Original Article

Compliance and Lifestyle of Children with Celiac Disease in the Iranian Children

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Abstract

Background: Celiac disease is popular and needs a proper and constant gluten-free diet. However, data on the experience of the disease by children are insufficient. A few children have difficulty adjusting their lifestyles, and gluten-free foods are difficult for them. The present study aimed to find influential factors in the growth disorders and nonresponse to the treatment diet in celiac patients.

Materials and Methods: We gave a list of all children with celiac disease to the project manager and according to the criteria extracted additional information from their files. Duodenal biopsies on 382 patients with suspected celiac disease and 93 patients with positive pathology were included in the study, regardless of antibody and genetic titer, then analyzed their information using appropriate statistical tests.

Results: The mean age of individuals was 9.48 ± 3.88, and 35 were male and 58 female. At the age of <5, there was more growth disorder than other age groups. The recovery percentage in short stature was significantly better in children with higher marches, and they responded better to the treatment regimen. Individuals with comorbidities had higher anti-tTG and lower Hb levels, higher incidence of growth disorder, did not respond to the treatment regimen. Those with a first-degree relative with celiac disease had a lower growth disorder than others.

Conclusion: Identifying and correcting nutritional disorders in patients with celiac disease need to evaluate persistent symptoms and identify their causes to plan appropriate treatment and follow-up of patients with celiac disease step by step and continuously.

Keywords: Celiac, celiac disease, gluten enteropathy, malabsorption syndromes, sprue

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Introduction

Celiac disease, or permanent gluten-sensitive enteropathy, has been mentioned as a public health problem worldwide. It is an autoimmune disease that can affect any organ, not just the gastrointestinal tract, and start at any age.[1-3] Maybe the ordinary and interesting past celiac disease report originated from Willem Dicke, a Dutch pediatrician, in 1940. At that time, the current line of children with celiac disease focused around a "banana diet" or "Fanconi diet."[4] In celiac disease, small bowel function is destroyed by chronic inflammation associated with the disappearance of intestinal villi after consuming gluten.[5,6] Celiac disease is a common cause of intolerance in the world. Data of screening studies indicate that about 1% of the world's population is affected by this disease. Outside the Indian subcontinent and Middle East nations, the epidemiological load of celiac disease in Asia may be minimized, particularly in Russia and Central Asia, where wheat is a chief meal and the inborn talent for celiac is similar to Europe.[7,8] Celiac disease, or gluten-sensitive enteropathy, is an immune-related enteropathy seen in genetically predisposed individuals as persistently sensitive to wheat gliadin or other barley prolamins in barley. The roles of both genetic

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and environmental factors have been investigated in the pathophysiology of celiac disease. The disease is significantly associated with HLA class II antigens, especially DQ2 and DQ8. Celiac enteropathy is caused by immune damage to small intestinal mucosal cells. Gliadin peptides, which are resistant to enzymes in the stomach and pancreas, reached the lamina propria of the small intestine by altering the intestinal wall's permeability and triggering immune and inflammatory reactions.[9,10] Infant nutrition, gastrointestinal infections, and intestinal bacteria may develop the celiac disease.[11]

Symptoms of celiac disease can manifest as intestinal problems or as a result of malnutrition. According to the studies and research, few studies consider on the response rate to a gluten-free diet.[12,13] Due to the high prevalence of celiac disease in the Iranian population and any study on the identification of various factors affecting treatment and complications in patients with celiac disease, the present study aimed to evaluate complications and response to treatment in children with celiac disease in northwestern Iran in a 5-year follow-up to reduce complications and nonresponse to treatment and increase the quality of treatment in patients.

Materials and Methods

The present study was a retrospective cohort study from 2007 to 2017 in northwestern Iran, examining 382 children suspected of having celiac disease. Among them, 93 children had biopsy-proven celiac disease.

The ethics committee of Tabriz University of Medical Sciences approved the study protocol with an ethical code of IR.TBZMED.REC.1398.272.

After coordinating with the management of hospitals and medical records, we gave a list of all children with celiac disease to the project manager and included the eligible patients by reviewing files and according to the inclusion and exclusion criteria and extracted additional information from their files. The weight-to-age ratio and height to age ratio is calculated based on patients' visits to the clinic to the month and entered in the WHO *Z*-score chart. *Z*-scores between −2 and −3 were considered medium stunting, and *Z*-scores of <−3 were considered weightless and severely stunting.

Ninety-three consecutive children following inclusion criteria were enrolled in the study according to celiac disease as per Revised ESPGHAN criteria.[14] Exclusion criteria were (1) any child <2 years, (2) those who did not have a documented positive serology and biopsy suggestive of celiac disease as per revised ESPGHAN criteria, (3) those on a gluten-free diet for <6 months, and (4) those children whose parents did not consent to be included in the study, parental dissatisfaction with telephone calls, insufficient information in pathology and clinic records, and children's nonvisit for follow-up. All children enrolled in the study after signing the written informed consent form were evaluated for dietary compliance. A child who had taken even one food article containing gluten in the past 5 days was considered noncompliant and those who had strictly taken no gluten in their diet in that period were considered compliant. Parents did diet recall for children in preschool age up to 5 years since parents were the only ones giving the eatables to these children. Children above 5 years of age, going to school and interacting with peers, were actively involved in the dietary recall along with the parents. After the dietary assessment, children and their parents were subjected to an interview by the investigator.

Celiac types were divided into five groups based on the following cases: typical celiac disease (the patient shows classic malabsorption symptoms such as diarrhea, fatty stools, severe weight loss, and abdominal distension),[15] atypical celiac disease (the patient shows unusual manifestations such as short stature, anemia, infertility, neurological symptoms, metabolic bone disease, and liver involvement),[16,17] silent celiac disease (the patient has morphological changes in small bowel biopsy in the absence of clinical signs of the disease. In most cases, the patient has a relative with celiac disease or high-risk relatives).[18] Latent celiac disease (the patient has a routine bowel biopsy in a period with a gluten-free regimen, but a small intestine biopsy shows atrophy of the intestinal villi another time. Children diagnosed with celiac disease by biopsy and on a gluten-free regimen relapsed with gluten restart for some time even though it was not recommended).[19,20] Potential celiac disease (this group showed no histology in the small intestine biopsy according to celiac disease, but they have immunological features such as antiendomysial antibodies and tissue transglutaminase increased intestinal intraepithelial lymphocytes in the biopsy. These patients are often genetically predisposed to celiac disease).[20]

Furthermore, the modified pathological MARSH classification (The Marsh classification was introduced by M.N. Marsh in 19921 as a means to characterize the spectrum of changes seen in the small intestinal architecture under a microscope (known as histological changes)) was included in the questionnaire based on the pathology report. It should be noted that patients' personal information was only available to the project manager, and we made a great effort to protect the information throughout the study. Changes in the percentages of moderate and severe underweight people evaluated based on age, sex, family history, tTg, MARSH, type of celiac disease, comorbid disease, hemoglobin level, and symptoms before and after the regimen.

Statistical analysis

The statistical analyses were conducted using IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.). The continuous variable was reported as mean and standard deviation, and the categorical variables were reported as frequency and percentages. In the analytical section, we utilized proper parametric and nonparametric tests according to statistical assumptions. The Chi-square test and independent *t*-test were used for the between-group analysis of categorical and continuous variables. The significance level was set at $P < 0.05$.

Results

In the study, we included 93 patients with celiac disease. The patients' mean age was 9.48 ± 3.88 years (2–19 years) and 35 (37.6%) of them were male. Eleven patients (11.8%) had a positive family history. Abdominal pain (40%) and diarrhea (28%) were the most common complaints of celiac patients, and only 6.5% of celiac patients had nondigestive symptoms.

As shown in Table 1, the incidence of underweight was 20.8% in individuals with gastrointestinal symptoms and 0% in individuals with nongastrointestinal symptoms, and the incidence of stunting was 13% in individuals with gastrointestinal symptoms and 25% in individuals with nongastrointestinal symptoms. There was no significant association between the incidence of underweight and demographic and disease-related factors ($P > 0.05$).

Individuals with hemoglobin <12 had more severe growth disorders, and the incidence of low weight was 18.8 in anemic individuals, and the incidence of short stature was 16.3 versus the incidence of low weight and short stature, 7.7. Individuals with higher anti-tTG antibody titer had more severe growth disturbance, and the incidence of low weight and short stature was 16.7% versus 11.1%.

Among the three age groups, individuals under 5 years of age had more growth disorders and no response to treatment. The incidence of low weight was 35.7%, and the incidence of short stature was 21.4%. Individuals with a higher MARSH biopsy were more likely to have growth disorder and failure to respond to treatment, and their incidence of low weight in the MARSH was 42.93, and their short stature was 14.3. Changes in the percentages of moderate and severe underweight people did not significantly differ based on age, sex, family history,

Table 1: Percentage of moderate to severe low weight before and after diet and its relation with variables

Underweight %	Before GFD		After GFD		Percentage of changes***		*P**
	Intermediate	Severe	Intermediate	Severe	Decrease	Increase	
Age (years)							
≤5	21.4	35.7	7.1	14.3	35.7	0	0.69
5-10	4.8	19.9	7.1	7.1	16.7	2.4	
≥10	10.8	10.8	18.9	14.5	8.1	21.6	
Gender							
Male	11.4	20	8.6	11.4	17.1	5.7	0.77
Female	8.6	17.2	13.8	10.3	17.2	10.3	
Family history							
No	11.1	18.5	12.3	11.1	19.8	8.6	0.24
Yes	0	9.1	9.9	9.1	0	9.1	
tTg							
Negative	0	11.1	22.2	0	11.1	11.1	0.64
Positive	11.1	11.1	16.7	5.6	16.7	11.1	
MARSH							
1	0	9.1	0	9.1	0	0	0.69
2	9.5	19	9.5	4.8	23.5	4.89	
3a	6.9	20.7	13.8	17.2	13.8	13.1	
3b	17.4	17.4	13	13	17.4	8.7	
3c	14.3	28.6	28.6	0	42.9	14.3	
Celiac disease							
Typical	11.4	12.9	10	8.6	15.7	8.6	0.52
Atypical	6.7	40	26.7	20	26.7	13.3	
Silent	0	25	0	25	0	0	
Potential	0	0	0	0	0	0	
Accompanying disease							
No	9.7	16.7	9.7	12.5	16.7	8.3	0.91
Yes	9.5	19	19	4.8	19	9.5	
Hemoglobin							
Low level	10	17.5	10	8.8	18.8	6.3	0.34
Normal	7.7	15.4	15.4	23.1	7.7	15.4	
Signs							
Digestive	11.7	14.3	13	6.5	20.8	9.1	0.52
Nondigestive	0	50	0	50	0	0	
Both	0	20	20	20	0	0	

**P*-value of Chi-square test, ***Changes in body weight. GFD: Gluten-free diet

tTg, MARSH, type of celiac disease, comorbid disease, hemoglobin level, and symptoms before and after the regimen. Changes in weight gain or loss as a percentage were also listed in Table 1.

Furthermore, changes in the percentages of moderate and severe short stature individuals did not significantly differ based on age, sex, family history, tTg, type of celiac disease, comorbid disease, hemoglobin level, and symptoms before and after the regimen. However, in the term of stunting, it was found that the percentage of improvement in short stature was significantly better in children with a higher march score (P = 0.04). As presented in Table 2, the percentage of improvement in short stature was significantly better in children with higher MARSH, and they responded better to the treatment regimen [Table 2].

Discussion

The present study was conducted to evaluate the clinical outcome of children with celiac disease for 10 years. In the study, we included 382 patients with suspected celiac disease, a well-planned gluten-free diet may provide adequate nutrition, and it may be restrictive. Strict adherence to a gluten-free diet may be more challenging in children and adolescents than in adults. The heterogeneous clinical picture of celiac disease makes it challenging to recognize and predisposes to long diagnostic delay, further increasing the risk of permanent growth failure.[21] To prevent this complication, it would be necessary to understand better the factors associated with poor growth in celiac disease.

The present study evaluated the clinical outcome of children with celiac disease for 10 years.

Table 2: Percentage of moderate to severe short stature before and after gluten-free diet and its relation with variables

Stunting %	Before GFD		After GFD		Percentage of changes***		*P**
	Intermediate	Severe	Intermediate	Severe	Decrease	Increase	
Age (years)							
≤5	14.3	14.3	14.3	7.1	21.4	0	0.54
5-10	0	9.5	9.5	7.1	10.8	18.9	
≥10	5.4	10.8	13.5	8.1	16.2	5.6	
Gender							
Male	2.9	14.3	14.3	11.4	14.3	2.9	0.61
Female	5.2	8.6	10.3	5.2	13.8	8.6	
Family history							
No	3.7	12.3	13.6	8.6	14.8	7.4	0.2
Yes	0	0	0	0	0	0	
tTg							
Negative	0	0	22.2	0	11.1	1.1	0.62
Positive	5.6	11.1	0	0	16.7	0	
MARSH							
1	0	0	9.1	0	0	9.1	0.04
2	4.8	19	9.5	4.8	23.8	0	
3a	3.4	10.3	10.3	17.2	6.9	13.8	
3b	8.7	8.7	17.4	4.3	21.7	4.3	
3c	0	14.3	14.3	0	14.3	0	
Celiac disease							
Typical	4.3	8.6	11.4	5.7	11.4	4.3	0.27
Atypical	6.7	20	6.7	20	26.7	13.3	
Silent	25	0	0	25	0	25	
Potential	0	0	0	0	0	0	
Accompanying disease							
No	4.2	11.1	8.3	8.3	12.5	5.6	0.57
Yes	4.8	9.5	23.8	4.8	19	9.5	
Hemoglobin							
Low level	5	11.3	11.3	5	16.3	2.5	0.11
Normal	0	7.7	7.7	23.1	0	23.1	
Signs							
Digestive	2.6	9.1	13	5.2	13	5.2	0.58
Nondigestive	0	25	0	25	25	25	
Both	0	20	0	20	20	0	

*P-value of Chi-square test, ***Improvement in short stature. GFD: Gluten-free diet

In a study by Janczyk W. *et al*., they introduced patients who had a celiac disease but had a high incidence of various complications and did not respond to a gluten-free regimen. The study indicated that if no latent source of gluten was detected, other causes of persistent villous atrophy, other than a celiac disease, should be considered, including inflammatory diseases, immunity, and endocrine diseases of the gastrointestinal tract. In severe cases of childhood celiac disease, which do not respond to a gluten-free regimen, enteropathy should be performed autoimmune, and the disease should be considered the resistant celiac disease.[22] A European study found that the time from the first symptoms to the diagnosis of celiac disease in children in five Central European countries was shorter and significantly shorter than in several adult studies. However, increasing awareness of the various symptoms of the disease and implementing proper diagnostic tools will reduce diagnostic delays.[23] A study included more than 60,000 children with type 1 diabetes. Anemia, osteoporosis, and neurological disorders were reported complications. The prevalence of celiac serological tests was higher than intestinal biopsy. Their investigation stated that celiac disease is a comorbidity in children with type 1 diabetes, mainly because of the similarity between celiac symptoms and neuropathic and gastrointestinal symptoms of diabetes.[24] Our study found that some patients did not have any changes in weight and height, and some patients had worsened status after treatment. However, there was less worsened condition in patients with high MARSH, but it did not significantly differ in other cases that require more detailed studies in subsequent studies.

In a study by Nurminen *et al*., who examined the effect of treatment on children's growth with celiac disease, 530 children with biopsy-proven celiac disease were included in the study. The researchers compared children with growth disorder and those with expected growth in serological histology and clinical features. Children with growth disorder were younger and had lower hemoglobin, higher celiac antibodies, higher alanine aminotransferase, and higher levels of thyroid-stimulating hormone. Furthermore, patients with growth disorder were at the age of under 3 years. Abdominal pain reduced the risk, while there was no effect of diarrhea, constipation, other chronic diseases, and lack of growth in patients with celiac disease.[25] Data from 653 children and adolescents from Croatia, Germany, Hungary, Italy, and Slovenia were reviewed in 2021 by Riznik *et al*. Comparing the clinical manifestations of celiac disease in children under 3 years of age with children 3 years of age or older, it was found that the signs and symptoms of malabsorption were significantly higher in younger children, while asymptomatic abdominal pain was greater in children and adolescents.[26] Our study indicated that only a higher march was associated with patients recovering after the diet. The difference may be due to differences in the sample size, differences in patients' demographic indices, differences in follow-up duration, and differences in inclusion and exclusion criteria.

Radlović *et al*. investigated the effect of a gluten-free treatment diet on children's growth with celiac disease. The effect of a gluten-free treatment diet was very significant. None of the children showed a slow growth rate or weight loss above 20%, increasing height percentiles and reducing weight loss after the treatment period. In 86 patients (95.5%), Hb control values were typical in the blood, while mild anemia was recorded in 4 patients on a gluten-free diet. It was concluded that a gluten-free treatment diet for 1–3 years had a very significant effect on children's growth rate and nutritional status with the classic form of celiac disease. There was no significant difference in the disease parameters between fully compatible and no compatible types.[9] Celiac disease pathogenesis persists inadequately described as recent studies suggest other environmental motives perform a crucial role. Leonard Maureen M. *et al*. prospectively examine the pathway of the gut microbiota starting 18 months, formerly celiac disease onset in 10 newborns who developed celiac and ten newborns who did not. A cross-sectional investigation at celiac onset identified an altered abundance of six microbial strains and several metabolites between cases and controls. They stated that early detection of changes in intestinal microbiota, functional pathways, and metabolites would limit autoimmune reactions.[27,28] Our study found that treatment diet significantly improved children's growth, and only children with higher MARSH had a better recovery than those with the lower MARSH. According to the present study's findings and the above studies, the treatment diet was necessary for patients with celiac disease and improved the patients' growth. However, patients were not examined more accurately based on compatibility and no compatibility to the present study's diet, so the issue requires further study.

Conclusion

Our study indicated that the incidence of growth failure was higher in younger individuals, those with atypical celiac disease, anemia, and higher antibody titers. GFD in patients with celiac disease improved their weights and heights, and it was found that patients' heights with higher MARSH significantly improved after the diet. Therefore, the therapeutic focus should be on a diet during diagnosis for all patients with celiac disease to improve their growth status.

Limitation

This study has several limitations. First, data on analyzed gluten content in foods in national food composition databases was lacking. Second, calculations of gluten content are estimated because they were based on self-reported dietary data. Third, because of the lack of a registry center, we lost information on some of the patients with celiac disease. The power of the research is a first follow-up study in the Iranian pediatric population

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Conflicts of interest
There are no conflicts of interest.

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