Caspian Journal of Internal Medicine 2025 (Autumn); 16(4): 797-800
DOI: 10.22088/cjim.16.4.797

Short communication

Association of celiac disease with type 1 diabetes: A cross-sectional analysis in 2022

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Received: 3 Oct 2024
Revised: 15 Dec 2024
Accepted: 25 Dec 2024
Published: 19 Oct 2025

Abstract

Background: Type 1 diabetes mellitus (T1DM) and celiac disease (CD) are autoimmune disorders with a common genetic basis. Celiac disease often presents asymptomatically, leading to delayed diagnosis and potential complications like anemia and growth delays. This research investigates the prevalence of celiac disease in T1DM patients at the Yazd Diabetes Center in 2022.

Methods: This cross-sectional study, uniquely designed and executed, involved 318 T1DM patients sampled via census. Levels of IgA anti-tissue transglutaminase (TTG) antibodies and serum IgA were measured, with individuals having TTG-IgA levels over 10 U/mL undergoing endoscopy and duodenal biopsy. The data were meticulously analyzed using SPSS V.22, with significance at a p-value < 0.05.

Results: Among the 318 patients, 25 (7.86%), comprising 15 (60%) females and 10(40%) males, underwent endoscopy and biopsy due to elevated TTG-IgA levels. Histopathological analysis revealed four (16%) patients with normal findings: 2 (8%) with Marsh type 1, 1 (4%) with Marsh type 2, and 18 (72%) with Marsh type 3. Patients with TTG levels exceeding 100 were all classified as Marsh type 3. Gender-wise, there was no significant difference in celiac disease type distribution. (P- value= 0.58)

Conclusion: This study's findings, which reveal a celiac disease prevalence in T1DM patients similar to global rates, have significant implications for clinical practice. The importance of routine celiac disease screening for these patients is underscored, as is the urgent need for extensive multi-center studies to deepen our understanding of this relationship and improve patient care.

Keywords: Type 1 Diabetes, Celiac disease, Endoscopy, Screening.

Citation:
Ordooei M, Edalatkhah R, Namiranian, khosravizade Z. Association of celiac disease with type 1 diabetes: A cross-sectional analysis in 2022. Caspian J Intern Med 2025; 16(4): 797-800.

Type 1 diabetes mellitus (T1DM) is a chronic metabolic ailment, prevalent as the primary form of diabetes in the juvenile and adolescent demographic. This condition arises from insulin insufficiency due to autoimmune or non-autoimmune destruction of beta cells in the islets of Langerhans, particularly in genetically predisposed individuals (1). Children and adolescents with T1DM, especially those with the HLA-DR3 marker, face increased susceptibility to various endocrine dysfunctions and autoimmune disorders, including Hashimoto's thyroiditis, Addison's disease, vitiligo, and celiac disease (2, 3). *Celiac disease* is a hereditary autoimmune disorder characterized by immune-mediated damage to intestinal epithelial cells in response to gluten. The worldwide prevalence of celiac disease is documented at 1.4%, with a slightly higher rate of 1.6% in Asia, while Iran's general population shows an approximate 2% prevalence (4-6). Using precise screening methodologies has led to an observed surge in estimated prevalence rates (7). Notably, the prevalence of celiac disease in individuals with T1DM surpasses that of the general population, reaching up to 6% (2). A minority of T1DM patients exhibit hallmark symptoms of celiac disease, such as abdominal distress, bloating, persistent diarrhea, weight fluctuations, and constipation (8, 9).

Instead, they commonly present with recurrent hypoglycemic episodes, poor blood glucose management, and growth impediments (8, 9). Given the long-term repercussions associated with these conditions, early detection and management of celiac disease in T1DM patients can improve glycemic control and mitigate complications such as growth anomalies, diabetic neuropathy, osteomalacia, and anemia (10, 11).

Given the high prevalence of celiac disease among individuals with T1DM, this study aimed to identify and evaluate the prevalence of this condition in the target population. The primary objective of this research is to investigate the relationship between T1DM and celiac disease and to identify patients who may have undiagnosed celiac disease, potentially leading to severe complications. The significance of this work lies mainly in its potential to improve patient's quality of life and prevent long-term complications associated with untreated celiac disease. By identifying previously unrecognized cases, timely therapeutic interventions can be implemented to mitigate serious outcomes.

Methods

It involved a cohort of 318 patients aged 1 to 18 diagnosed with type 1 diabetes who sought care at the Diabetes Clinic of Yazd University of Medical Sciences between October 2022 and October 2023. The sampling methodology involved a census of all T1DM cases attending this specialized facility during the study duration. Inclusion criteria adhered to the diagnosis standards outlined by the American Diabetes Association. Patients with congenital IgA deficiency were excluded due to the potential for altered immune responses that could lead to misleading serological results.

Individuals with Down syndrome and Turner syndrome were also excluded, as these genetic conditions may predispose patients to various autoimmune disorders, thereby complicating the interpretation of the relationship between T1DM and celiac disease. Additionally, the exclusion of individuals with a family history of celiac disease among first-degree relatives was necessary to minimize the risk of genetic confounding, as such a history significantly increases the likelihood of developing celiac disease. The diagnosis of celiac disease was confirmed after parental consent acquisition. Initial assessments integrated the quantification of Tissue Transglutaminase IgA (tTG-IgA) and Serum IgA levels. The laboratory technique for measuring IgA and anti-tissue transglutaminase (tTG) antibody levels involves using standardized serum kits and enzyme-linked immunosorbent assay (ELISA) methods. If tTG-IgA levels were ten or greater, an upper gastrointestinal endoscopy was conducted under the supervision of a pediatric gastroenterologist, with a minimum of four samples extracted from the distal duodenum. Subsequently, the biopsy specimens underwent conventional histopathological scrutiny and were stained with hematoxylin-eosin. The extent of villous atrophy, crypt hyperplasia, and intraepithelial lymphocyte count were evaluated by the Marsh classification.

Statistical analysis: The gathered data were input into SPSS software Version 22 for comprehensive analysis. A significance threshold of a p-value < 0.05 was adopted. Analytical procedures encompassed chi-square tests, as well as paired and independent t-tests, for robust statistical evaluation.

Results

A comprehensive investigation involving 318 patients diagnosed with T1DM (51.2% female and 48.8% male) revealed a mean age of 17.92±1.793 years (age range: 2 to 29 years). The serological screening for celiac disease employed anti-tissue transglutaminase IgA antibodies and serum IgA levels, ensuring the comprehensive nature and validity of our research. The prevalence of celiac disease based on serology stood at 7.8%, while the pathology-based prevalence was 6.6%.The mean duration between diabetes and celiac disease diagnoses was 1.451±43.5 years. None of the patients exhibited IgA deficiency (<70 ng/dL). Elevated IgA anti-tissue transglutaminase antibody levels (tTG) exceeding 10 AU/mL were observed (mean 33.821±37.124).

Among those positive for tTG antibodies, one patient reported a history of dermatitis, and chronic diarrhea was noted in two of the 25 positive cases. All tTG-positive patients underwent upper endoscopy and duodenal biopsy. Of the 25 individuals (7.86%) with positive serology who underwent biopsy, 4 displayed normal histology, while 21 (6.6%) exhibited celiac disease-related histopathological alterations. Among these 21 patients, histopathological changes were classified as follows: 2 (8%) exhibited Marsh type 1, 1 (4%) presented as Marsh type 2, and 18 (72%) were categorized as Marsh type 3. Patients with tTG levels surpassing 100 were uniformly categorized as Marsh type 3 (P-value = 0.0001). Notably, the distribution of celiac disease types across male and female groups revealed no statistically significant variance (P- value= 0.58).

Table 1. Distribution of histopathological (Marsh) findings according to anti-tTG IgA antibody levels

TTg IgA Level			Histopathology				
			Normal	Marsh I	Marsh II	Marsh III	Total
TTG	10-100	Frequency	4	2	1	1	8
		(%)	16%	8%	4%	4%	32%
	>100	Frequency	0	0	0	17	17
		(%)	0.0%	0.0%	0.0%	68%	68%
Total		Frequency	8	2	1	18	25
		(%)	16%	8%	4%	72%	100.0%

P-value: 0.0001, tTG: Tissue Transglutaminase. TTG: anti-tissue transglutaminase.

Discussion

Historically, the true prevalence of celiac disease in the general population has been documented as less than 1%, with many cases remaining asymptomatic. Consequently, a considerable number of celiac disease cases go undiagnosed (12, 13). Screening initiatives targeted at high-risk cohorts, such as individuals with T1DM, can effectively unveil previously undetected celiac disease cases. This study, conducted at the Yazd Diabetes Center to ascertain celiac disease prevalence among T1DM patients, yielded an overall prevalence of 6.6%. According to the research conducted in Iran, the prevalence of celiac disease among patients with T1DM is approximately 5.66%. (14) Comparable studies in Europe have reported confirmed celiac disease prevalences through biopsy in children and adults with T1DM at 3.6% and 5.7%, respectively (15, 16). In North America, prevalence ranges between 1.4% and 5.1% among pediatric patients and 3.5% to 6% among adults (17). In African studies, prevalence rates appear higher, with positive serology rates in Libya at 21.3% and prevalence at 10.25%, (18) and in Egypt, seropositivity at 28% and prevalence at 15.2%. (19) Saudi Arabia reported positive serology and celiac disease prevalences in T1DM patients at 20.9% and 10%, respectively (20).

The observed prevalence of celiac disease in Yazd (6.6%) may be higher than in other regions due to specific genetic predispositions in the local population or differences in dietary habits, which could influence gluten exposure and immune responses. More extensive studies are needed to elucidate these factors. Given the impact of HLA genotype distribution on celiac disease prevalence, regional variations are anticipated. Routine celiac disease screening for T1DM patients offers potential benefits, including improved glycemic control and mitigating complications like osteopenia and malignancies.

The study's strengths include its inclusion of all diabetic patients (both adults and children) within a specific geographic locale. Limitations include the modest sample size, which potentially affects generalizability. Nevertheless, this study identified celiac disease cases in a high-risk population using consistent diagnostic criteria for T1DM and celiac disease. This study underscores the comparable prevalence of celiac disease in T1DM patients globally. Routine screening for celiac disease in all T1DM patients and large-scale multi-center investigations are imperative for comprehensive understanding and management.

Acknowledgments

The researchers are grateful to the study participants and their families and to all personnel of Shahid Sadoughi Hospital.

Funding: None.

Ethics approval: The research plan of this study was approved by the Research Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd with code: (IR.SSU.MEDICINE.REC.1401.106).

Conflicts of interest: The authors declared no conflict of interest.

Authors' contribution: Mahtab Ordooei: Conception and design of the study. Nasim Namiranian: Data collection and analysis. Zahra khosravizade: Drafting the manuscript. Roohollah Edalatkhah: Reviewing and finalizing the manuscript.

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