



# The Association between Nutritional Factors during Infancy and Childhood and the Onset and Severity of Symptoms in Patients with Celiac Disease

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Article Type	ABSTRACT
Research Paper	<p><b>Background and Objective:</b> Celiac disease (CD), which is caused by an inappropriate immune response to the dietary protein gluten found in wheat, barley, and rye, is very rare in children, and most of the cases remain undiagnosed until later in childhood, often after the age of 10. The present study was conducted to determine the association between nutritional factors during infancy, the age of CD diagnosis, and the severity of disease manifestations in patients referred to Imam Khomeini Hospital in Urmia.</p> <p><b>Methods:</b> This cross-sectional study was conducted on 120 patients with CD referred to Imam Khomeini Hospital in Urmia. Demographic information, clinical symptoms of the patients, information related to the time of onset and diagnosis of the disease, and disease severity were extracted and examined using a questionnaire.</p> <p><b>Findings:</b> The mean age of the patients was <math>22.1 \pm 6.2</math> years and the mean age of onset of the disease was <math>17.7 \pm 7.2</math> years. 60% of the patients were breastfed for 24 months and 23.3% for 18 months. The time to initiate complementary feeding in 70.8% of the patients was at 6 months of age, of which 51.7% used cow's milk and formula milk and 17.5% used broth. 53.3% of the patients were breastfed and 46.7% used formula milk. The results of this study showed that the total severity of CD symptoms in patients who were breastfed for 3 to 24 months increased from 3 to 72, respectively (<math>p &lt; 0.001</math>). The total severity of symptoms in patients was reported to be 23 and 25 in the age range of 5-10 years and 26-30 years, respectively (<math>p &lt; 0.001</math>). The total severity of symptoms in patients whose complementary feeding was initiated at 5 months of age was 3 and at 6 months of age was 85 (<math>p &lt; 0.001</math>). A significant relationship was observed between the type of complementary feeding after infancy and the total severity of CD symptoms, and patients whose complementary feeding was cow's milk and broth showed a higher total severity of CD symptoms (total severity of CD symptoms was 4 for complementary feeding with pudding and 4 for complementary feeding with cow's milk and broth) (<math>p = 0.024</math>).</p> <p><b>Conclusion:</b> The results of this study demonstrate a significant association between the age of onset of the disease, duration of breastfeeding, time to initiate complementary feeding, and type of complementary feeding with the severity of CD symptoms during infancy and childhood and thereafter.</p> <p><b>Keywords:</b> <i>Celiac, Breast Milk, Gluten, Nutrition, Infant.</i></p>

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## Introduction

Celiac disease (CD) is a common but poorly understood problem in many European and American countries (1-3). The reason for the challenge of this disease is the high incidence of untreated CD (4, 5). This disease usually begins in infancy or early childhood (two weeks to one year of age). Therefore, its clinical manifestations can occur at any age. About 20% of patients are over 60 years old at the time of diagnosis, and according to reports, the prevalence of this disease in Iran is about 1% (6). Clinical symptoms of this disease in adults include diarrhea, bloating, sudden weight loss, steatorrhea, and in children, it is usually accompanied by gastrointestinal symptoms and malabsorption with poor growth (7). Other symptoms of this disease in children include fatigue, impaired child growth, and amyotrophy (8-10). The only current treatment for CD is the use of gluten-free diets throughout the person's life (11).

The cause of CD is not fully understood. Although the genes responsible for CD have not been identified, genetic predisposition is a prerequisite for CD (12). CD is considered an immunological disease, the main autoantigen of which is tissue transglutaminase (13). CD affects the intestinal mucosa and causes destruction of the intestinal villi, which is closely related to the intake of wheat gluten or other gluten-containing products (14).

Studies have shown that environmental factors such as infant feeding patterns may influence the immunological process of the body and lead to sensitivity to certain foods (15). Evidence suggests that the immune system response to an antigen is modified by other factors such as breastfeeding, and this change is due to the immunomodulatory process of the body (16, 17). Breastfeeding is highly beneficial for children's health, and exclusive breastfeeding is recommended for the first 4–6 months of life (18, 19). Breast milk protects children against intestinal infections by enhancing passive immunity through factors such as IgA antibodies, lysozyme, lactoferrin, and various cytokines (20). This effect may be important because frequent gastrointestinal infections are likely to increase the risk of CD (21, 22). In addition, some studies have shown that intestinal permeability is reduced in breastfed infants (23). Immunomodulation, fewer infections, and reduced intestinal permeability may be the possible explanations for the protective potential of breast milk consumption against CD (24). In addition, breast milk contains some gluten ingested by lactating mothers, and this early exposure may theoretically lead to the development of antigen tolerance (25, 26).

Breastfed infants have a different gut microbiota than formula-fed infants, and changes in gut microbiota are associated with the risk of CD (27). Radlovic et al. demonstrated that there was no significant difference in the age of CD diagnosis between infants who were introduced to gluten-containing foods before 4 months of age and between 4 and 6 months of age (28). The results of this study showed that breastfeeding and the time of gluten introduction did not affect the severity of the disease. However, a study by Ivarsson et al. showed that the gradual introduction of gluten-containing foods from the fourth month of life, along with extended breastfeeding, reduced the incidence of CD (29).

CD is a highly prevalent immune-mediated illness that negatively impacts the quality of life of affected individuals and their families. Potential preventive strategies for CD focus on early infant feeding practices, namely breastfeeding and the timing and manner of introducing gluten into the infant's diet. A systematic review of available data suggests that the risk of CD may be reduced by breastfeeding. It is unclear whether this practice prevents the disease or only delays the onset of symptoms. Due to the lack of consistency in the results of studies about the effect of breastfeeding on the severity of CD symptoms, and considering that no study has been conducted in Iran on the possible effect of childhood and infant nutrition on the severity of CD symptoms, the present study was conducted to investigate the possible association between infant and childhood nutrition, the onset time and severity of CD symptoms.

## Methods

After approval by the Ethics Committee of Urmia University of Medical Sciences with the code IR.UMSU.REC.1398.227, this cross-sectional study was conducted on 120 patients with CD in the age range of 1 and 30 years referred to Imam Khomeini Hospital in Urmia. The patients were clinically evaluated by a gastroenterologist and entered the study after a definitive diagnosis of the disease and after receiving informed consent from them. Patient information was extracted and recorded based on a questionnaire which included age, duration of breastfeeding, time of starting complementary foods, type of complementary foods, time of CD diagnosis, gender, parental education level, birth order, and economic status. Furthermore, data related to the time of onset and diagnosis of the disease, family history, along with demographic information as well as information related to clinical manifestations and severity of CD symptoms based on weight loss, malnutrition, anemia, and diarrhea were extracted from the patient files and entered into SPSS 16. Coding and qualitative analysis were performed in cases where the information was qualitative. Quantitative variables were reported as Mean $\pm$ SD and qualitative variables as frequency (percentage). To examine the relationship between variables, the chi-square statistic and the Eta and Cramer's V correlation tests were used, and  $p < 0.05$  was considered significant.

## Results

120 patients with CD who met the inclusion criteria were examined in this study. 48 (40%) of the patients were male and 72 (60%) were female. The mean age of the patients was reported to be  $22.1 \pm 6.2$  years, with a minimum of 5 years and a maximum of 30 years. The largest number of patients was in the age group of 26 to 30 and the smallest age group of patients was between 5 and 10 years. The results related to the frequency distribution of clinical symptoms of CD with severe pain showed that 50% of them had severe pain, 2.5% of them had severe constipation, 19.2% of them had severe diarrhea, 28.3% of them had severe weight loss, and 40% of them had severe bloating. Moreover, the results of the frequency distribution of the severity of symptoms in CD (maximum severity of symptoms in each individual) showed that 79.2% of them had severe symptoms, 10.8% of them had moderate symptoms, and 10% of them had mild symptoms.

The results of the frequency distribution of the duration of breastfeeding in CD showed that 60% of them were breastfed for 24 months and 23.3% of them were breastfed for 18 months. Furthermore, the frequency distribution of time to initiate complementary feeding showed that 70.8% of them had started complementary feeding at 6 months of age. The results of the frequency distribution of complementary feeding type in CD showed that 51.7% and 17.5% of them had used cow's milk or formula and broth as complementary feeding, respectively. Moreover, the results of the frequency distribution of postnatal feeding type in CD showed that 53.3% of them had used breast milk and 46.7% of them had used formula. The relationship between the duration of breastfeeding and the severity of CD symptoms was calculated using the Chi-square test. The results showed that there was a significant relationship between the duration of breastfeeding and the severity of CD symptoms ( $p < 0.001$ ). The Eta correlation also showed that there was a significant relationship between the duration of breastfeeding and the severity of CD symptoms ( $r = 0.22$ ) (Table 1).

The results showed that there is a significant relationship between the age at onset of the disease and the severity of CD symptoms ( $p < 0.001$ ). Also, the Eta correlation showed that there is a significant relationship between the age at onset of the disease and the severity of CD symptoms ( $r = 0.78$ ). The results of this study show that the older the age at onset of the disease, the greater the severity of CD symptoms (Table 2).

**Table 1. Association between duration of breastfeeding and severity of CD symptoms**

<b>Duration of breastfeeding</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Total</b>
3 months	0	0	3	3
6 months	0	0	3	3
12 months	0	0	3	3
16 months	0	0	7	7
18 months	0	12	16	28
24 months	12	1	59	72
Total	12	13	91	116
Chi-square statistic	21.493			
p-value	<0.001			

**Table 2. Relationship between age at onset and severity of CD symptoms**

<b>Age at onset of the disease</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Total</b>
5-10 years	0	0	23	23
11-15 years	6	3	18	27
16-20 years	3	3	18	24
21-25 years	0	1	20	21
26-30 years	3	6	16	25
Total	12	13	95	120
Chi-square statistic	19.461			
p-value	<0.001			

The results of evaluating the relationship between the time to initiate complementary feeding and the severity of CD symptoms using the Chi-square test showed that there was a significant relationship between these two factors ( $p < 0.001$ ). The Eta correlation also showed that the relationship between the time to initiate complementary feeding and the severity of CD symptoms was significant ( $r = 0.23$ ). Therefore, it can be concluded that later initiation of complementary feeding leads to more severe CD symptoms (Table 3).

A significant relationship was observed between the type of supplementary feeding and the severity of CD symptoms ( $p = 0.024$ ). The results of Cramer's V correlation also showed that this relationship was significant ( $r = 0.38$ ). Also, the results of this study showed that broth as supplementary feeding was more commonly seen in CD with severe symptoms (Table 4).

**Table 3. Relationship between time to initiate complementary feeding and severity of CD symptoms**

<b>Time to initiate complementary feeding</b>	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Total</b>
5 months of age	0	3	0	3
6 months of age	9	7	69	85
12 months of age	0	0	7	7
Total	9	10	76	95
Chi-square statistic	19.568			
p-value	<0.001			

**Table 4. Association between type of supplementary feeding and severity of CD symptoms**

Type of supplementary feeding	Mild	Moderate	Severe	Total
Cow's milk	3	0	4	7
Pudding	0	0	4	4
Broth	0	0	21	21
Cow's milk and broth	3	3	18	24
Cow's milk and formula	0	0	6	6
Total	6	3	53	62
Chi-square statistic	17.641			
p-value	0.024			

## Discussion

According to the results of this study, longer breastfeeding and extended breastfeeding after the introduction of gluten-containing foods delayed the onset of CD. Long-term breastfeeding significantly reduced the risk of CD symptoms during the first year of life. The results of some studies show that breastfeeding duration is the most important predictor of CD progression, which is consistent with the results of this study (30-33). In this study, a significant relationship was found between the age at onset of the disease and the severity of CD symptoms, and accordingly, the older the age at onset, the more severe the CD symptoms. According to some studies, there was no reduction in the risk of CD in infants who were exclusively breastfed compared with those who received formula or mixed milk (30-33). The results of the study by Peters et al. showed that the risk of CD was lower in infants who had ever been breastfed compared with infants who had never been breastfed (33). In a retrospective study, Decker et al. demonstrated that a higher number of children with CD were breastfed compared to controls, which is in contrast with the results of the present study (34).

The role of breastfeeding duration in the prevention of CD has been evaluated in many studies and showed that shorter breastfeeding duration increases the incidence of CD (31-33, 35-37.). However, the results of a study by Ascher et al. were contrary to the results of the present study (38). The results of a study by Ivarsson et al. indicated that gradual introduction of gluten-containing products from the fourth month of life, along with extended breastfeeding, reduces the incidence of CD (29). Vriezinga et al. showed that the cumulative incidence of CD among three-year-old patients was 2.5%, which was similar in the gluten and placebo groups. Moreover, the increased levels of type 2 transglutaminase and Anti-gliadin were similar in the gluten and placebo groups (39). Therefore, breastfeeding, either alone or after the introduction of gluten, did not significantly affect the development of CD. The differences in the results of these studies may be due to the diversity of variables in these studies.

Based on a study by Vajpayee et al., the mean age of patients at the time of CD diagnosis in the breastfed and non-breastfed groups was  $3.68 \pm 1.55$  and  $2.70 \pm 1.65$  years, respectively (40). CD started in 40.42% of patients who had been given gluten-containing foods before 6 months of age, but this rate was 12.58% in children who had been given gluten-containing foods later, which is a significant difference, and is similar and consistent with the results of this study. In the present study, there was a significant relationship between the type of feeding and the time to initiate complementary feeding and the severity of CD symptoms, and broth as a type of complementary feeding was seen more in severe CD symptoms; therefore, the earlier the time to initiate complementary feeding, the greater the severity of CD symptoms.

The results of a study by Jansen et al. demonstrated that starting gluten-containing foods after the age of 6 months does not increase the risk of CD (41). In contrast to the results of the present study, the results of a study by Størdal et al. showed that there was no significant relationship between the type of complementary feeding after infancy and the severity of CD symptoms (17). According to the results, the incidence of CD in children who were given gluten-containing foods at 5 to 6 months of age, after 6 months of age, and before 5 months of age was 3.68, 4.15, and 4.24 per 1000, respectively. They also observed that starting gluten-containing foods later increased the risk of CD, and breastfeeding for more than 12 months was also associated with an increased risk of CD. Ivarsson et al. (38) showed that the risk of CD was lower in children under 2 years of age who were breastfed at the time of gluten introduction, and this risk was lower in children who were breastfed even after gluten introduction. The risk of CD was higher in children whose gluten introduction occurred at a high volume compared to children whose gluten introduction occurred at a low or moderate volume. Some studies have reported that breastfeeding at the time of gluten introduction and longer breastfeeding is associated with a delay and prevention of the disease (35). In a study on children at risk for autoimmune diseases, Norris et al. did not find any protective effect in breast milk (42). D'Amico et al. showed that children with CD who were exclusively breastfed had a delayed onset of disease and a lower rate of severe disease symptoms compared to those who were not exclusively breastfed (43).

The results of this study showed that later initiation of gluten-containing foods along with extended breastfeeding resulted in delayed CD symptoms. Furthermore, in this study, a significant relationship was found between the type of feeding and time to initiate complementary feeding and the severity of CD symptoms. Therefore, according to the results of this study, the gradual initiation of feeding with gluten-containing products along with extended breastfeeding in children reduces the risk of CD.

**Conflict of interest:** The authors of the article have no conflict of interest.

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