Original Research

Extra-digestive manifestations of celiac disease

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Abstract

Introduction. Celiac disease (CD) is a chronic autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals, presenting with a diverse range of symptoms that extend beyond the gastrointestinal tract. The condition's systemic nature is evidenced by its extra-digestive manifestations, which can affect various organs including the skin, joints, liver, and nervous system.

Methods. This descriptive, retrospective study was conducted at a tertiary care center, focusing on adult patients diagnosed with CD who exhibited extra-digestive symptoms. Data were extracted from medical records of patients admitted between January 1, 2010 and June 30, 2024. Variables included demographic information, primary diagnosis, and associated extra-digestive manifestations. Descriptive statistical methods were employed for data analysis.

Results. The sample included 108 patients with CD, the mean age was 43.21 years, with a predominance of females (76.85%). Iron deficiency anemia was the most common extra-digestive manifestation, affecting 20.37% of patients, followed by hypoproteinemia (18.52%) and Hashimoto's thyroiditis (14.81%). Co-occurrence analysis revealed frequent combinations of conditions, such as anemia with cardiovascular diseases and depressive disorders. Notable associations with neurological conditions like gluten ataxia and peripheral neuropathy were also observed.

Conclusion. This study highlights the extensive extra-digestive manifestations of celiac disease, underscoring its systemic impact. The high prevalence of autoimmune conditions such as Hashimoto's thyroiditis and rheumatoid polyarthritis among CD patients reflects the need for holistic management strategies. Discrepancies between our findings and existing literature, particularly regarding skin and neurological conditions, emphasize the need for further research to better understand these associations and the long-term effects of a gluten-free diet.

Keywords: celiac disease, extra-digestive manifestations, autoimmune conditions, neurological symptoms, gluten-free diet

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Introduction

Celiac disease (CD) is a chronic immune disorder triggered by gluten in genetically predisposed individuals [1]. The clinical presentation of CD is highly variable and includes symptoms that can impact nearly every system in the body [2].

CD has numerous extradigestive manifestations, therefore it can be considered a systemic disease and not only a disease limited to the gastrointestinal tract. These symptoms can affect multiple organs, including the skin, joints, liver, and nervous system. Common extradigestive symptoms include dermatitis herpetiformis, arthritis, which can lead to joint pain and swelling; and liver disorders such as primary biliary cirrhosis. Additionally, individuals with CD may experience neurological symptoms like headaches, peripheral neuropathy, ataxia [3] and brain fog.

Recent genetic studies have revealed that CD and other autoimmune

diseases (AD) share common genetic loci, despite their phenotypic differences [4]. The frequent co-occurrence of immune-mediated disorders in celiac disease (CD) patients and their relatives may be due to genetic overlap and environmental factors. There is notable overlap in HLA haplotypes between CD and other autoimmune diseases (ADs). Additionally, about 64% of the CD-associated non-HLA loci are shared with other ADs, many of which are linked to inflammation and immune response genes [5].

Thyroid diseases, such as Grave's disease and Hashimoto's thyroiditis, are more common in patients with CD, with a prevalence of 2% to 7% [6]. In CD patients, up to 26% show serological signs of autoimmune thyroid disease, 10% have thyroid dysfunction, and the risk of thyroid disease is three times higher compared to controls [7].

The first study linking biopsy-confirmed CD to neurological deficits was published by Cooke and Smith in 1966 [8]. Since then, numerous neurological symptoms have been linked to CD, affecting 10 to 12% of patients. The most common conditions are gluten ataxia (GA) and peripheral neuropathy, which can occur even in the absence of gastrointestinal symptoms [9].

Peripheral neuropathy associated with CD is characterized by symmetrical sensorimotor axonal neuropathy and distal sensory loss [10]. Studies suggest that gluten sensitivity could be the cause in 34% of idiopathic neuropathy cases. In these cases, at least 9% of patients have biopsy-confirmed CD, and 80% exhibit HLA types linked to CD. This indicates a significant connection between gluten sensitivity and neuropathy, highlighting the importance of considering CD in patients with unexplained neuropathic symptoms [11].

Demyelinating disease, is another neurological disorder associated with CD. A study in Spain estimated that 11% of multiple sclerosis patients also had CD, although this finding has not been consistently confirmed by other research. While a gluten-free diet (GFD) is recommended for managing both conditions, the long-term effects of the diet on neurological symptoms are still unclear [12].

Sjogren's syndrome (SS) is an autoimmune disorder characterized by lymphocytic infiltration and dysfunction of exocrine glands, leading to dry mucosal surfaces (sicca symptoms) [13]. Research indicates a notable correlation between SS and celiac disease (CD), with CD being confirmed by small bowel pathology. The prevalence of CD among SS patients is reported to be between 4.5% and 15% [14].

The link between celiac disease (CD) and dilated cardiomyopathy may stem from nutritional deficiencies, such as iron and carnitine, as well as shared inflammatory and autoimmune mechanisms. Increased intestinal permeability in CD allows systemic absorption of antigens and infectious agents, which can cause myocardial damage through immune-mediated pathways. Additionally, immune cross-reactivity against antigens in both the small intestine and myocardium may contribute to myocardial injury [15]. A potential link between CD and pericarditis has been noted, primarily in a few case reports showing a good response to a gluten-free diet (GFD). However, this association has not been conclusively demonstrated at present [16].

Patients with celiac disease have been documented with thromboembolic events such as thromboembolism, atrial fibrillation, cardiovascular disease, small bowel infarction, pregnancy loss, Budd-Chiari syndrome, and portal and splenic vein thrombosis. Contributing factors include hyperhomocysteinemia, MTHFR gene variants, and the structural similarity between factor XIII and tissue transglutaminase (tTG). Additionally, deficiencies in protein C and S due to vitamin K malabsorption, along with elevated thrombin-activatable fibrinolysis inhibitor levels, further contribute to these conditions [3].

Several psychiatric disorders, including excessive anxiety, depression, apathy, bipolar disorder, irritability and sleep complaints, have been associated with CD [17,18]. The underlying mechanisms of neurological involvement in celiac disease (CD) are debated, with theories suggesting gluten-mediated pathogenesis such as antibody cross-reaction or direct neurotoxicity. Severe deficiencies in essential nutrients like B vitamins, vitamin D, and iron may also contribute to neurological and psychiatric symptoms. Understanding these complex interactions is essential for developing effective therapeutic strategies and improving patient management [19].

Linking celiac disease (CD) to mental health issues is complex, as persistent symptoms can worsen mood. Untreated CD is associated with higher rates of depression, anxiety, and eating disorders. Although mechanisms like gut-brain axis disruptions are suggested, the impact of a gluten-free diet (GFD) on mental health is unclear due to limited long-term studies. Persistent psychiatric symptoms and the social challenges of a GFD highlight the need for mental health support and consultations [20].

The findings from this study aim to provide insights into the extra-digestive manifestations of celiac disease in adult patients, potentially aiding in better management and treatment strategies for these patients.

Methods

Study design and setting

This descriptive, retrospective study was conducted at a single tertiary care center. The focus was on collecting and analyzing data related to adult patients diagnosed with celiac disease who presented with various extra-digestive manifestations.

Data collection

Data were obtained from the medical records of patients admitted in a tertiary center. The inclusion criteria were as follows: Adult patients (age 18 and above); Diagnosed with celiac disease; Records available within the study period (January 1, 2010 to June 30, 2024). Patients were included if they had a documented diagnosis of celiac disease (CD) based on serological and/or histopathological findings. Exclusion criteria: none unless subjects had CD.

Variables and measures

The collected data included the following variables: Demographic Information (Age; Gender) Primary Diagnosis (Main diagnosis recorded at the time of presentation) Extra-Digestive Manifestations **(**Various conditions and symptoms associated with celiac disease).

Data analysis

The collected data were entered into a structured database and analyzed using descriptive statistical methods. The analysis focused on: Demographic Analysis **(**Age distribution, including mean, median, standard deviation, and range, Gender distribution), Prevalence of Conditions **(**Proportion of patients presenting with each extra-digestive manifestation), Co-occurrence of Conditions: Analysis of the frequency with which different conditions appeared together in the same patients

Ethical considerations

The study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Given the retrospective nature of the study, patient consent was not required; however, patient confidentiality was maintained throughout the data collection and analysis process.

Results

Demographic analysis

A total of 108 adult patients diagnosed with celiac disease were included in the study, with their data collected from January 1, 2010 to June 30, 2024. The mean age of the patients was 43.21 years (SD = 13.92), with ages ranging from 18 to 77 years. The age distribution indicated that a quarter of the patients were 32 years or younger, and half were 42 years or younger, while the upper quartile included patients aged up to 53 years. The median age was 42 years, indicating a relatively young cohort. The gender distribution revealed a predominance of female patients, with 83 females (76.85%) and 25 males (23.15%).

Prevalence of extra-digestive manifestations

The analysis revealed that iron deficiency anemia was the most common extra-digestive manifestation among the patients, affecting 22 individuals. Other frequently observed conditions included hypoproteinemia (20 patients) and Hashimoto's thyroiditis (16 patients). Notably, cardiovascular diseases and lupus were also prevalent, observed in 13 and 12 patients, respectively. Conditions such as anemia with folic acid/B12 deficiency, depressive disorder, anxiety disorder, and rheumatoid polyarthritis were present in a smaller, yet significant number of patients. Less common manifestations included asthma, type 2 diabetes, epilepsy, dermatomyositis, type 1 diabetes, fibromyalgia, uterine fibroids, and erythema nodosum (Table I).

Co-occurrence of conditions

The co-occurrence analysis indicated that certain conditions frequently appeared together in the same patients. For example, anemia with folic acid/B12 deficiency co-occurred with cardiovascular diseases, depressive disorder, and Hashimoto's thyroiditis in 3 patients each. Rheumatoid polyarthritis was found to co-occur with Hashimoto's thyroiditis in 3 patients (Figure 1).

Table I. Prevalence of extra-digestive manifestations in adult patients with celiac disease.

Condition	Prevalence	Condition	Prevalence
Iron deficiency anemia	22 (20.37%)	Psoriasis	8 (7.41%)
Hypoproteinemia	20 (18.52%)	Type 2 diabetes	5 (4.63%)
Hashimoto's thyroiditis	16 (14.81%)	Asthma	5 (4.63%)
Cardiovascular diseases	13 (12.04%)	Dermatomyositis	3 (2.78%)
Lupus	12 (11.11%)	Epilepsy	3 (2.78%)
B12/folic acid deficiency anemia	10 (9.26%)	Type 1 diabetes	2 (1.85%)
Depressive disorder	10 (9.26%)	Fibromyalgia	2 (1.85%)
Anxiety disorder	9 (8.33%)	Uterine fibroids	1 (0.93%)
Rheumatoid polyarthritis	9 (8.33%)	Erythema nodosum	1 (0.93%)
Sjogren's syndrome	8 (7.41%)		

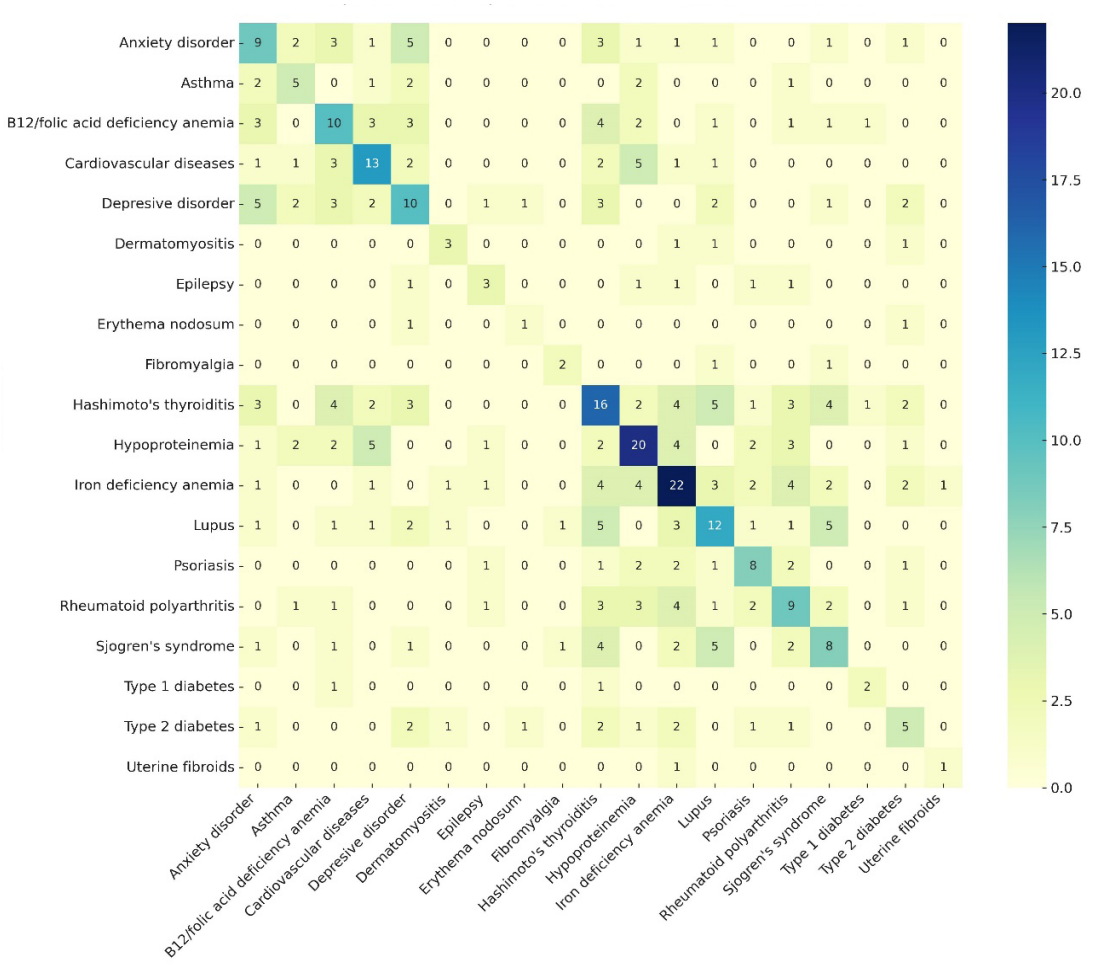

Figure 1. Co-occurrence of extra-digestive manifestations.

Discussion

The onset and manifestation of diseases associated with celiac disease (CD) are complex and multifactorial, involving shared genetic predispositions and similar pathogenic mechanisms with conditions such as type 1 diabetes mellitus (T1D). Our study reveals a notable prevalence of autoimmune conditions like Hashimoto's thyroiditis and rheumatoid polyarthritis among CD patients, suggesting a pattern of multiple autoimmune disorders occurring concurrently. This observation aligns with the broader understanding of CD's complexity, which involves both established and less-understood genetic and immunological factors [3].

Comparing our findings with existing literature, such as studies by Lebwohl et al., which highlight a higher risk of acne and eczema in CD patients, we observe a different prevalence in our results. Our study identifies psoriasis as the most frequent skin condition among CD patients, with less emphasis on acne and eczema. This discrepancy may arise from differences in study populations, methodologies, or diagnostic criteria, indicating that while both sources recognize a connection between CD and skin conditions, specific conditions and their prevalence can vary [21,22].

The link between CD and neurological conditions, including transient cognitive impairments, is less explored, with proposed mechanisms involving nutritional deficiencies, elevated inflammatory cytokines, and low brain serotonin [23]. A recent study of 1143 CD patients on a gluten-free diet (GFD) reported that 89% experienced neurocognitive symptoms such as grogginess and difficulty concentrating [24]. Although our study acknowledges the neurological impacts of CD, it does not specifically address the prevalence of these symptoms or the effectiveness of a GFD in managing them. This highlights a gap between our findings and broader research

on neurological manifestations in CD [2].

Research also connects CD with cardiovascular issues such as cardiomyopathy, thrombosis, and ischemic heart disease, noting improvements with a GFD, though some effects may be irreversible. Fousekis et al. documented increased cardiovascular risks in CD patients, but our study primarily highlights valvular insufficiency, lacking detailed data on other cardiovascular conditions or the impact of a GFD. This suggests the need for further investigation into the cardiovascular implications of CD [25].

Similarly, psychiatric disorders like depression and anxiety are more prevalent in CD patients, attributed to immune responses and nutritional deficiencies. Our study confirms the higher incidence of these disorders but lacks comprehensive data on other psychiatric conditions and the psychological impact of a GFD, indicating areas for further research [2].

Overall, while our data support many associations identified in the literature, particularly regarding autoimmune and psychiatric conditions, there are variations in prevalence and focus. This underscores the need for further research to fully understand the complex relationships between CD and its associated conditions. The variety of systemic symptoms emphasizes the importance of a comprehensive approach to diagnosis and management, aiming to address all potential complications and improve the overall health and quality of life for those affected by celiac disease.

Strengths and limitations

This study's strengths include its extensive data collection from a tertiary care center, which provides valuable insights into the prevalence of various extra-digestive manifestations of celiac disease (CD). The detailed prevalence data, particularly regarding autoimmune conditions such as Hashimoto's thyroiditis and rheumatoid polyarthritis, enhance our understanding of the systemic nature of CD. However, the study's retrospective design introduces potential biases and limits causative interpretations. Additionally, the single-center approach may affect the generalizability of the findings, and the absence of long-term follow-up data restricts insights into the progression of conditions and the sustained impact of a gluten-free diet (GFD). Furthermore, while the study identifies cardiovascular and neurological conditions associated with CD, it lacks specific prevalence data and details on the efficacy of GFD in managing these conditions.

Conclusions

This study underscores the complex and systemic nature of celiac disease (CD), highlighting its significant extra-digestive manifestations. The high prevalence of autoimmune conditions such as Hashimoto's thyroiditis and rheumatoid polyarthritis among CD patients illustrates the broad spectrum of CD's impact beyond the gastrointestinal tract. The findings emphasize the need for comprehensive management strategies that address both gastrointestinal and extra-digestive symptoms to improve patient outcomes and quality of life.

The study also reveals discrepancies between our results and existing literature, particularly concerning skin conditions and the prevalence of neurological and cardiovascular issues. This variation highlights the importance of continued research to refine our understanding of these associations and to explore the long-term effects of a gluten-free diet on CD-related conditions.

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