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Celiac Disease in Sabzevar: Prevalence Patterns and Clinical Manifestations

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Abstract

Background: Celiac disease is a systemic immune-mediated disorder that develops in genetically predisposed individuals following the consumption of gluten and prolamin proteins found in wheat and barley. Considering the wide range of clinical presentations of celiac disease and its association with other autoimmune disorders, and given the lack of sufficient data regarding its clinical spectrum, this applied research was conducted to assess the prevalence and clinical manifestations of celiac disease. This study aimed to determine the prevalence and clinical manifestations of CD in Sabzevar County, Iran.

Methods: This cross-sectional study reviewed the medical records of 2,000 patients referred to Heshmatieh Hospital in Sabzevar. Patients with symptoms suggestive of CD or with type 1 diabetes underwent serological testing (anti-tTG, total IgA). Those with positive serology underwent duodenal biopsy, classified according to the Marsh criteria. Demographic and clinical data were analyzed using SPSS.

Results: The prevalence of celiac disease was 2.7%. The mean age was 10.09 years (SD = 3.24), and 64.8% were female. Growth disturbances were the most common manifestation (59.2%), followed by diabetes-related symptoms (29.6%). Gastrointestinal symptoms were present in only 14.8%. Mean anti-tTG IgA titer was 194.03 IU/dL (SD=168.6), and higher titers correlated with more advanced Marsh grades (Marsh 3C: 281.52 IU/dL).

Conclusion: Celiac Disease demonstrates a considerable prevalence of 2.7% within this high-risk pediatric population in Sabzevar. These findings highlight the critical need for heightened physician awareness of extraintestinal manifestations to facilitate earlier diagnosis and effective management.

Key Words: Anti-tissue transglutaminase, Celiac disease, Iran, Marsh classification, Prevalence.

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1- INTRODUCTION

Celiac disease is a major malabsorption disorder characterized by enteritis, leading to impaired absorption of essential nutrients (1,2). It is a lifelong condition that may develop at any age (1–4). Celiac disease is a systemic, immune-mediated disorder triggered in genetically susceptible individuals by the ingestion of gluten and related prolamin proteins found in wheat, rye, and barley (1,2). Gluten, the principal protein component of these grains, is responsible for the onset of celiac manifestations following dietary exposure. The global distribution of celiac disease appears to have been influenced by the expansion of wheat consumption as well as human migration patterns. Agricultural practices may also help explain the varying prevalence of the disease across countries. For instance, certain states in India show relatively high prevalence rates, as wheat serves as the primary staple food in these regions. Iran ranks among the highest wheat-consuming nations worldwide, with an estimated per capita consumption of 160 kg per year (5). A distinctive feature of the Iranian diet is its heavy reliance on bread, wheat, and rice as major energy sources. Consequently, adherence to a gluten-free diet poses a significant challenge for both patients and healthcare providers in this context. This challenge is further complicated in Middle Eastern countries, where access to gluten-free dietary alternatives remains limited (6). In recent years, significant changes have been observed in the epidemiology of celiac disease (7). A considerable increase in both the prevalence and incidence of the disease has been reported, which can at least partly be attributed to the development of more sensitive serological tests and greater awareness of the disorder (1,2,7,8). Over the past three to four decades, both the age of onset and the prevalence of celiac disease appear to have shifted markedly. Until only a few years ago, gluten intolerance was thought to be a disorder that almost exclusively affected Europeans, who defined the classical clinical features of celiac patients. As early as a decade ago, celiac disease was considered extremely rare in Middle Eastern countries. Nonetheless, comparisons of more recent studies from Europe and the Middle East demonstrate that the disease is common in both regions and occurs at roughly similar prevalence rates. This recognition can largely be attributed to the practical use of serological screening tests that measure anti-gliadin antibodies (AGA), anti-endomysial antibodies (EMA), and, more recently, anti-tissue transglutaminase antibodies (anti-Ttg IgA), which have enabled the diagnosis of many latent or subclinical cases of celiac disease. The prevalence of the condition across different populations worldwide appears to vary according to dietary patterns (7).

At present, celiac disease is recognized as a global disorder, affecting approximately 0.7% of the world's population (3,9). Reported prevalence rates vary across regions, with estimates of 0.4% in South America, 0.5% in Africa and North America, 0.6% in Asia, and 0.8% in Europe and Oceania. Celiac disease tends to affect women more frequently than men, with a female-to-male ratio of approximately 3:1 (5). However, studies conducted in general populations have not consistently demonstrated a marked difference in prevalence between the two genders (8). The prevalence of celiac disease is significantly higher in children than in adults. On average, children tend to experience much more rapid disease progression compared to adults (3,4). Among children with type 1 diabetes, the prevalence of celiac disease has been reported to range between 2.4% and 16.4% (10–13). The prevalence of celiac disease

among Iranian school children has been estimated at 0.6%. Nevertheless, the majority of patients remain undiagnosed due to the iceberg pattern of clinical presentation and the wide variability of symptoms. This implies that many individuals with celiac disease are asymptomatic or present with latent forms of the disorder. In Iran, celiac disease is a relatively common cause of chronic diarrhea, and it has been reported in 2–8% of patients with type 1 diabetes in Iran, Israel, and Saudi Arabia (6). The clinical manifestations of celiac disease vary considerably from one individual to another. Presentations may range from asymptomatic cases to severe malabsorption, often identified through screening of high-risk groups. Celiac disease is generally classified into gastrointestinal and extraintestinal forms. Overall, children tend to exhibit more extraintestinal manifestations compared with adults (3,4). The principal gastrointestinal symptoms include chronic diarrhea, recurrent abdominal pain, nausea, vomiting, and abdominal distension/flatulence. Common extraintestinal features include growth failure, short stature, treatment-resistant iron-deficiency anemia, osteopenia, delayed puberty, dental enamel hypoplasia, irritability, chronic fatigue, neuropathy, arthritis, arthralgia, amenorrhea, and elevated liver enzymes.

Dermatitis herpetiformis is a well-recognized cutaneous manifestation of celiac disease (14,15). Patients with celiac disease also have a three- to ten-fold higher risk of developing other autoimmune disorders compared with the general population (16,17). The most common associated condition is type 1 diabetes, owing to shared genetic factors and overlapping pathogenic mechanisms with celiac disease (18,19). Complications of celiac disease include refractory celiac disease, intestinal lymphoma, and small bowel adenocarcinoma, which typically occur in older patients, i.e., after the age of 50, and in those who fail to adhere strictly to a gluten-free diet. Although the overall mortality rate in celiac patients is higher than in the general population, such complications remain rare (<1%) (20,21). Despite increased awareness and the widespread use of diagnostic tests, up to 95% of individuals with celiac disease remain undiagnosed (22–24). Early diagnosis is essential for preventing long-term complications (20,21); however, diagnosis is often challenging due to the heterogeneity of clinical manifestations across patients (14,15).

Several diagnostic approaches are available, including serological assays for anti-tissue transglutaminase antibodies and anti-endomysial antibodies, commonly used in screening, as well as duodenal biopsy (3,4,8,9). A definitive diagnosis generally requires the demonstration of small intestinal atrophy in the presence of circulating celiac-specific antibodies and/or a rapid clinical and serological response to a gluten-free diet. Celiac disease is strongly associated with specific human leukocyte antigen (HLA) haplotypes, particularly HLA-DQ2 and HLA-DQ8 (1,2). Recent guidelines suggest that, in a subset of children who fulfill prominent clinical and serological criteria, duodenal biopsy may be safely omitted. Celiac disease can occur at any age, from early childhood to late adulthood; yet, two incidence peaks are typically observed: the first within the first two years of life after gluten introduction, and the second during the second or third decade of life. Some reports have also described a third peak in the fifth decade (7). Importantly, reliance on a single clinical criterion for diagnosis imposes the risk of leaving a substantial proportion of patients undetected (8).

Although most patients respond to a gluten-free diet, approximately 20%

continue to experience persistent or recurrent symptoms. Multiple factors contribute to these residual or new symptoms in patients on a gluten-free diet, with inadvertent gluten consumption being the most common cause (3,9). Factors associated with a more favorable clinical course include early diagnosis following symptom onset and a positive family history of celiac disease (3,4).

Given the wide spectrum of clinical manifestations and the association of celiac disease with other autoimmune disorders, as well as the lack of sufficient data on the clinical spectrum in Sabzevar, this study was undertaken to evaluate the prevalence and clinical features of celiac disease in the region. Understanding the diverse clinical presentations in this population will facilitate accurate early diagnosis in patients with atypical symptoms, thereby preventing subsequent complications.

Accordingly, this study determined the prevalence and clinical manifestations of celiac disease in Sabzevar County, with a particular focus on extraintestinal manifestations. Patients suspected of having celiac disease were initially evaluated based on their clinical features and underwent serological testing. Those with positive serology subsequently underwent endoscopy with duodenal biopsy, which was sent to a recognized reference laboratory in Mashhad for definitive diagnosis. Given the wide spectrum of clinical manifestations, the association of CD with other autoimmune disorders, and the lack of sufficient regional data from Sabzevar, this study was undertaken to evaluate the prevalence and clinical features of CD. Understanding the diverse clinical presentations in this population will facilitate accurate early diagnosis in patients with atypical symptoms, thereby preventing subsequent complications.

2- MATERIALS AND METHODS

This cross-sectional, retrospective study was conducted at Heshmatieh Hospital in Sabzevar, Iran, following approval from the Committee of Ethics in Human Research ([IRMEDSAB.REC.1400.154]). The population of Sabzevar County is approximately 306,310. Medical records of 2,000 patients referred to the gastroenterology and endocrinology clinics were reviewed. Data were collected from all patients aged ≤18 years who presented with symptoms such as chronic diarrhea, chronic abdominal pain, short stature, treatment-resistant anemia, delayed puberty, or type 1 diabetes. Patients with clinical suspicion of CD were identified from medical records. Missing data were supplemented via telephone follow-up.

Patients underwent serological testing (anti-tissue transglutaminase antibodies [anti-Ttg IgA] and total IgA). Those with positive serology were referred for endoscopy and duodenal biopsy. Biopsy samples were analyzed at a reference laboratory in Mashhad and classified according to the Marsh criteria. Patients with positive serology but negative endoscopy were classified as potential CD.

Patients with clinical suspicion of celiac disease were identified from medical records, and any missing or incomplete data were supplemented through follow-up and telephone contact.

All necessary diagnostic procedures, including serological testing, endoscopy, and biopsy for definitive diagnosis, had been performed before data collection. Specifically, patients with clinical suspicion of celiac disease were initially requested to undergo serological testing. Those with positive serology were subsequently referred to Vasei Hospital for endoscopy and duodenal biopsy, and the samples were sent to a recognized

reference laboratory in Mashhad for definitive diagnosis. Final classification was determined according to the Marsh criteria. Patients with positive celiac-related serology but negative endoscopy findings were classified as potential celiac cases.

2-1. Questionnaire and Data Analysis

Data were collected using a structured, nine-section questionnaire covering demographics, clinical symptoms, and laboratory findings. Data were analyzed using SPSS version 26. Descriptive statistics (mean, SD, frequency, percentage) were calculated. Due to non-normal distributions (Kolmogorov-Smirnov test), the Kruskal-Wallis test was used for quantitative variables and the chi-square test for categorical variables. Statistical significance was set at $P < 0.05$. Confidentiality was maintained for all participants.

3- RESULTS

In this study, among the 2,000 pediatric patients referred to the gastroenterology and endocrinology clinics of Heshmatieh Hospital, 54 cases of CD were identified, yielding a prevalence of 2.7% in this high-risk cohort.

The mean age of participants in the study was 10.09 years (SD = 3.24). Among the 54 participants, 19 (35.2%) were male, and 35 (64.8%) were female. Regarding clinical manifestations, 11 participants presented with gastrointestinal symptoms, distributed as follows: 2 participants (3.7%) had isolated abdominal pain, 4 participants (7.5%) had abdominal pain with flatulence and nausea, 1 participant (1.8%) had abdominal pain with diarrhea, 2 participants (3.7%) had abdominal pain accompanied by diabetic symptoms, and 2 participants (3.7%) had abdominal pain along with growth disorders.

Growth disturbances were identified in 32 participants (59.2%), including 14 participants (25.9%) with low weight and short stature, 12 participants (22.2%) with short stature alone, 3 participants (5.5%) with low weight alone, 2 participants (3.7%) with growth disorders accompanied by gastrointestinal symptoms, and 1 participant (1.8%) with growth disorders accompanied by diabetic manifestations.

Diabetic manifestations, i.e., polyuria and polydipsia, were observed in 16 participants (29.6%), of whom 2 participants (3.7%) also presented with gastrointestinal symptoms and 1 participant (1.8%) presented with growth disturbances. Finally, only 1 participant (1.8%) out of 54 participants was identified with hypothyroidism symptoms. The mean height of participants was 132.06 cm (SD = 17.69), and the mean weight was 29.92 kg (SD = 13.19). The mean level of anti-tissue transglutaminase antibodies (Anti-tTG) was 194.03IU/dL (SD = 168.6), and the mean serum IgA level was 109.95 mg/dL(SD=81.44).

Regarding Marsh classification, 15 participants (27.77%) were classified as Marsh 0 or 1 (potential celiac disease), while 33 participants (61.12%) were classified as Marsh 2 or 3 (typical celiac disease). Additionally, 2 participants were identified as celiac based solely on positive serology and HLA-DQ positivity.

Table-1. Demographic and clinical characteristics of study participants.

Variable		Frequency	%
Gender	**Female**	35	64.8
	Male	19	35.2
Gastrointestinal symptoms		11	20.4
Growth impairment symptoms		32	59.2
Diabetes symptoms		16	29.6
Hypothyroidism		1	1.8

Table-2. Detailed clinical manifestations of study participants

Variable	Symptoms	Frequency	%
Gastrointestinal symptoms	Abdominal pain	2	3.7
	Abdominal pain + constipation and nausea	4	7.4
	Abdominal pain + diarrhea	1	1.8
	Abdominal pain + diabetes	2	3.7
	Abdominal pain + growth impairment	2	3.7
Growth impairment symptoms	Short stature + low weight	14	25.9
	Short stature	12	22.2
	Low weight	3	5.5
	Accompanied by gastrointestinal symptoms	2	3.7
	Accompanied by diabetes	1	1.8
Diabetes symptoms	Diabetes + gastrointestinal symptoms	2	3.7
	Diabetes + growth impairment symptoms	1	1.8
Hypothyroidism symptoms	----	1	1.8

As shown in Figure 1, the most frequent clinical manifestations of celiac disease were growth disturbances, affecting 59.2% of participants. The second most common manifestations were related to diabetes, observed in 29.6% of individuals. The distribution of other clinical groups is also illustrated in Figure 1.

Overall, as illustrated in Figure 2, hypothyroidism symptoms accounted for the lowest proportion of clinical manifestations, while short stature combined with low weight represented the highest proportion of celiac disease manifestations.

As shown in Figure3, among growth disturbances, short stature combined with low weight accounted for the highest proportion of clinical manifestations, whereas growth disturbances accompanied by diabetes represented the lowest. Regarding gastrointestinal symptoms, abdominal pain with constipation and nausea was the most frequently observed, while abdominal pain with diarrhea occurred least frequently.

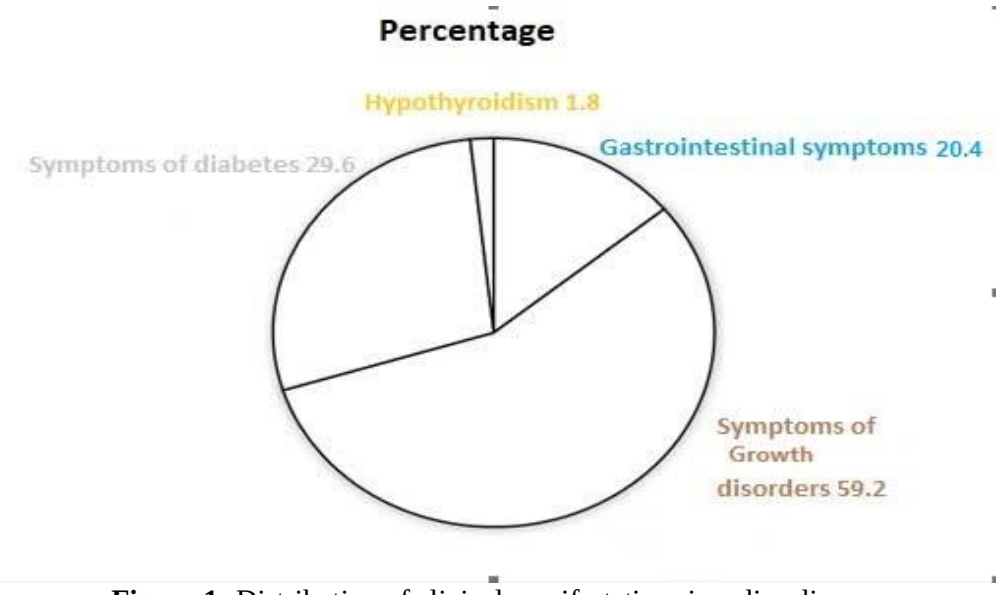

Figure-1: Distribution of clinical manifestations in celiac disease.

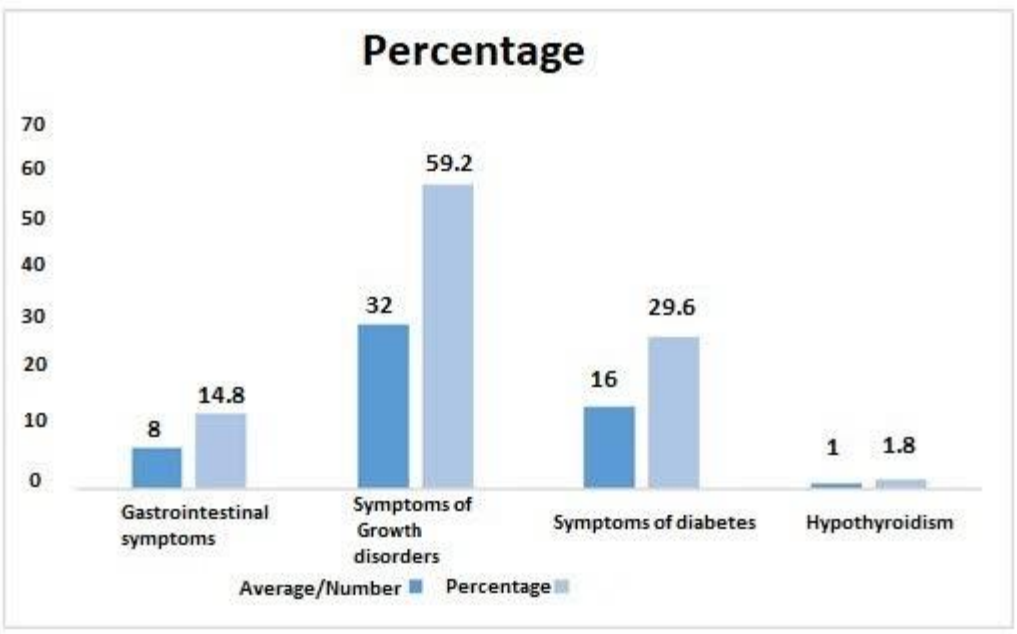

Figure-2: Clinical manifestations of celiac disease.

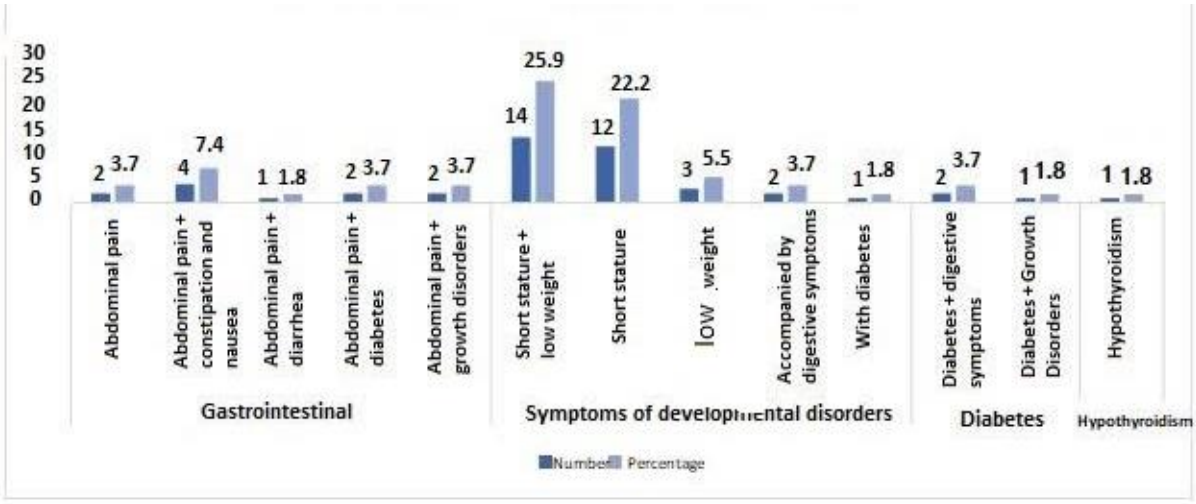

Figure-3: Detailed clinical manifestations of celiac disease.

As shown in Figure 4, the highest prevalence of celiac disease among high-risk participants was observed in those with diabetes manifestations, including both typical and potential celiac cases. In participants with hypothyroidism or a positive family history, only typical celiac disease was observed.

Table 3 displays the distribution of participants according to Marsh classification. Of the 54 participants, 48 underwent endoscopy with biopsy and were assigned a Marsh grade. Among these 48, 15 (27.78%) were classified as potential celiac disease, including 7 (12.96%) with Marsh 0 and 8 (14.81%) with Marsh 1. The remaining 33 (61.11%) were classified as typical celiac disease, distributed as follows: 3 (5.56%) with Marsh 3A, 15 (27.78%) with Marsh 3B, and 15 (27.78%) with Marsh 3C. Of the 6(11.12%) participants without a Marsh grade, 2 were diagnosed based on positive serology and HLA-DQ typing, and the other 4 did not undergo endoscopy.

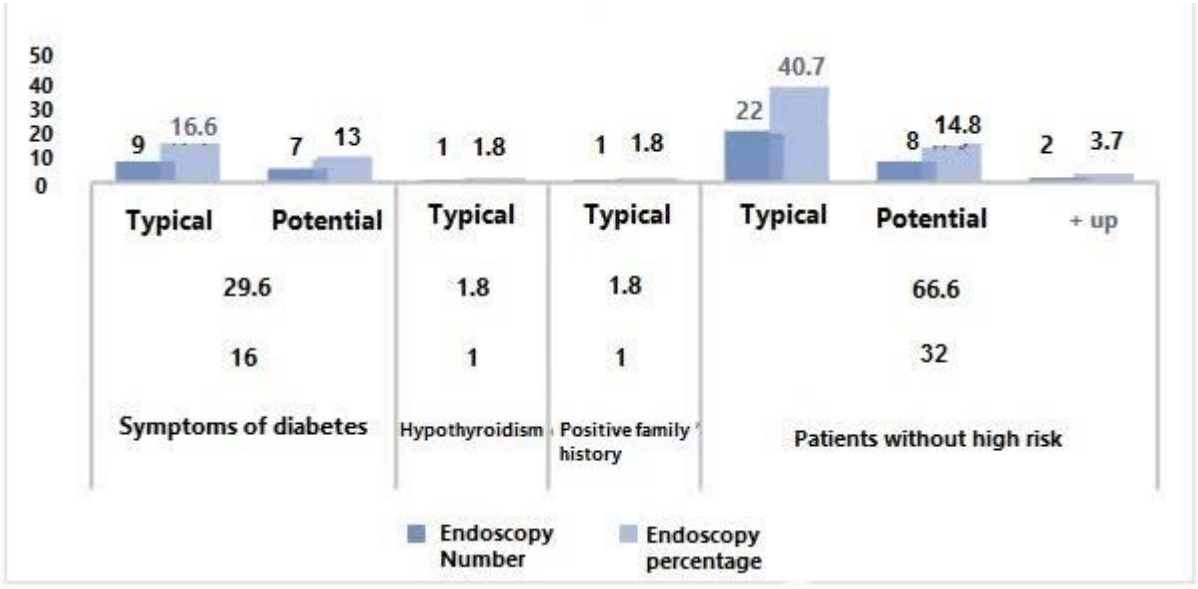

Figure-4: Celiac disease in high –risk patients.

Table-3. Types and grades of celiac disease based on Marsh classification.

Variable		Frequency	%
Potential Celiac	**Marsh 0**	7	12.96
	Marsh 1	8	14.81
Typical Celiac	**Marsh 2**	0	0
	Marsh 3A	3	5.56
	Marsh 3B	15	27.78
	Marsh 3C	15	27.78
HLA-DQ+	**HLA-DQ+**	2	3.7
No Endoscopy	**No Endoscopy**	4	7.5

In the present study, a total of 48 cases of celiac disease were identified via biopsy and classified according to the Marsh criteria. The mean anti-tissue transglutaminase antibody (Anti-Ttg IgA) titer was 194.03 IU/dL (SD = 168.6), with a minimum titer of 20 IU/dL and a maximum of 800 IU/dL. Among these, 7 participants in Marsh 0 had a mean Anti-Ttg IgA titer of 45.53 IU/dL (SD = 40.80; range: 20-98), and 8 participants in Marsh 1 had a mean titer of 101.62 IU/dL (SD = 51.48; range: 40-197). No cases were observed in Marsh 2.

In Marsh 3A, 3 participants had a mean Anti-Ttg IgA titer of 171.20 IU/dL (SD = 116.66; range: 72.6-300), while 15 participants in Marsh 3B had a mean titer of 219.80 IU/dL (SD = 101.00; range: 38-455). Finally, 15 participants in Marsh 3C had a mean titer of 281.52 IU/dL (SD = 236.61; range: 29-800). These results indicated a clear correlation between Anti-tTG titer levels and Marsh classification: higher antibody titers corresponded with more advanced Marsh grades.

Based on Table 5, data analysis indicated that a total of 18 participants (33.3%) were classified as high-risk for celiac disease. Among these, 16 participants with diabetes and one participant (1.8%) with hypothyroidism were diagnosed via biopsy. Only one participant (1.8%) had a positive family history of celiac disease.

Table-4. Relationship between Anti-Ttg IgA serology levels and Marsh classification.

Marsh classification level	f	Serological mean level	SD	Minimum serological mean	Maximum serological mean
0	7	45.53	40.80	20	98
1	8	101.62	51.48	40	197
Marsh 3A	3	171.20	116.66	72.6	300
Marsh 3B	15	219.80	101.00	38	455
Marsh 3C	15	281.52	236.61	29	800

Table-5. Coexistence of celiac disease in high-risk participants.

Variable	Frequency	%	Endoscopy		
			Celiac	Frequency	%
Diabetes symptoms	16	29.6	Typical	9	16.7
			Potential	7	13
Hypothyroidism symptoms	1	1.8	Typical	1	1.8
Positive family history	1	1.8	Typical	1	1.8
Patients without high risk	32	66.6	Typical	22	40.7
			Potential	8	14.8

4- DISCUSSION

Celiac disease is currently recognized as a global disorder, with an estimated prevalence of approximately 0.7% worldwide (9). In the present study, the prevalence of celiac disease was 2.7% in the group referred to the clinic.

Biopsy-confirmed celiac disease was 2.4% among 2,000 participants and 0.15% in the general population of Sabzevar. As observed, the prevalence in females in Sabzevar was higher, consistent with global reports (5), at 1.7% compared to 0.9% in males. In this study, the prevalence of extra-intestinal manifestations of celiac disease among the pediatric population was 59%, with short stature combined with low weight being the most common extra-intestinal manifestation. These findings are consistent with previous studies (4). The prevalence of celiac disease in Sabzevar was 0.17%, and chronic diarrhea was observed in only 1.8% of celiac patients in this region. This finding is not consistent with previous studies, which reported that celiac disease is a relatively common cause of chronic diarrhea in Iran and is diagnosed in 2–8% of patients with type 1 diabetes (6).

According to the present study, in investigations using serological tests, the prevalence of celiac disease was 1.7% in children under 10 years and 1% in the 10-18-year age group. In studies using biopsy for diagnosis, the prevalence was 1.55% in children under 10 years and 0.85% in those aged 10-18 years. These rates are lower than the prevalence reported in other regions of Iran (8). The prevalence of celiac disease has increased significantly over the past three decades due to greater physician awareness and the widespread use of highly sensitive and specific diagnostic tests for this condition (1,2). Despite this increased awareness and diagnostic capability, a substantial number of celiac patients remain undiagnosed (22-24). In Sabzevar, with an estimated prevalence of 0.17%, it appears that many patients remain undiagnosed.

The risk of autoimmune diseases in individuals with celiac disease is three- to tenfold higher than in the general population (16,17). The most common comorbidity is type 1 diabetes, which shares genetic factors and pathogenic mechanisms with celiac disease (18,19). The prevalence of celiac disease in patients with type 1 diabetes has been reported to

be approximately five times higher than in the general population (25), ranging from 2.4% to 16.4% in pediatric populations (10-13). In the present study in Sabzevar, 31.4% of patients with autoimmune disorders such as diabetes and hypothyroidism were affected, of which 29.6% had type 1 diabetes. Given the broad spectrum of celiac disease manifestations, encompassing both intestinal and extra-intestinal symptoms, it is essential for physicians across specialties, and particularly general practitioners (GPs), to consider celiac disease as a key differential diagnosis in patients with suspicious symptoms. Early recognition and diagnosis are crucial to prevent long-term complications.

4-1. Limitations

One limitation of this study was patient refusal to undergo endoscopy, leading to the exclusion of 13 participants. Another limitation of this study was that we only examined the prevalence, clinical manifestations, and biopsy-based Marsh classification of celiac disease.

4-2. Suggestions for Further Research

Future studies could utilize larger populations and investigate atypical manifestations, such as refractory celiac disease, osteopenia, permanent enamel defects, and others. Additionally, complications such as hyposplenism, intestinal lymphoma, and small bowel adenocarcinoma could be evaluated. It is also recommended to assess symptom control and improvement following adherence to a gluten-free diet.

5- CONCLUSION

Given that Sabzevar County had a pediatric specialty center and a gastroenterologist and endocrinologist, and the current population was approximately 306,310, the prevalence of this disease was calculated to be 0.018. This rate is significantly lower than the global average. This low prevalence may indicate a lack of awareness or inadequate understanding of celiac disease, especially among general practitioners, regarding its diverse clinical presentations. Despite advancements in serological and biopsy-based diagnostics, a significant proportion of patients remain undiagnosed, emphasizing the need for increased awareness among people and physicians, especially general practitioners. Early identification and management are essential to reduce the burden of complications and improve patient outcomes.

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