



# Celiac Disease Screening in the Siblings of Pediatric Patients with a Confirmed Diagnosis: A Cross-sectional Study

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## Abstract

**Background:** The close relatives of patients with celiac disease (CD), particularly their siblings, are known to be at a higher risk for CD development.

**Objectives:** Our aim was to determine the prevalence of CD in siblings of confirmed CD patients in Lorestan province, Iran, in 2020.

**Methods:** In this cross-sectional study, anti-tissue transglutaminase (tTG) antibody levels were measured in 140 siblings of children with CD. Duodenal biopsies were taken to confirm the diagnosis in those with positive serological tests. The subjects' demographic and clinical data were recorded into a pre-designed questionnaire, and the collected data were analyzed by SPSS software version 22 at a significance level of 0.05.

**Results:** Twelve out of 140 subjects (8.6%) tested positive for tTG IgA, eight of them (66.7%) were girls, and most of them (75%) were  $\leq$  15 years old. Half of the newly diagnosed patients were in the Marsh IIIc category. The Marsh grading had no significant relationship with the serum levels of tTG IgA antibodies ( $P = 0.319$ ). The most common gastrointestinal symptom was bloating (66.7%), and the most common extraintestinal symptoms were anemia (58.3%) and dental and oral diseases (58.3%).

**Conclusions:** We found a high prevalence (8.6%) of CD among the siblings of children with confirmed CD. Since the early diagnosis of CD can lead to better management, particularly in pediatrics, it is recommended screen patients' family members as soon as the diagnosis of CD is confirmed.

**Keywords:** Celiac Disease, Anti-tTG, Screening

## 1. Background

Celiac disease (CD) is an autoimmune disorder of the small intestine, identified by serological and histological characteristics. The disease is predominant in females, and its prevalence is estimated to be around 1:71 in children and 1:357 in adults (1-4). This disorder may present with gastrointestinal symptoms such as diarrhea, abdominal pain, nausea, and vomiting, or extraintestinal manifestations, including failure to thrive, anemia, osteoporosis, delayed puberty, and neuropathy (5). Gluten consumption in genetically susceptible individuals causes an enteropathy leading to villous atrophy and impaired absorption of nutrients (6). In fact, the presence of human leukocyte antigen (HLA) haplotypes of DQ2 and DQ8 is a major risk factor for the incidence of CD (7), increasing the risk of the

disease among the first-degree relatives of patients, especially their siblings (8, 9). The familial occurrence of the disease is reported to range from 2.8% to 22% (10). Therefore, screening CD patients' family members and their siblings, even if they are asymptomatic, is of great importance (8, 11). However, due to the absence of typical gastrointestinal symptoms of CD in children, most (90%) of them may remain undiagnosed (6, 12). Since the risk of growth failure due to CD has been shown to be relatively high in younger children, the diagnosis of CD is of special significance in pediatric patients (13).

The serologic tests that identify anti-tissue transglutaminase IgA antibodies (tTG-IgA) are useful to evaluate patients with suspected CD and are known as the first diagnostic step in this condition (6). Endoscopy and duodenal biopsy evaluation are the gold standard to confirm

the diagnosis of CD in highly suspected patients (14). In terms of histopathological features, duodenal mucosal lesions in CD patients are classified according to the modified Marsh classification (Marsh I, II, and III (a, b, c)), according to which a normal intestinal mucosa is considered to be flat (15, 16). The late diagnosis of the disease and leaving patients untreated may lead to various complications like osteoporosis, infertility, cancer, etc. (5). In regions with a high prevalence of CD, nationwide guidelines are crucial for the early detection and treatment of patients in order to prevent potential drastic complications, including growth retardation in children (13).

Our country, Iran, is among the regions with a high prevalence of CD. A meta-analysis showed that the prevalence of CD among Iranians is about 2% (17). However, there is a scarcity of data on the epidemiological features of CD in Lorestan province, Western Iran.

## 2. Objectives

Owing to the high concordance of CD among the siblings of affected individuals and the importance of the early diagnosis of the disease in these people to prevent its long-term complications, as well as due to the scarcity of data on CD in our province, we aimed to evaluate the prevalence of CD among the siblings of pediatric CD patients in Lorestan province, Iran, in 2020.

## 3. Methods

### 3.1. Study Design and Participants

This cross-sectional study was conducted on 140 siblings (aged 1 to 27 years old) of pediatric patients with confirmed CD (based on clinical presentations, as well as serological and histological findings (referred to the Celiac Disease Clinic of Shahid Rahimi Hospital of Khorramabad city, Lorestan province). Entry criteria included being a sibling of a CD patient, agreement to participate in the study and the absence of gastroenteritis and upper respiratory infections at the time of testing. Exclusion criteria were having chronic infections, already being diagnosed with CD, and IgA deficiency. The minimum sample size was estimated to be 138 individuals according to the following formula. All children who met the inclusion criteria were enrolled until the final sample size was achieved.

$$n = \frac{z\left(1 - \frac{\alpha}{2}\right)^2 p(1-p)}{d^2}$$

$$= 138$$

$$z\left(1 - \frac{\alpha}{2}\right)^2 = 1.96; p = 10\%; q = 90\%; d = 0.05.$$

### 3.2. Ethical Considerations

This study was approved by the Research Ethics Committee of Lorestan University of Medical Sciences with the ethical code of IR.LUMS.REC.1398.250. The importance of the disease and the role of screening tests among first-degree relatives, especially the siblings of CD patients, in the timely diagnosis of the condition were explained to parents. Written informed consent forms were signed by parents. Checklists were designed to collect the data anonymously, and the participants were assured that their personal information would remain confidential.

### 3.3. Serological Screening

Peripheral blood samples from the siblings of children with confirmed CD were collected by a lab technician. Then the serum samples were separated using centrifugation and screened for anti-tissue transglutaminase (anti-tTG) IgA antibodies. Also, total IgA level was measured by an enzyme-linked immunosorbent method using a generic assay kit. For all the participants in this study, anti-tTG IgA antibody was measured at the same laboratory using the same kit. Concentrations of anti-tTG IgA  $\geq 30$  IU/mL were considered positive.

### 3.4. Confirmation of CD by Endoscopy

Subjects with tTGA positivity underwent endoscopic biopsy taking for histopathological evaluations to confirm the diagnosis. Increased intraepithelial lymphocytes (IELs), crypt hyperplasia, and villous atrophy were considered the characteristic features of CD, which were then classified according to the modified Marsh classification (Marsh I, II, and III (a, b, c)) (14-16).

### 3.5. Questionnaire for Data Collection

Upon enrollment, we retrieved the demographic and clinical characteristics of the subjects, like age, sex, height, weight, place of residence, and gastrointestinal and non-gastrointestinal symptoms, into a researcher-made checklist. Weight loss, as a non-gastrointestinal manifestation, was defined as losing  $\geq 5\%$  of body weight within 30 days or losing  $\geq 10\%$  of body weight within 180 days. Children aged  $\geq 12$  years answered the questionnaire mainly by themselves and otherwise, with the support of their parents.

### 3.6. Data Analysis

The data were analyzed using IBM SPSS Version 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). The measures of central tendency and dispersion, as well as tables and graphs, were used to describe quantitative data. The Chi-square test was used to examine the relationship between categorical variables. P-value  $< 0.05$  was considered statistically significant.

## 4. Results

### 4.1. Demographic Characteristics

In the present study, 140 siblings of children with CD in Lorestan province of Iran were screened for the disease. The mean age of the subjects was  $12.6 \pm 6.6$  years, with a minimum age of 1 year and a maximum age of 27 years. Sixty individuals (42.9%) had an age below 10 years, 34 (24.3%) were between 10 and 14 years old; 30 (21.4%) were between 15 and 19 years old, and 16 (11.4%) were  $\geq 20$  years old. In terms of gender, 77 (55%) of the subjects were girls, and 63 (45%) were boys. In terms of the place of residence, most of the participants resided in Khorramabad city (47.8%) (Table 1).

**Table 1.** Frequency Distribution of the Place of Residence in the Studied Population

Variables	Absolute	Relative	Cumulative
<b>Place of residence (city)</b>			
Khorramabad	67	47.8	47.8
Aleshtar	14	10	57.8
Noorabad	8	5.7	63.5
Kuhdasht	27	19.2	82.7
Rumeshkan	11	7.8	90.5
Aligudarz	5	3.6	94.1
Borujerd	3	2.1	96.2
Azna	3	2.1	98.3
Poldokhtar	2	1.7	100

### 4.2. Serologic Findings

Anti-tTG IgA was positive ( $\geq 30$ ) in 12 subjects (8.6%). Out of the 12 subjects with positivity for anti-tTG IgA, eight (66.7%) were girls, and four (33.3%) were boys. Nine of them (75%) were  $\leq 15$  years old, and three (25%) were  $\geq 15$  years old. Also, seven out of the 12 subjects (58.3%) were living in Khorramabad, two (16.7%) in Aleshtar, one (8.3%) in Noorabad, one (8.3%) in Kuhdasht, and one (8.3%) in Aligudarz.

### 4.3. Histological Features

Among 12 subjects with positivity for anti-tTG IgA who underwent duodenal biopsy, the Marsh stage II was detected in two (16.7%), IIIa also in two (16.7%), IIIb in two (16.7%), and IIIc in six (50%) people. This distribution of different Marsh categories had no significant relationship with the serum level of anti-tTG IgA antibodies ( $P = 0.319$ , Table 2).

### 4.4. Clinical Features of Newly Identified Patients

The most common gastrointestinal symptoms of CD patients identified through this screening process were bloating (66.7%) and chronic diarrhea (58.3%). The most common extraintestinal symptoms in these newly-diagnosed patients were anemia (58.3%) and dental and oral problems (58.3%) (Figures 1 and 2).

## 5. Discussion

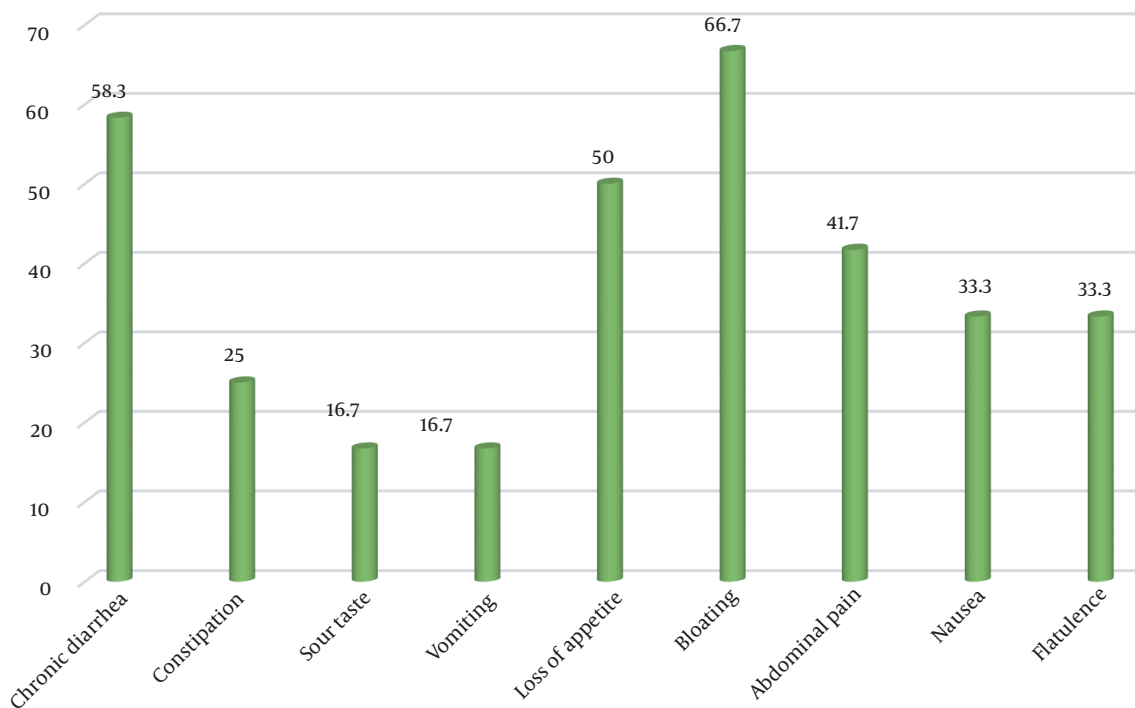
In the present study, 140 siblings of children with CD in Lorestan province were screened for the disease. The results showed a prevalence of 8.6% of CD among these individuals. The prevalence of CD among the relatives of CD patients has been widely investigated; however, the epidemiological patterns vary greatly in different geographical regions. Dogan et al. (18), in a study in Turkey, demonstrated that 7.25% of the siblings of CD patients were diagnosed with CD. Grover and colleagues (19), in a study in North India, reported a prevalence of 15.6% for CD among the siblings of confirmed cases. A similar study conducted by Bardella et al. (10) on an Italian population revealed a significantly higher prevalence of silent CD among the siblings of affected individuals. In a recent study, 23.8% of the patients' siblings were diagnosed with CD.

In our study, 66.7% of the siblings who tested positive for anti-tTG IgA were girls, and 75% of whom were  $\leq 15$  years old. Tapsas et al., in a study on a pediatric population, reported that the majority of the patients identified through screening were between five and 14.9 years old (20). This is consistent with the findings of our study. The higher susceptibility of females to CD has also been reported in several studies (21-23). Nevertheless, Bardella et al. (10) found that male siblings of CD patients were affected in 40.9% of cases, while this rate was 26.9% among female siblings. The female predominance may be justified by a combination of genetic factors, such as gene variants residing on X chromosome, as well as other underlying factors, including pregnancy and menstruation, which affect intestinal permeability (23).

In the present study, the typical gastrointestinal symptoms of CD in the newly-identified patients included bloating, chronic diarrhea, and abdominal pain, which are mainly caused by villous atrophy in the small intestine, which was in accordance with previous research findings. Also, CD can present with non-gastrointestinal signs and symptoms, from a slight elevation in transaminases to hepatic failure and even liver cancer (24). The most common extraintestinal symptoms in our patients were anemia, dental and oral problems, skin rashes, and headache. It has been reported that the presence of extraintestinal

**Table 2.** The Frequency Distribution of Anti-tTG Ab Levels in the Siblings of Children with Confirmed Coeliac Disease According to Marsh Classification<sup>a</sup>

Marsh Stage	tTG Ab Levels				Total	P-Value
	30 to 99	100 to 199	200 to 299	300 ≤		
Marsh II	2 (100)	0 (0)	0 (0)	0 (0)	2 (100)	0.319 <sup>b</sup>
Marsh IIIa	0 (0)	0 (0)	1 (50)	1 (50)	2 (100)	
Marsh IIIb	0 (0)	0 (0)	2 (100)	2 (100)	2 (100)	
Marsh IIIc	3 (50)	1 (16.7)	1 (16.7)	1 (16.7)	6 (100)	

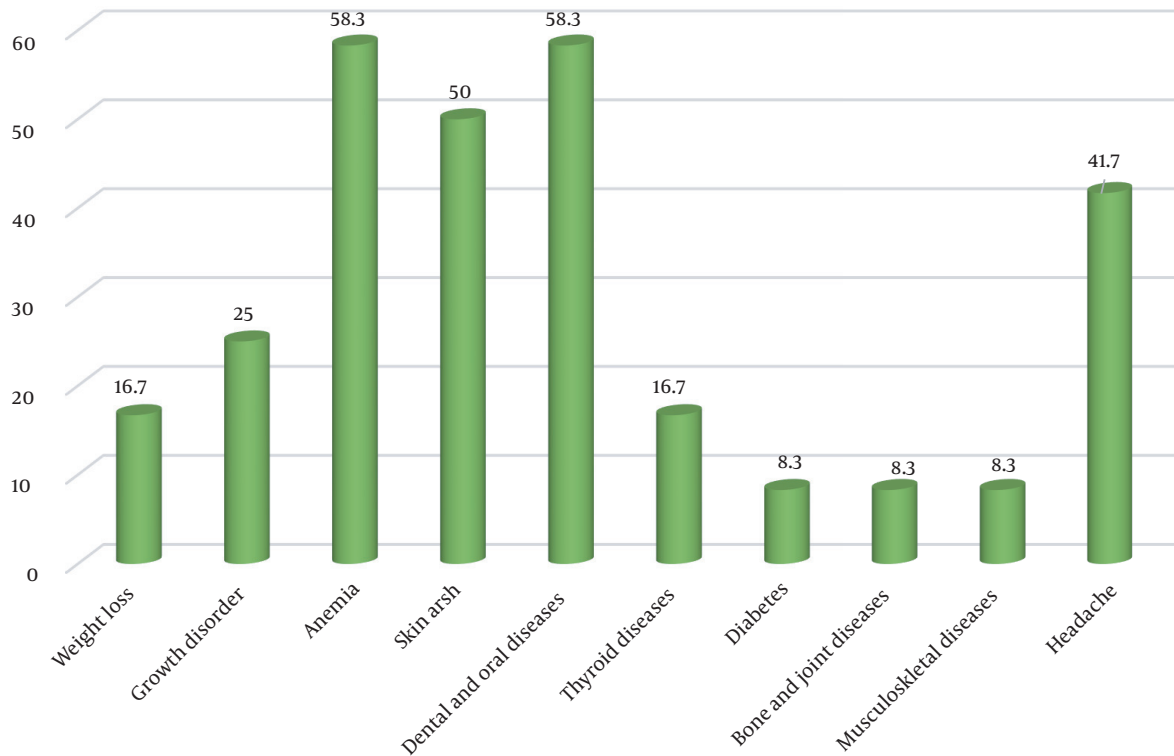
<sup>a</sup> Values are expressed as No. (%).<sup>b</sup> Chi-square test**Figure 1.** Frequency of gastrointestinal symptoms in the studied population.

manifestations is associated with more severe villous atrophy (25). Previous studies have also reported a variety of extraintestinal symptoms in CD patients, including growth retardation as the most frequent extraintestinal manifestation in pediatric populations (26). Children with growth failure have been assumed to be younger and have lower hemoglobin and higher levels of autoantibodies (13). Other studies have reported anemia, fatigue, and headache as the most common extraintestinal manifestations in children with CD (26-28).

Some manifestations of CD such as vomiting and anemia are assumed to occur more frequently in patients with higher histological grades (i.e., Marsh IIIb and IIIc) (29).

Our results showed that half of the newly-diagnosed patients were in the Marsh IIIc stage, indicating disease progression to the final stages of the disease, increasing the possibility of the presence of other CD-related complications.

Overall, genetic predisposition (carrying HLA DQ2 and/or DQ8 haplotypes) is an essential risk factor for the incidence of CD (30). However, despite the high risk of CD among the close relatives of patients, the concordance of CD varies from 49 to 83% among monozygotic twins. Furthermore, non-HLA genetic factors have been confirmed to contribute to the incidence of CD. In western societies, about 40% of the overall population carry one or both of



**Figure 2.** Frequency of extraintestinal symptoms in the studied population.

HLA-DQ2/HLA-DQ8 haplotypes; however, only 1% of these people develop CD (31). These findings suggest a role for environmental factors in the development of this disease (9, 32). Therefore, screening the close relatives of known CD cases, even if they are asymptomatic, is crucial to prevent the progression of the disease to late stages and modify environmental risk factors contributing to disease aggravation in high-risk groups (33-35).

### 5.1. Limitations

A number of limitations can be noted for this study. Some parents of CD patients did not agree to have their healthy children screened for CD, so they were not included in the study. Furthermore, as the studied population mostly consisted of children, we had difficulty collecting their subjective symptoms.

### 5.2. Conclusions

In conclusion, we found a high prevalence (8.6%) of CD among the siblings of CD patients in Lorestan province of Iran. Since the early diagnosis of CD can lead to its better management, particularly in pediatrics, it is recommended to perform screening tests for patients' family

members, especially their siblings, as soon as a patient is diagnosed. This approach can help prevent serious complications such as growth failure. It is advisable to conduct similar studies in other provinces of the country to help the health care system better allocate services to susceptible individuals.

### Footnotes

**Authors' Contribution:** Dr. Shokoufeh Ahmadipour conceptualized and designed the study; Dr. Mohammad Rostami Nejad critically reviewed the manuscript for important intellectual content; Dr. Saba Soleimani collected the data; Dr. Golnaz Mahmoudvand drafted the initial manuscript; Dr. Khatereh Anbari analyzed the data, and Mr. Arian Karimi Rouzbahani coordinated data collection and finalized the manuscript. All authors read and approved the final manuscript.

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**Data Reproducibility:** The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to ethical considerations.

**Ethical Approval:** This study was approved by the Research Ethics Committee of Lorestan University of Medical Sciences with the ethical code IR.LUMS.REC.1398.250. (Link: [ethics.research.ac.ir/ProposalCertificate.php?id=110132](https://ethics.research.ac.ir/ProposalCertificate.php?id=110132))

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**Informed Consent:** The importance of the disease and screening tests among the first-degree relatives, especially siblings, of CD patients were explained to parents, and they were requested to sign a written informed consent form.

## References

- Caio G, Volta U, Sapone A, Leffler DA, De Giorgio R, Catassi C, et al. Celiac disease: a comprehensive current review. *BMC Med*. 2019;**17**(1):142. [PubMed ID: 31331324]. [PubMed Central ID: PMC6647104]. <https://doi.org/10.1186/s12916-019-1380-z>.
- Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2018;**16**(6):823–836 e2. [PubMed ID: 29551598]. <https://doi.org/10.1016/j.cgh.2017.06.037>.
- Taheri M, Sabzali S, Hakim A, Sajadi N, Hakimzade M, Ziaiekajbaf T, et al. The prevalence of celiac disease in children with unexplained failure to thrive in South West of Iran. *Int J Pediatr*. 2017;**5**(4):4663–9.
- Mariné M, Farre C, Alsina M, Vilar P, Cortijo M, Salas A, et al. The prevalence of coeliac disease is significantly higher in children compared with adults. *Aliment Pharmacol Ther*. 2011;**33**(4):477–86. <https://doi.org/10.1111/j.1365-2036.2010.04543.x>.
- Sahin Y. Celiac disease in children: A review of the literature. *World J Clin Pediatr*. 2021;**10**(4):53–71. [PubMed ID: 34316439]. [PubMed Central ID: PMC8290992]. <https://doi.org/10.5409/wjcp.v10.i4.53>.
- Parzanese I, Qehajaj D, Patrinicola F, Aralica M, Chiriva-Internati M, Stifter S, et al. Celiac disease: From pathophysiology to treatment. *World J Gastrointest Pathophysiol*. 2017;**8**(2):27–38. [PubMed ID: 28573065]. [PubMed Central ID: PMC5437500]. <https://doi.org/10.4291/wjgp.v8.i2.27>.
- Dieli-Crimi R, Cenit MC, Nunez C. The genetics of celiac disease: A comprehensive review of clinical implications. *J Autoimmun*. 2015;**64**:26–41. [PubMed ID: 26194613]. <https://doi.org/10.1016/j.jaut.2015.07.003>.
- Wessels MMS, de Rooij N, Roovers L, Verhage J, de Vries W, Mearin ML. Towards an individual screening strategy for first-degree relatives of celiac patients. *Eur J Pediatr*. 2018;**177**(11):1585–92. [PubMed ID: 29974211]. <https://doi.org/10.1007/s00431-018-3199-6>.
- Singh P, Arora S, Lal S, Strand TA, Makharia GK. Risk of Celiac Disease in the First- and Second-Degree Relatives of Patients With Celiac Disease: A Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2015;**110**(11):1539–48. [PubMed ID: 26416192]. <https://doi.org/10.1038/ajg.2015.296>.
- Bardella MT, Elli L, Velio P, Fredella C, Prampolini L, Cesana B. Silent celiac disease is frequent in the siblings of newly diagnosed celiac patients. *Digestion*. 2007;**75**(4):182–7. [PubMed ID: 17848794]. <https://doi.org/10.1159/000107979>.
- Goldberg D, Kryszak D, Fasano A, Green PH. Screening for celiac disease in family members: is follow-up testing necessary? *Dig Dis Sci*. 2007;**52**(4):1082–6. [PubMed ID: 17380406]. <https://doi.org/10.1007/s10620-006-9518-1>.
- Whitburn J, Rao SR, Paul SP, Sandhu BK. Diagnosis of celiac disease is being missed in over 80% of children particularly in those from socioeconomically deprived backgrounds. *Eur J Pediatr*. 2021;**180**(6):1941–6. [PubMed ID: 33569662]. <https://doi.org/10.1007/s00431-021-03974-8>.
- Nurminen S, Kivela L, Taavela J, Huhtala H, Maki M, Kaukinen K, et al. Factors associated with growth disturbance at celiac disease diagnosis in children: a retrospective cohort study. *BMC Gastroenterol*. 2015;**15**:1–8. [PubMed ID: 26438321]. [PubMed Central ID: PMC4595273]. <https://doi.org/10.1186/s12876-015-0357-4>.
- Garnier-Lengline H, Cerf-Bensussan N, Ruemmele FM. Celiac disease in children. *Clin Res Hepatol Gastroenterol*. 2015;**39**(5):544–51. [PubMed ID: 26186878]. <https://doi.org/10.1016/j.clinre.2015.05.024>.
- Marsh NM, Johnson WM, Rostami K. Mucosal histopathology in celiac disease: a rebuttal of Oberhuber's sub-division of Marsh III. *Gastroenterol Hepatol Bed Bench*. 2015;**8**(2):99–109. [PubMed ID: 25926934]. [PubMed Central ID: PMC4403022].
- Pena AS. What is the best histopathological classification for celiac disease? Does it matter? *Gastroenterol Hepatol Bed Bench*. 2015;**8**(4):239–43. [PubMed ID: 26468342]. [PubMed Central ID: PMC4600512].
- Mohammadibakhsh R, Sohrabi R, Salemi M, Mirghaed MT, Behzadifar M. Celiac disease in Iran: a systematic review and meta-analysis. *Electron Physician*. 2017;**9**(3):3883–95. [PubMed ID: 28461861]. [PubMed Central ID: PMC5407219]. <https://doi.org/10.19082/3883>.
- Dogan Y, Yildirimaz S, Ozercan IH. Prevalence of celiac disease among first-degree relatives of patients with celiac disease. *J Pediatr Gastroenterol Nutr*. 2012;**55**(2):205–8. [PubMed ID: 22241509]. <https://doi.org/10.1097/MPG.0b013e318249378c>.
- Grover R, Puri AS, Aggarwal N, Sakhuja P. Familial prevalence among first-degree relatives of celiac disease in North India. *Dig Liver Dis*. 2007;**39**(10):903–7. [PubMed ID: 17723324]. <https://doi.org/10.1016/j.dld.2007.07.161>.
- Tapsas D, Hollen E, Stenhammar L, Falth-Magnusson K. The clinical presentation of coeliac disease in 1030 Swedish children: Changing features over the past four decades. *Dig Liver Dis*. 2016;**48**(1):16–22. [PubMed ID: 26520057]. <https://doi.org/10.1016/j.dld.2015.09.018>.
- Meijer CR, Auricchio R, Putter H, Castillejo G, Crespo P, Gyimesi J, et al. Prediction Models for Celiac Disease Development in Children From High-Risk Families: Data From the PreventCD Cohort. *Gastroenterology*. 2022;**163**(2):426–36. [PubMed ID: 35487291]. <https://doi.org/10.1053/j.gastro.2022.04.030>.
- Kotze L, Kotze LR, Moreno I, Nisihara R. Immune Mediated Diseases in Patients with Celiac Disease and Their Relatives: A Comparative Study of Age and Sex. *Arq Gastroenterol*. 2018;**55**(4):346–51. [PubMed ID: 30785517]. <https://doi.org/10.1590/S0004-2803.201800000-77>.
- Jansson-Knodell CL, Hujoel IA, West CP, Taneja V, Prokop LJ, Rubio-Tapia A, et al. Sex Difference in Celiac Disease in Undiagnosed Populations: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2019;**17**(10):1954–1968 e13. [PubMed ID: 30448593]. <https://doi.org/10.1016/j.cgh.2018.11.013>.
- Shannahan S, Leffler DA. Diagnosis and Updates in Celiac Disease. *Gastrointest Endosc Clin N Am*. 2017;**27**(1):79–92. [PubMed ID: 27908520]. <https://doi.org/10.1016/j.giec.2016.08.011>.
- Jericho H, Guandalini S. Extra-Intestinal Manifestation of Celiac Disease in Children. *Nutrients*. 2018;**10**(6). [PubMed ID: 29895731]. [PubMed Central ID: PMC6024684]. <https://doi.org/10.3390/nu10060755>.

26. Laurikka P, Nurminen S, Kivela L, Kurppa K. Extraintestinal Manifestations of Celiac Disease: Early Detection for Better Long-Term Outcomes. *Nutrients*. 2018;**10**(8). [PubMed ID: 30081502]. [PubMed Central ID: PMC6115849]. <https://doi.org/10.3390/nu10081015>.
27. Nurminen S, Kivela L, Huhtala H, Kaukinen K, Kurppa K. Extraintestinal manifestations were common in children with coeliac disease and were more prevalent in patients with more severe clinical and histological presentation. *Acta Paediatr*. 2019;**108**(4):681-7. [PubMed ID: 29569302]. <https://doi.org/10.1111/apa.14324>.
28. Jericho H, Sansotta N, Guandalini S. Extraintestinal Manifestations of Celiac Disease: Effectiveness of the Gluten-Free Diet. *J Pediatr Gastroenterol Nutr*. 2017;**65**(1):75-9. [PubMed ID: 28644353]. <https://doi.org/10.1097/MPG.0000000000001420>.
29. Demircioglu F, Unal F, Bekdas M. Investigation of celiac disease according to Marsh classification in childhood. *Bangladesh J Med Sci*. 2017;**16**(2):259-65. <https://doi.org/10.3329/bjms.v16i2.26700>.
30. Pascual V, Medrano LM, Lopez-Palacios N, Bodas A, Dema B, Fernandez-Arquero M, et al. Different Gene Expression Signatures in Children and Adults with Celiac Disease. *PLoS One*. 2016;**11**(2). e0146276. [PubMed ID: 26859134]. [PubMed Central ID: PMC4747499]. <https://doi.org/10.1371/journal.pone.0146276>.
31. Medrano LM, Dema B, Lopez-Larios A, Maluenda C, Bodas A, Lopez-Palacios N, et al. HLA and celiac disease susceptibility: new genetic factors bring open questions about the HLA influence and gene-dosage effects. *PLoS One*. 2012;**7**(10). e48403. [PubMed ID: 23119005]. [PubMed Central ID: PMC3485232]. <https://doi.org/10.1371/journal.pone.0048403>.
32. Lebowitz B, Rubio-Tapia A. Epidemiology, Presentation, and Diagnosis of Celiac Disease. *Gastroenterology*. 2021;**160**(1):63-75. [PubMed ID: 32950520]. <https://doi.org/10.1053/j.gastro.2020.06.098>.
33. Nellikkal SS, Hafeed Y, Larson JJ, Murray JA, Absah I. High Prevalence of Celiac Disease Among Screened First-Degree Relatives. *Mayo Clin Proc*. 2019;**94**(9):1807-13. [PubMed ID: 31447136]. <https://doi.org/10.1016/j.mayocp.2019.03.027>.
34. Kauma S, Kaukinen K, Huhtala H, Kivela L, Pekki H, Salmi T, et al. The Phenotype of Celiac Disease Has Low Concordance between Siblings, Despite a Similar Distribution of HLA Haplotypes. *Nutrients*. 2019;**11**(2). [PubMed ID: 30823533]. [PubMed Central ID: PMC6412523]. <https://doi.org/10.3390/nu11020479>.
35. Mishra A, Prakash S, Kaur G, Sreenivas V, Ahuja V, Gupta SD, et al. Prevalence of celiac disease among first-degree relatives of Indian celiac disease patients. *Dig Liver Dis*. 2016;**48**(3):255-9. [PubMed ID: 26691992]. <https://doi.org/10.1016/j.dld.2015.11.007>.