal symptoms of CD are still overlooked by clinicians. Improving healthcare professionals' awareness of these symptoms may lead to earlier diagnosis and earlier initiation of a gluten-free diet. Timely treatment can help avoid long-term complications and significantly improve patients' prognosis and quality of life.

Key words: celiac disease; gluten-free diet; extraintestinal manifestations.

Introduction

Celiac disease (CD) is an autoimmune disorder that develops in genetically predisposed individuals in response to gluten intake, leading to characteristic changes in blood markers and intestinal tissue. Gluten refers to a group of alcohol-soluble proteins found in grains such as wheat, rye, barley and spelt [1].

Pathophysiology

The pathophysiology of this condition is characterized by a well-defined triad: specific genetic susceptibility (HLA-DQ2 and HLA-DQ8), the environmental triggers and an autoimmune response against the self-antigen tissue transglutaminase (tTG). HLA-DQ2 homozygosity significantly increases the risk of early-onset CD in children with a first-degree affected relative. This condition has a strong hereditary component, evidenced by its ~10-15% familial recurrence and ~75-80% concordance rate among monozygotic twins. Despite this, only ~3% of genetically compatible individuals develop disease, suggesting the importance of non-HLA genes and environmental cofactors [1]. At the immune level, gluten-derived peptides presented by antigen-presenting cells activate CD4+ T helper cells, which drive a cascade of B and T cell responses and production of disease-specific antibodies, leading to enterocyte destruction and duodenal inflammation [2].

Environmental factors are increasingly recognized in disease pathogenesis. Viral infections - particularly rotavirus, reovirus, CMV, EBV, adenovirus, and enterovirus - may act as potential triggers in genetically susceptible individuals. [3,4]. Some studies suggest that rotavirus vaccination may reduce CD risk. Additionally, exposure to certain bacteria such as Pseudomonas may influence immune sensitivity to gluten by modulating inflammatory pathways or inducing cross-reactivity between microbial and gluten peptides [4].

Modern hygienic environments and reduced microbial exposure - in line with the hygiene hypothesis - have been proposed as contributing factors, potentially explaining the sharp rise in autoimmune diseases, including celiac disease, in industrialized societies over recent decades. Other key elements involved in disease development include loss of intestinal barrier integrity, pro-inflammatory innate immune activation, dysbiosis of the gut microbiota, and imbalance between Th1 and Th2 responses [1].

Epidemiology

The global prevalence of celiac disease is estimated at approximately 1.4% based on serological testing, while biopsy-confirmed diagnoses average around 0.7%, with variation depending on sex, age, and geographic region [5]. In the general population, the overall rate of CD is approximately 0.75%. However, this percentage rises to as much as 4.5% in high-risk groups, including first-degree relatives of CD patients, individuals with suggestive clinical features such as diarrhea, abdominal pain, or constipation, and those diagnosed with related disorders like type 1 diabetes, Down syndrome, anemia, infertility, or osteoporosis [6].

Among European countries, the highest prevalence has been reported in Finland (2%), Sweden (1.9%), and Italy (1.62%) [7]. In Poland, the estimated prevalence among children is around 0.25%; however, this likely underrepresents the true burden, as it includes only the pediatric population and large-scale, nationwide screening among adults has not yet been conducted [8].

Globally, a significant number of cases remain undiagnosed. This diagnostic gap is influenced by various factors, including the level of awareness among healthcare providers and the public, accessibility of diagnostic procedures, socioeconomic status, and individual perception of health, as well as demographic aspects such as age and sex [9].

A comprehensive population-based study conducted in Tromsø, Norway, involving 12,981 adults with histopathological confirmation, demonstrated a prevalence of 1.47% in the adult population, with approximately 75% of cases previously unrecognized. These findings highlight the need to maintain a low threshold for CD testing, even in patients without classic gastrointestinal symptoms, as many adults perceive their mild or nonspecific complaints as normal and therefore remain undiagnosed [10].

Diagnosis

The diagnosis of celiac disease is based on a combination of serological testing, histopathological examination of duodenal biopsies, and clinical assessment [11,12]. Currently, serological evaluation relies on highly sensitive and validated assays, including anti-endomysial

antibodies (EmA), anti-tissue transglutaminase antibodies (anti-tTG), and deamidated gliadin peptide antibodies (DGP) [13]. Among these, anti-tTG IgA is considered more sensitive than EmA IgA, although its specificity may be slightly lower. In adult patients, testing should include anti-tTG IgA along with total serum IgA to exclude selective IgA deficiency. When anti-tTG IgA levels are markedly elevated and total IgA is within the normal range, duodenal biopsy may be pursued without additional EmA testing [1].

The next diagnostic step involves endoscopic and histological evaluation. Upper gastrointestinal endoscopy with mucosal assessment of the small intestine can reveal typical abnormalities such as fissures, nodularity, mosaic pattern, atrophy of the duodenal bulb with visible submucosal vessels, and scalloping or reduction of Kerckring folds. However, up to one-third of newly diagnosed individuals may show a macroscopically normal duodenal appearance, underscoring the necessity of biopsy even in the absence of endoscopic lesions [14]. Histological analysis typically reveals characteristic features, including villous atrophy, crypt hyperplasia, reduced enterocyte height, and increased intraepithelial lymphocyte (IEL) infiltration, all of which reflect the underlying mucosal injury [6]. Still, discrepancies between serological and histological findings can arise, and limitations in biopsy sampling may lead to inconclusive outcomes [11].

Clinically, CD traditionally presents with gastrointestinal symptoms such as diarrhea and weight loss, reflecting intestinal immune-mediated injury [15]. However, a considerable number of patients exhibit extraintestinal symptoms affecting the nervous system, liver, skin, and musculoskeletal or reproductive systems. These manifestations are often associated with more severe disease but are not always proportional to the degree of intestinal mucosal damage [16].

Description of the state of knowledge

Cutaneous and mucosal changes

Celiac disease is frequently associated with a range of skin disorders, the most common being dermatitis herpetiformis (DH), which is considered a specific cutaneous manifestation of this autoimmune condition. Other dermatological conditions, such as psoriasis, urticaria, and atopic dermatitis, also show higher prevalence in patients, highlighting the importance of recognizing these skin symptoms in the clinical management of the disease [17].

DH, also known as Duhring disease, causes intense itching and burning due to clusters of papules and vesicles, primarily located on the extensor surfaces of the elbows, knees, and buttocks, with possible involvement of the upper back, abdomen, scalp, and face. DH occurs

more frequently in males than in females and is rare in children. The skin lesions typically clear completely with a strict gluten-free diet (GFD). While some patients may need dapsone for symptom control initially, long-term management is usually achieved with diet alone [17,18].

Another extraintestinal manifestation of the condition is recurrent aphthous stomatitis. Oral symptoms were more common in affected individuals than controls and linked to delayed diagnosis, abdominal complaints, female sex, and reduced quality of life. The GFD helped reduce these oral lesions [19].

In a meta-analysis by Patompong Ungprasert, it was reported that patients with psoriasis have an approximately threefold higher risk of developing this disorder. Psoriasis is characterized by well-defined, red, and infiltrated plaques covered with coarse, silvery scales, typically found on the elbows, knees, scalp, as well as the periumbilical and lumbar regions, though any anatomical site may be affected [20,21]. Another meta-analysis showed that IgA anti-gliadin antibodies (AGA) were positive in about 14% of psoriatic patients compared to 5% of matched controls. Furthermore, a positive correlation was observed between the presence of antibodies related to CD and the severity of psoriasis symptoms [22]. The association between this autoimmune disorder and other autoimmune diseases like type 1 diabetes and autoimmune thyroid disease is well established, likely due to shared genetic factors such as at-risk HLA haplotypes. These genetic links may also explain the connection between the described illness and psoriasis. In affected individuals, increased keratinocyte proliferation leads to higher levels of interleukins IL-1 and IL-18, which promote a Th1 immune response. Additionally, intestinal barrier dysfunction in untreated celiac disease might allow immune triggers to enter the body, increasing the risk of autoimmune diseases including psoriasis. Malabsorption related to the disease may also cause vitamin D deficiency, potentially worsening skin symptoms.

Other symptoms have also been reported, and it is important to recognize several types of dermatitis associated with CD including urticaria (about 50% increased risk), chronic urticaria (nearly double the risk), atopic dermatitis (over threefold higher odds), and rosacea (approximately 45% increased risk). Additionally, other skin conditions with less clear links to celiac disease may be observed [23].

Anemia

The development of anemia and iron deficiency in celiac disease may already be present in children with normal villous morphology, highlighting the need for early diagnosis and dietary treatment [24]. Iron deficiency is the most common cause of anemia associated with this condition and a frequent clinical feature even without anemia, affecting 12% to 69% of

untreated patients [25]. This deficiency leads to fatigue, reduced muscle oxygenation, decreased muscle strength, and impaired physical performance. Additionally, iron plays a crucial role in brain development from early life, contributing to neural myelination, learning, behavior, and the synthesis of neurotransmitters such as serotonin and dopamine [26].

At diagnosis, anemia related to CD mainly results from villous atrophy in the proximal small intestine, which impairs nutrient absorption-especially iron-and mucosal inflammation that triggers anemia of chronic disease (ACD). Treatment with oral iron supplementation can be challenging due to side effects like abdominal discomfort, constipation, and diarrhea, which may reduce compliance. Moreover, substances such as tea, coffee, calcium, and fiber can decrease intestinal iron absorption [27].

Apart from iron deficiency, anemia in the described disease may also arise from deficiencies in folate or vitamin B12, blood loss, or coexistence with other diseases such as inflammatory bowel disease (IBD). The similarity of symptoms between CD and IBD can delay diagnosis, so both conditions should be considered when managing anemia. Folate deficiency may present with symptoms such as glossitis and inflammation of the mouth corners. Vitamin B12 deficiency is also common and may cause peripheral myeloneuropathy [26,28].

Effective anemia management is essential to improve patients' health-related quality of life and to relieve chronic fatigue, which correlates with anemia severity [27].

Bone abnormalities

Celiac disease is increasingly recognized as a significant risk factor for impaired bone health. This untreated disorder is commonly associated with reduced bone mineral density (BMD) in both children and adults, often resulting in osteopenia, osteoporosis, and an elevated risk of fragility fractures in adults [29]. Meta-analyses of case-control and cross-sectional studies have shown that individuals with clinically diagnosed CD face nearly twice the risk of fractures compared to non-celiac individuals. Furthermore, prospective studies have demonstrated that the presence of this autoimmune condition increases the overall risk of any fracture by 30% and the risk of hip fracture by 69% [30]. Alterations in bone density have been reported in more than 60% of newly diagnosed adults. Osteoporosis in these patients was significantly associated with being aged ≥45 years, male sex, underweight status, and severe villous atrophy (Marsh 3C), suggesting that BMD screening at diagnosis may be particularly relevant in these subgroups [31]. In a pooled analysis involving 563 premenopausal women and men from five countries (UK, Brazil, India, Hungary, and Poland), the overall prevalence of osteoporosis among affected patients was 14.4%, while osteopenia was observed in 39.6% of cases [32].

These findings underscore the need for early skeletal assessment, especially in individuals with additional risk factors.

Given these risks, early diagnosis is critical. A strict GFD, once implemented, may prevent the onset of metabolic bone disease or potentially reverse existing damage [29]. Evidence supports the beneficial effects of GFD on bone health, particularly in younger populations. Most studies have shown significant improvement in BMD within the first year of dietary intervention, although recovery in adults often remains incomplete [15]. In young women with newly diagnosed disease, one year of strict GFD combined with calcium and vitamin D supplementation led to measurable improvements in both volumetric bone density and microarchitecture, as assessed by high-resolution peripheral quantitative computed tomography (HR-pQCT) [33]. However, in older patients and those diagnosed later in the disease course, full skeletal recovery may be limited despite good dietary adherence. For this reason, screening for celiac disease is advised in all patients with unexplained low BMD, recurrent fractures, or osteoporosis - even without gastrointestinal symptoms [29].

Bone health monitoring should be an integral part of management. Baseline evaluation of BMD using dual-energy X-ray absorptiometry (DEXA) is recommended for all adults, especially in those with signs of malabsorption, delayed diagnosis, or clinical features suggestive of bone disease. Early assessment is also warranted in specific high-risk groups, such as postmenopausal women, men over 50 years old, and individuals with a history of fragility fractures [14].

Reproductive system abnormalities in females and males

Celiac disease may also affect female reproductive health, but the association between the disorder and infertility remains unclear and debated. Some meta-analyses have identified a higher seroprevalence of gluten-sensitive enteropathy among women with infertility, with pooled estimates ranging from approximately 1.3% to 1.6%, corresponding to an estimated threefold increased odds of CD in infertile women compared to controls [34]. However, this relationship is not universally accepted. Other investigations have reported that the prevalence of the condition in infertile women does not exceed that of the general population, indicating that routine screening for CD in infertility cases may yield limited clinical benefit [35].

Awareness of the potential beneficial effects of a strict gluten-free diet on fertility in women with celiac disease is crucial, although current evidence remains inconclusive due to the limited number of studies involving female patients [34]. Such conflicting findings underscore the need for further research to clarify the role of CD in reproductive health.

Additionally, untreated CD has been linked to an increased risk of miscarriage, particularly in the years preceding diagnosis. Conversely, women with adequately treated disease appear to have miscarriage rates comparable to those without CD [8].Another obstetric concern is an increased risk of adverse pregnancy outcomes, including fetal growth restriction (FGR), stillbirth, preterm delivery (PTD), low birth weight (LBW), and small for gestational age (SGA) neonates [36,37,38]. Meta-analytic evidence demonstrates that women with CD exhibit a significantly higher incidence of these complications compared to control populations, irrespective of disease treatment status [37]. Early diagnosis and strict adherence to a GFD significantly reduce the risk of adverse obstetric outcomes compared to undiagnosed cases, which carry substantially higher risks of these complications [36,37].

Furthermore, pregnant women with celiac disease are predisposed to higher rates of hyperemesis gravidarum, Clostridium difficile colitis, venous thromboembolism, and prolonged hospitalizations exceeding three days [39]. These data underscore the imperative for timely identification and rigorous dietary management in pregnant patients to improve maternal and fetal prognoses and reduce the incidence of obstetric complications.

Neuropsychiatric involvement

Neurological manifestations are increasingly recognized in patients with celiac disease, with a higher prevalence of peripheral neuropathies, gluten ataxia, epilepsy, migraine/headaches, and cognitive impairments compared to the general population [29]. Although neurological symptoms are rare in pediatric patients, up to 36% of adults with the disorder present with neurological findings [40]. Systematic reviews indicate a substantially increased risk of gluten neuropathy and gluten ataxia in affected individuals, with reported prevalence of neuropathy reaching up to 39%, while ataxia is less common, ranging between 0% and 6%. Importantly, adherence to a strict GFD has been shown to improve symptoms of both neuropathy and ataxia, underscoring the clinical relevance of early diagnosis and dietary management. Due to the variability in reported prevalence, clinicians are advised to consider CD in the differential diagnosis of patients presenting with ataxia or unexplained neurological symptoms [41].

Epilepsy is approximately 1.8 times more common among individuals with this condition, and conversely, its prevalence is over twofold higher in patients with epilepsy compared to the general population. Certain epileptic syndromes like adult fixation off sensitivity (FOS) and temporal lobe epilepsy (TLE) with hippocampal sclerosis exhibit higher rates of gluten sensitivity. A notable clinical entity is celiac disease, epilepsy, and cerebral calcification (CEC) syndrome, frequently reported in the literature. Treatment with a GFD is effective in

approximately 53% of patients with gluten-related epilepsy, resulting in seizure reduction, dose reduction, or discontinuation of antiepileptic drugs. Therefore, patients with epilepsy of unknown etiology should be screened for serological markers of gluten sensitivity to identify those who may benefit from dietary intervention [42].

Also, psychiatric comorbidities are frequently observed in patients with untreated the disorder, with increased rates of depression, anxiety, eating disorders, as well as neurodevelopmental conditions such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), compared to the general population [15,43]. Although the precise biological mechanisms underlying these associations remain unclear, hypotheses include dysregulation of the gut-brain axis, white matter tract alterations, and chronic systemic inflammation [15]. Depression and anxiety are particularly prevalent in untreated patients and contribute significantly to impaired quality of life [44]. A systematic review demonstrated that individuals with CD have approximately a 2-fold higher risk of depression and up to a 6-fold increased risk of anxiety compared to healthy controls [43,45]. Adherence to a GFD may lead to improvement in anxiety symptoms; however, depressive symptoms often persist despite dietary treatment. This persistence has been partially attributed to psychosocial burdens associated with long-term GFD adherence, including social isolation, anxiety related to unintentional gluten contamination, and the stigmatization related to dietary restrictions [21,43]. Biological contributors, such as serotonin deficiency due to malabsorption of tryptophan, coexisting hypothyroidism, and dysregulation of the hypothalamic-pituitary-adrenal axis, have also been proposed [21]. Eating disorders (ED), particularly anorexia nervosa, occur with increased frequency in patients with the disease [42]. The bidirectional relationship between these diseases warrants careful diagnostic consideration, as misdiagnosis or underrecognition may result in delayed treatment and increased morbidity [46]. Importantly, current evidence does not support an increased risk of schizophrenia or bipolar disorder in patients with CD. Their prevalence among patients remains comparable to that observed in the general population, suggesting no clinically relevant association [43].

Other extraintestinal manifestation

Lastly, we describe disorders related to the cardiovascular system, kidneys, and liver. Numerous studies have demonstrated an increased atherogenic cardiovascular risk in patients with CD, particularly involving coronary and peripheral arteries. This elevated risk is frequently accompanied by a higher prevalence of traditional cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes mellitus. The underlying mechanism is thought to

involve chronic systemic inflammation driven by the injured intestinal mucosa, which promotes endothelial dysfunction and vascular damage [47].

In addition to cardiovascular involvement, such patients exhibit a significantly increased risk of various renal pathologies, including glomerulonephritis and progression to end-stage renal disease, underscoring the impact of systemic autoimmunity and chronic inflammation on renal function [48].

Liver abnormalities are also common in affected individuals, with hypertransaminasemia reported in approximately 21% of adult patients. The predominant cause is celiac hepatitis, a mild inflammatory liver condition related to gluten exposure. Importantly, strict adherence to a gluten-free diet results in normalization of liver enzymes in over 85% of cases, highlighting the therapeutic role of dietary management in hepatic manifestations of CD [49].

Treatment of celiac disease

The cornerstone of the management of celiac disease is lifelong adherence to a gluten-free diet [11]. A well-balanced GFD requires careful nutritional monitoring, including adequate intake of iodine, iron, calcium, and vitamin D, ideally under dietitian supervision [2]. While adherence to the diet effectively restores the villous-to-crypt ratio and reduces intestinal inflammation, residual mucosal immune abnormalities-such as increased populations of CD3+ and TCRγδ+ lymphocytes-may persist irrespective of diet duration [50]. Due to the significant burden of strict gluten avoidance and its impact on quality of life, approximately 40% of patients report dissatisfaction with their restrictive diet [51]. Recent research has focused on developing non-dietary treatments, with a few reaching advanced clinical trial stages [52]. Larazotide acetate, a zonulin antagonist, aims to reduce intestinal permeability. It has shown promise in controlling gluten-related symptoms but does not fully restore epithelial barrier integrity. This treatment may help patients tolerate small, accidental gluten exposures or short “gluten-free holidays” [53]. Another approach involves gluten-specific proteases (e.g., ALV003/latiglutenase), which break down gluten fragments in the stomach. While effective against minor gluten contamination, recent trials showed no significant benefit in symptom or histologic improvement in patients with moderate to severe celiac disease symptoms [1]. Other investigational therapies include IL-15 monoclonal antibodies (AMG 714), currently in phase 2 trials, and vaccines such as Nexvax2, which aim to induce immune tolerance to gliadin peptides. Although early trials showed some adverse effects (abdominal pain and vomiting), vaccines may potentially offer a definitive cure if proven effective [54,55].

Summary

As presented above, celiac disease may manifest through a wide range of extraintestinal symptoms that are often seemingly unrelated. It is making accurate diagnosis challenging especially when only a single symptom is present without accompanying gastrointestinal signs.This paper confirms the association between celiac disease and an increased risk of long-term complications, many of which could likely be avoided through early diagnosis and prompt initiation of a gluten-free diet. There is also substantial evidence presented in the article indicating that the implementation of a strict GFD, in most cases, prevents the progression of associated conditions or may even lead to their complete resolution.Since widespread serological screening is not currently recommended, emphasis should be placed on raising the awareness of healthcare professionals about the broad spectrum of celiac disease manifestations. For pediatricians, this involves recognizing early signs that may appear in childhood and lead to lasting consequences if left untreated. On the other hand, many extraintestinal symptoms emerge later in life, underscoring the need for adult care providers to also be equally well-informed. Primary care plays a pivotal role in early detection, as effective first-line recognition of atypical or subtle symptoms. Raising the level of knowledge and clinical vigilance in this setting is essential to improve case identification and reduce the burden of undiagnosed celiac disease at the population level. Future research should aim to better define the prevalence, onset, response to dietary treatment, and long-term prognosis of extraintestinal manifestations. Furthermore, the mechanisms behind the disease's broad clinical variability remain poorly understood. Advancing our understanding in these areas could not only enhance diagnostic accuracy but also shed light on the broader pathogenesis of autoimmune diseases.

Disclosure

Author's contribution

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References

1. Caio G, Volta U, Sapone A. Celiac disease: a comprehensive current review. BCM Med. 2019 Jul 23;17:142. doi: 10.1186/s12916-019-1380-z.
2. Aitella E, Cozzolino D, Ginaldi L, Romano C. Celiac Disease: A Transitional Point of View. Nutrients. 2025 Jan 10;17(2):234. doi: 10.3390/nu17020234.
3. Welch NL, Welch T, Songtanin B. Viral Triggered Celiac Disease: A Case Report. Cureus. 2023 Jun 14;15(6):e40429. doi: 10.7759/cureus.40429.
4. Iversen R, Sollid ML. The Immunobiology and Pathogenesis of Celiac Disease. Annu Rev Pathol. 2023 Jan 24:18:47-70. doi: 10.1146/annurev-pathmechdis-031521-032634.
5. Singh P, Arora A, Strand TA et al. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018 Jun;16(6):823-836.e2. doi: 10.1016/j.cgh.2017.06.037.
6. Parzanese I, Qehajaj D, Patrinicola F. et al. Celiac disease: From pathophysiology to treatment. World J Gastrointest Pathophysiol. 2017 May 15;8(2):27-38. doi: 10.4291/wjgp.v8.i2.27.
7. Gatti S, Rubio-Tapia A, Makharia G. et al. Patient and Community Health Global Burden in a World With More Celiac Disease. Gastroenterology. 2024 Jun;167(1):23-33. doi: 10.1053/j.gastro.2024.01.035.
8. Bai JC, Fried M, Corazza GR et al. World Gastroenterology Organisation global guidelines on celiac disease. J Clin Gastroenterol. 2013 Feb;47(2):121-6. doi: 10.1097/MCG.0b013e31827a6f83.

9. Mendia I, Segura V, Ruiz-Carnicer Á et al. Rapid Anti-tTG-IgA Screening Test for Early Diagnosis of Celiac Disease in Pediatric Populations. Nutrients. 2023 Nov 26;15(23):4926. doi: 10.3390/nu15234926.
10. Kvamme JM, Sørbye S, Florholmen J et al. Population-based screening for celiac disease reveals that the majority of patients are undiagnosed and improve on a gluten-free diet. Sci Rep. 2022 Jul 25;12(1):12647. doi: 10.1038/s41598-022-16705-2.
11. Baldi S, Ruiz-Carnicer Á, Comino I et al. Editorial: Gluten-related disorders: pathogenesis, diagnosis, and treatment. Front Nutr. 2025 Mar 13:12:1585381. doi: 10.3389/fnut.2025.1585381.
12. Ivanova M, Bottiglieri L, Sajjadi E et al. Malignancies in Patients with Celiac Disease: Diagnostic Challenges and Molecular Advances. Genes (Basel). 2023 Jan 31;14(2):376. doi: 10.3390/genes14020376.
13. Volta U, Fabbri A, Parisi C et al. Old and new serological tests for celiac disease screening. Expert Rev Gastroenterol Hepatol. 2010 Feb;4(1):31-5. doi: 10.1586/egh.09.66.
14. Al-Toma A, Volta U, Auricchio R et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. United European Gastroenterol J. 2019 Apr 13;7(5):583-613. doi: 10.1177/2050640619844125.
15. Laurikka P, Kivelä L, Kurppa K et al. Review article: Systemic consequences of coeliac disease. Aliment Pharmacol Ther. 2022 Jul;56 Suppl 1(Suppl 1):S64-S72. doi: 10.1111/apt.16912.
16. Laurikka P, Nurminen S, Kivelä L et al. Extraintestinal Manifestations of Celiac Disease: Early Detection for Better Long-Term Outcomes. Nutrients. 2018 Aug 3;10(8):1015. doi: 10.3390/nu10081015.
17. Nardecchia S, Auricchio R, Discepolo V et al. Extra-Intestinal Manifestations of Coeliac Disease in Children: Clinical Features and Mechanisms. Front Pediatr. 2019 Mar 5:7:56. doi: 10.3389/fped.2019.00056.
18. Salmi T, Hervonen K, Reunala T. Dermatitis herpetiformis - a cutaneous manifestation of coeliac disease. Chapter 8. Coeliac Disease and Gluten-Related Disorders 2022, pp. 161-177.
19. Manninen J, Paavola S, Kurppa K et al. Prevalence of oral manifestations in coeliac disease and associated factors. BMC Gastroenterol. 2025 Mar 3;25(1):126. doi: 10.1186/s12876-025-03699-0.

20. Ungprasert P, Wijarnpreecha K, Kittanamongkolchai W. Psoriasis and Risk of Celiac Disease: A Systematic Review and Meta-analysis. Indian J Dermatol. 2017 Jan-Feb;62(1):41-46. doi: 10.4103/0019-5154.198031.
21. Durazzo M, Ferro A, Brascugli I et al. Extra-Intestinal Manifestations of Celiac Disease: What Should We Know in 2022?. J Clin Med. 2022 Jan 4;11(1):258. doi: 10.3390/jcm11010258.
22. Abenavoli L, Dastoli S, Bennardo L et al. The Skin in Celiac Disease Patients: The Other Side of the Coin. Medicina (Kaunas). 2019 Sep 9;55(9):578. doi: 10.3390/medicina55090578.
23. Rodrigo L, Beteta-Gorriti V, Alvarez N et al. Cutaneous and Mucosal Manifestations Associated with Celiac Disease. Nutrients. 2018 Jun 21;10(7):800. doi: 10.3390/nu10070800.
24. Repo M, Lindfors K, Mäki M et al. Anemia and Iron Deficiency in Children With Potential Celiac Disease. J Pediatr Gastroenterol Nutr. 2017 Jan;64(1):56-62. doi: 10.1097/MPG.0000000000001234.
25. Bianchi IP, Aronico N, Santacroce G et al. Nutritional Consequences of Celiac Disease and Gluten-Free Diet. Gastroenterol. Insights 2024, 15(4), 878-894; https://doi.org/10.3390/gastroent15040061.
26. Martín-Masot R, Nestares MT, Diaz-Castro J et al. Multifactorial Etiology of Anemia in Celiac Disease and Effect of Gluten-Free Diet: A Comprehensive Review. Nutrients. 2019 Oct 23;11(11):2557. doi: 10.3390/nu11112557.
27. Stefanelli G, Viscido A, Longo S et al. Persistent Iron Deficiency Anemia in Patients with Celiac Disease Despite a Gluten-Free Diet. Nutrients. 2020 Jul 22;12(8):2176. doi: 10.3390/nu12082176.
28. Khan KM, Jialal I. Folic Acid Deficiency. 2023 Jun 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-.
29. Santonicola A, Wieser H, Gizzi C et al. Associations between Celiac Disease, Extra-Gastrointestinal Manifestations, and Gluten-Free Diet: A Narrative Overview. Nutrients. 2024 Jun 9;16(12):1814. doi: 10.3390/nu16121814.
30. Heikkilä K, Pearce J, Mäki M et al. Celiac disease and bone fractures: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2015 Jan;100(1):25-34. doi: 10.1210/jc.2014-1858.

31. Galli G, Lahner E, Conti L et al. Risk factors associated with osteoporosis in a cohort of prospectively diagnosed adult coeliac patients. United European Gastroenterol J. 2018 Oct;6(8):1161-1168. doi: 10.1177/2050640618784340.
32. Ganji R, Moghbeli M, Sadeghi R et al. Prevalence of osteoporosis and osteopenia in men and premenopausal women with celiac disease: a systematic review. Nutr J. 2019 Feb 7;18(1):9. doi: 10.1186/s12937-019-0434-6.
33. Zanchetta MB, Longobardi V, Costa F et al. Impaired Bone Microarchitecture Improves After One Year On Gluten-Free Diet: A Prospective Longitudinal HRpQCT Study in Women With Celiac Disease. J Bone Miner Res. 2017 Jan;32(1):135-142. doi: 10.1002/jbmr.2922.
34. Castaño M, Gómez-Gordo R, Cuevas D et al. Systematic Review and Meta-Analysis of Prevalence of Coeliac Disease in Women with Infertility. Nutrients. 2019 Aug 20;11(8):1950. doi: 10.3390/nu11081950.
35. Glimberg I, Haggård L, Lebwohl B et al. The prevalence of celiac disease in women with infertility-A systematic review with meta-analysis. Reprod Med Biol. 2021 Mar 22;20(2):224-233. doi: 10.1002/rmb2.12374.
36. Arvanitakis K, Siargkas A, Germanidis G et al. Adverse pregnancy outcomes in women with celiac disease: a systematic review and meta-analysis. Ann Gastroenterol. 2023 Jan-Feb;36(1):12-24. doi: 10.20524/aog.2022.0764.
37. Saccone G, Berghella V, Sarno L et al. Celiac disease and obstetric complications: a systematic review and metaanalysis. Am J Obstet Gynecol. 2016 Feb;214(2):225-234. doi: 10.1016/j.ajog.2015.09.080.
38. Alsabbagh Alchirazi K, Jansson-Knodell C, Abu-Omar Y et al. Maternal, obstetrical, and neonatal outcomes in celiac disease. Scand J Gastroenterol. 2024 May;59(5):547-552. doi: 10.1080/00365521.2024.2311849.
39. Elliott B, Czuzoj-Shulman N, Spence AR et al. Effect of celiac disease on maternal and neonatal outcomes of pregnancy. J Matern Fetal Neonatal Med. 2021 Jul;34(13):2117-2123. doi: 10.1080/14767058.2019.1658733.
40. Trovato CM, Raucci U, Valitutti F et al. Neuropsychiatric manifestations in celiac disease. Epilepsy Behav. 2019 Oct;99:106393. doi: 10.1016/j.yebeh.2019.06.036.
41. Mearns ES, Taylor A, Thomas Craig KJ et al. Neurological Manifestations of Neuropathy and Ataxia in Celiac Disease: A Systematic Review. Nutrients. 2019 Feb 12;11(2):380. doi: 10.3390/nu11020380.

42. Julian T, Hadjivassiliou M, Zis P. Gluten sensitivity and epilepsy: a systematic review. J Neurol. 2019 Jul;266(7):1557-1565. doi: 10.1007/s00415-018-9025-2.
43. Clappison E, Hadjivassiliou M, Zis P. Psychiatric Manifestations of Coeliac Disease, a Systematic Review and Meta-Analysis. Nutrients. 2020 Jan 4;12(1):142. doi: 10.3390/nu12010142.
44. Zingone F, Swift GL, Card TR, et al. Psychological morbidity of celiac disease: A review of the literature. United European Gastroenterol J. 2015 Apr;3(2):136-45. doi: 10.1177/2050640614560786.
45. Sharma N, Singh K, Senapati S. Celiac disease poses significant risk in developing depression, anxiety, headache, epilepsy, panic disorder, dysthymia: A meta-analysis. Indian J Gastroenterol. 2021 Oct;40(5):453-462. doi: 10.1007/s12664-021-01215-2.
46. Mårild K, Størdal K, Bulik CM et al. Celiac Disease and Anorexia Nervosa: A Nationwide Study. Pediatrics. 2017 May;139(5):e20164367. doi: 10.1542/peds.2016-4367.
47. Dore MP, Mereu S, Saba PS et al. Celiac Disease and Cardiovascular Risk: A Retrospective Case-Control Study. J Clin Med. 2023 Mar 7;12(6):2087. doi: 10.3390/jcm12062087.
48. Rathore SS, Shaikh SP, Zaidi HR et al. Association between celiac disease and risk of kidney diseases: a systematic review and meta-analysis. Minerva Gastroenterol (Torino). 2025 May 21. doi: 10.23736/S2724-5985.25.03733-7.
49. Jena A, Kumar-M P, Kumar A et al. Liver abnormalities in celiac disease and response to gluten free diet: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2023 Jan;38(1):11-22. doi: 10.1111/jgh.16039.
50. Mandile R, Maglio M, Mosca C et al. Mucosal Healing in Celiac Disease: Villous Architecture and Immunohistochemical Features in Children on a Long-Term Gluten Free Diet. Nutrients. 2022 Sep 7;14(18):3696. doi: 10.3390/nu14183696.
51. Aziz I, Evans KE, Papageorgiou V, Sanders DS. Are patients with coeliac disease seeking alternative therapies to a gluten-free diet? J Gastrointestin Liver Dis. 2011 Mar;20(1):27-31.
52. McCarville JL, Caminero A, Verdu EF. Pharmacological approaches in celiac disease. Curr Opin Pharmacol. 2015 Dec;25:7-12. doi: 10.1016/j.coph.2015.09.002.
53. Leffler DA, Kelly CP, Green PH et al. Larazotide acetate for persistent symptoms of celiac disease despite a gluten-free diet: a randomized controlled trial. Gastroenterology. 2015 Jun;148(7):1311-9.e6. doi: 10.1053/j.gastro.2015.02.008.

54. Murray JA, Kelly CP, Green PHR et al. No Difference Between Latiglutenase and Placebo in Reducing Villous Atrophy or Improving Symptoms in Patients With Symptomatic Celiac Disease. Gastroenterology. 2017 Mar;152(4):787-798.e2. doi: 10.1053/j.gastro.2016.11.004.
55. Anderson RP, Jabri B. Vaccine against autoimmune disease: antigen-specific immunotherapy. Curr Opin Immunol. 2013 Jun;25(3):410-7. doi: 10.1016/j.coi.2013.02.004.