Nutrition and Food Sciences Research Vol 8, No 1, Jan-Mar 2021, pages:29-34

Original Article

Clinical and Laboratory Surveys of the Iranian Celiac Patients

Manoochehr Karami[1], Behrooz Afshar [2], Alireza Monsef Esfahani [3], Bashirian Saeed [4], Leyla Halimi[5]*

1- Associate Professor of Epidemiology, Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran

2- Assistant Professor of Gastroenterology and Hepatology, Department of Internal Medicine, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

3- Professor of Pathology, Department of Pathology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

4-Associate Professor of Health Education and Promotion, Department of Public Health, School of Health, Hamadan University of Medical Sciences, Hamadan, Iran

5- Researcher in Clinical Research Development Unit of Shahid Beheshti Hospital, Hamadan University of Medical Science, Hamadan, Iran

Received: July 2020 **Accepted:** September 2020

ABSTRACT

Background and Objectives: As an autoimmune disease, celiac is triggered by exposure to dietary gluten in genetically susceptible individuals, leading to various gastrointestinal and non-gastrointestinal symptoms. The aim of the current study was to accurately investigate epidemiology of the celiac disease in Hamadan Province, Iran.

Materials and Methods: This study was carried out as a case series at Hamadan University of Medical Sciences, Hamadan, Iran, 2016–2018. The participants were selected using census method. Data analysis was carried out using SPSS Software v.18 and descriptive statistics.

Results: From 72 participants, 68.1% were females and 31.9% were males. In addition, the mean age of the participants was 32.47 y ±17.21; 15.27% of them had known genetic backgrounds. Serological results revealed that 47% of the participants had tTG antibody. Based on the disease severity classification, the highest frequency (57%) was linked to Marsh III. Furthermore, 10% of celiac patients were simultaneously diagnosed with diabetes.

Conclusions: In this study, celiac was mostly diagnosed in young to middle-age people (30–40 y), the majority of whom were females. It seems that the incidence of diabetes and CD is one of the most significant health problems in the province. High severity of the disease (Marsh III) was important as well. Of the disease symptoms, gastrointestinal symptoms were more common; from which, diarrhea and abdominal pain were more common. In non-gastrointestinal symptoms, anemia was the most common symptom.

Keywords: Clinical and laboratory characteristics, Celiac disease (CD), Gluten, Transglutaminase, Diet, Anemia

Introduction

Prior to the 20th century, celiac disease (CD) was considered relatively rare in most European countries(1). Using sensitive non-invasive screening tests for CD, it is now possible to detect CD in people. The widespread use of serological tests in screening programs has proven that CD includes various clinical manifestations (2). In fact, CD may vary by ethnicity, which is due to genetic and environmental factors seen in all sexes and ages(3, 4). As an autoimmune disease, CD is triggered by exposure to dietary gluten in genetically susceptible individuals, leading to various gastrointestinal and non-gastrointestinal symptoms(1). In addition, clinical manifestations of the disease vary from asymptomatic manifestations found by routine screening assays of autoimmune disorders to symptomatic manifestations such as diarrhea, constipation and anemia(2, 3). These symptoms may overlap with those of gastrointestinal and non-gastrointestinal diseases(4). Autoimmune diseases such as type I diabetes and thyroid are more common in CD patients(4). Therefore, CD patients are often screened for pathologies linked to their disease(5). Due to differences in reported statistics, clinical and laboratory differences between the patients, subclinical statuses of the disease and lack of appropriate study in Hamadan Province, Eastern Iran, the current study was designed to further precisely assess epidemiology of the disease in the province. Hopefully, findings can be used to

***Address for correspondence:** Leyla Halimi, Researcher in Clinical Research Development Unit of Shahid Beheshti Hospital, Hamadan University of Medical Science, Hamadan, Iran. E-mail address: lhhalimi20@yahoo.com

describe effective strategies for the diagnosis and treatment of CD.

Materials and Methods

This study was carried out as a case series in a specialized clinic of Hamedan University of Medical Sciences, 2016–2018. Inclusion criteria were willingness to participate in the study and diagnosed sensitivity to gluten. Exclusion criterion was the lack of willingness to participate in the study. The CD patients were identified and selected via census sampling. Laboratory information of the patients were collected after serological assessments, assessing severity of the disease through pathological diagnosis based on the endoscopic biopsy specimens. Extracted data were recorded in a checklist modified by Iran Celiac Association used in previous studies. In serological assessments, the reference range for tTG-IgA assay was 0–20 U and scores more than 20 were considered positive. In general, anti-tTG antibodies are highly sensitive and specific for the diagnosis of CD (sensitivity of 90–98% and specificity of 95–97%)(6). In pathological studies, four samples were collected from the duodenum part (D1 and D2) and results were reported based on modified Marsh classification (Marsh IIIa–c). Generally, diagnosis of CD autoimmune pathology relied on the subjective histological assignment of biopsies into Marsh score categories(7).

Data analysis was carried out using SPSS Software v.18 (IBM Analytics, USA) and descriptive statistics. Non-digestive symptoms included anemia (defined as hemoglobin in women < 120 g/l and in men < 130 g/l), stress, depression, fatigue, dermatitis herpetiformis, osteoporosis, dental problems, thyroid problems, headache, musculoskeletal pain in arms and legs, cardiovascular diseases, hair loss, weight loss (≥ 5% weight loss over past 3 m or ≥ 10% weight loss over past 6 m), seizure, fever, allergy and diabetes (fasting plasma glucose ≥ 126 mg/dl or 7.0 mmol/l; fasting was defined as no caloric intakes for at least 8 h). Gastrointestinal symptoms included anorexia, abdominal pain, constipation, diarrhea (more than 3 times per day), nausea, vomiting, vomiting blood and flatulence. A pathologist and one of the investigators reviewed all biopsies. The severity of intestinal damages was graded based on the scale proposed by Oberhuber et al., including PVA (partial villous atrophy, Marsh IIIa), STVA (subtotal villous atrophy, Marsh IIIb) and TVA (total villous atrophy, Marsh IIIc)(8).

Results

From 72 patients, 49 were females (68.1%) and 23 were males (31.9%). In addition, the minimum and the maximum ages of the participants included three and 65 years, respectively. The mean age of the participants was 32.47 y ±17.21. Regarding marital status, 33 participants were single (45.9%), 36 were married (50%) and three were divorced (4.2%). Moreover, 15.27% of the participants had known genetic backgrounds. Regarding educational level, 10% of the participants were illiterated, 61% had non-academic degrees and 29% had academic degrees. Assessments of the serological results revealed that 47% of the participants had positive tTG antibodies. Based on the modified Marsh classification, the highest frequency (57%) was linked to Marsh III, where 36% were linked to March IIIa intensity (Table 1).

Table 1. Results of the frequency distribution of the disease scopes based on the villous atrophy in celiac patients

Variable	*n*	%
Normal	4	5.6
Marsh I	5	6.9
Marsh II	16	22.2
Marsh IIIa	26	36.1
Marsh IIIb	11	15.3
Marsh IIIc	4	5.6
Unknown	6	3.8
Total	72	100

Patients' complaints varied and were compared between gastrointestinal and non-gastrointestinal groups (Tables 2 and 3). Nearly 40.3% of the CD patients were diagnosed with anemia (Table 3).

Table 2. Frequency distribution of gastrointestinal symptoms in celiac patients from Hamedan Province

Variable	N	%
Abdominal pain		
Yes	24	33.3
No	48	66.7
Total	72	100
Constipation		
Yes	14	19.4
No	58	80.6
Total	72	100
Diarrhea		
Yes	23	31.9
No	49	68.1
Total	72	100
Nausea		
Yes	10	13.9
No	62	86.1
Total	72	100
Vomiting		
Yes	9	12.5
No	63	87.5
Total	72	100
Vomiting blood		
Yes	2	2.8
No	70	97.2
Total	72	100
anorexia		
Yes	2	2.8
No	70	97.2
Total	72	100
Flatulence		
Yes	11	15.3
No	61	84.7
Total	72	100

Table 3. Frequency distribution of non-gastrointestinal symptoms in celiac patients from Hamedan Province

Variable	*n*	%
Anemia		
Yes	29	40.3
No	43	59.7
Total	72	100
Stress		
Yes	6	8.3
No	66	91.7
Total	72	100
Depression		
Yes	2	2.8
No	70	97.2
Total	72	100
Fatigue		
Yes	6	8.3
No	66	91.7
Total	72	100
Dermatitis herpetiformis		
Yes	3	4.2
No	69	95.8
Total	72	100
Osteoporosis		
Yes	1	1.4
No	71	98.6
Total	72	100
Dental problems		
Yes	2	2.8
No	70	97.2
Total	72	100
Thyroid problems		
Yes	2	2.8
No	70	97.2
Total	72	100
Headache		
Yes	6	8.3
No	66	91.7
Total	72	100
Musculoskeletal pain in arms and legs		
Yes	1	1.4
No	71	98.6
Total	72	100
Cardiovascular diseases		
Yes	2	2.8
No	70	97.2
Total	72	100
Hair loss		
Yes	2	2.8
No	70	97.2
Total	72	100
Weight loss		
Yes	12	16.7
No	60	83.3
Total	72	100
Seizure		
Yes	1	1.4
No	71	98.6
Total	72	100
Fever		
Yes	1	1.4
No	71	98.6
Total	72	100
Allergy		
Yes	1	1.4
No	71	98.6
Total	72	100

In total, 10% of the CD patients were simultaneously diagnosed with diabetes (Table 4). To investigate frequency of CD patients based on the period between the onset of symptoms and definite diagnosis of the disease by a physician, the highest frequency included 1–3 m (39%) and 10–12 m (21%).

Table 4. Frequency distribution of simultaneous diagnosis of diabetes in celiac patients

Variable	*n*	%
Normal	65	90.2
Type I	4	5.55
Type II	3	4.16
Total	72	100

Discussion

In the present study, frequency of the disease was two times higher in women, compared to men (68% vs. 32%), which was similar to the results of similar studies in Iran. In a study by Ale Taha et al., a higher prevalence of CD in women was reported, compared to men. Female to male ratio of the disease was reported 1:2 to 1:3 in various studies(9). Indeed, CD can occur at any age and is common in childhood, adolescence and adulthood. In the present study, the lowest and the highest ages of the patients included three and 65 years, respectively, and the most common age group of these patients was 30–40 years with a mean of 37.8 years. Rresults of other studies showed that 20% of the patients were aged more than 60 years when diagnosed with the disease(10-12). In a study by Shahbazkhani et al., the mean age of CD patients was 39.79 y ±16.77(13). Ahmadi et al. reported the mean age of CD patients as 34.57 y ±1.24(14). While findings from the present study were similar to other studies, Khoshnia demonstrated that the mean age of CD patients was 50 years(15). Serological results of CD patients showed that most of the serological evidence were associated to TTG-IgA (47%). In fact, tissue transglutaminase is the target antigen for the production of antibodies with high sensitivity and specificity. In addition, relationships are reported between the presence of these antibodies and the degree of villous atrophy(16, 17). Assessing epidemiology of CD in Iran, Nejad et al. (2011) showed necessity of carrying out serological tests in high-risk groups in developing countries for the initial diagnosis of CD. In European and Eastern Mediterranean countries, the disease includes no specific and common symptoms. Furthermore, wheat is a major nutritional component in Iran. Exposure to wheat proteins induces immune tolerance and hence develops emergence of milder symptoms, which may be confused with other gastrointestinal disorders(18).

In the present study, severity of the disease was higher based on the pathology as 57% of patients had Marsh III. However, further studies are needed to prove the level of CD severity in Hamedan Province. Similar results were

reported by Khoshnia et al. in Gonbad, Iran(15). In the current study, 15% of the CD patients had genetic backgrounds. Moreover, CD was diagnosed in 5–12 cases with Down Syndrome. The CD was associated with Turner and Williams syndromes, low immunoglobulin A and other autoimmune disorders as well (19-21). Regarding coincidence of diabetes and CD, nearly 10% of the CD patients had diabetes, 6% of whom had type I and 4% had type II diabetes. Results of similar studies revealed a higher percentage of coincidence CD and diabetes in Hamedan Province. In a study by Shahbazkhani et al., results showed a relatively high prevalence of CD in patients with diabetes type I (2.4%), compared to the general population (1.66%)(22). The coincidence of diabetes and CD has been reported in studies from other countries(23). Furthermore, CD was diagnosed in 3–5% of patients with diabetes type II(24, 25).

Based on the clinical symptoms of the disease, gastrointestinal symptoms were more common, compared to non-gastrointestinal symptoms. In addition, abdominal pain (33%) and diarrhea (32%) were the most prevalent gastrointestinal symptoms, whereas anemia (40%) included the highest frequency within non-gastrointestinal symptoms. Since iron deficiency anemia is a common finding in CD, focusing on this symptom can greatly help physicians diagnose the disease. Prevalence of CD in primary care patients presenting gastrointestinal symptoms is 2–4% (26-28). In addition to patients with positive family histories of CD, patients with longstanding or refractory abdominal symptoms from several case-finding studies appear to verify this fact (26, 29, 30). In a study by Khoshnia et al., abdominal bloating and diarrhea were the most common symptoms, respectively, and non-gastrointestinal symptoms were present in more than half of the patients(15). The clinical manifestations of CD vary with the patient's age, as well as the duration and extent of the disease. Various forms of the disease are characterized by diarrhea, failure to thrive, loss of appetite and muscle weakness. However, adults may have diarrhea as a major symptom of CD(31). Based on the studies in Iran and Iraq, CD was accounted for approximately 20% of the cases of chronic diarrhea in adults(32, 33). In another study in Kuwait, CD was the cause of chronic diarrhea in 20% of children(34). In developing countries, patients with chronic diarrhea or iron deficiency anemia should clinically be suspicious of CD.

In the present study, patients varied greatly regarding the time distance between the emergence of symptoms and a definitive diagnosis, Delays sometimes ranged 1–3 m, 1–3 y and over 3 y, reported at 38.9 and 20.8 as well as 1.11 and 9.7, respectively. Low clinical suspicions by the Iranian physicians have led to less diagnoses of CD for several years(35-37). For example, Shahbazkhani et al. showed that up to 12% of patients with irritable bowel disease (IBD) had CD(36). In the present study, despite that 40.3% of CD patients had anemia, no significant relationships were found with severity of the disease based on the Marsh classification system(p = 0.82) and with tTG antibody-IgA(p = 0.32). Iron deficiency anemia is a known manifestation of CD in adults and can be the only manifestation of this disease(38). Akbari et al. reported anemia in 52% of Iranian adult patients at the time of CD diagnosis, regardless of their histological Marsh graded (39). Based on the findings of the present study, CD is quite common in patients with iron deficiency (nearly half of the patients) and can be considered as one of the underlying causes of iron-deficiency anemia with unknown causes.

Limitations

Limitations of the present study included lack of ontime diagnosis of CD and lack of using similar protocols by internal medicine and gastrointestinal specialists and pediatricians. Various clinical manifestations of the disease were reported in various individuals.

Conclusions

In this study, celiac was mostly diagnosed in young to middle-age people (30–40 year-old), a majority of whom were females. In addition, it seems that the incidence of diabetes and CD is one of the most significant problems linked to the disease in the province. It is noteworthy that the disease was highly severe (Marsh III). Of the disease symptoms, gastrointestinal symptoms were more common; from which, diarrhea and abdominal pain were more common. In non-gastrointestinal symptoms, anemia was the most common symptom.

Acknowledgement

This article was extracted from a research study with ethical code of IR.UMSHA.REC.1397.653. Information are published grouply with no names or details of the patients are used. The authors express their gratitudes to the Vice-Chancellor for Research and Technology of Hamadan University of Medical Sciences and the Clinical Research Development Unit of Shahid Beheshti Hospital for their helps in this study. The authors declare no conflicts of interest.

Financial disclosure

The authors declare no financial interests.

Funding/Support

The current study was supported by Clinical Research Development Unit of Shahid Beheshti Hospital**,** Hamadan University of Medical Sciences.

References

1. Kelly CP, Bai JC, Liu E, Leffler DA. Advances in diagnosis and management of celiac disease. Gastroenterology. 2015;148(6):1175-86.

2. Rastogi A, Bhadada SK, Bhansali A, Kochhar R, Santosh R. Celiac disease: a missed cause of metabolic bone disease. Indian journal of endocrinology and metabolism. 2012;16(5):780.
3. Dieterich W, Ehnis T, Bauer M, Donner P, Volta U, Riecken EO, et al. Identification of tissue transglutaminase as the autoantigen of celiac disease. Nature medicine. 1997;3(7):797.
4. Mogul D, Nakamura Y, Seo J, Blauvelt B, Bridges JF. The unknown burden and cost of celiac disease in the US. Expert review of pharmacoeconomics & outcomes research. 2017;17(2):181-8.
5. Biagi F, Gobbi P, Marchese A, Borsotti E, Zingone F, Ciacci C, et al. Low incidence but poor prognosis of complicated coeliac disease: a retrospective multicentre study. Digestive and Liver Disease. 2014;46(3):227-30.
6. Hopper AD, Hadjivassiliou M, Hurlstone DP, Lobo AJ, McAlindon ME, Egner W, et al. What is the role of serologic testing in celiac disease? A prospective, biopsy-confirmed study with economic analysis. Clinical Gastroenterology and Hepatology. 2008;6(3):314-20.
7. Charlesworth RPG, Agnew LL, Scott DR, Andronicos NM. Celiac disease gene expression data can be used to classify biopsies along the Marsh score severity scale. Journal of Gastroenterology and Hepatology.34(1):169-77.
8. Oberhuber G. Histopathology of celiac disease. Biomedicine & pharmacotherapy. 2000;54(7):368-72.
9. Aletaha N, POURSHAMS A, Shahbazkhani B. Celiac Disease. 2007.
10. Catassi C, Rätsch I, Fabiani E, Rossini M, Coppa G, Giorgi P, et al. Coeliac disease in the year 2000: exploring the iceberg. The Lancet. 1994;343(8891):200-3.
11. Green PH, Jabri B. Coeliac disease. The Lancet. 2003;362(9381):383-91.
12. James MW, Scott BB. Coeliac disease: the cause of the various associated disorders? European journal of gastroenterology & hepatology. 2001;13(9):1119-21.
13. Shahbazkhani B, Mehrabi G, Nasiritosi M, Forotan H, Asefirad S. Celiac disease in cryptogenic hypertransaminasemia. Tehran University Medical Journal. 2010;68(7).
14. Ahmadi B, Zaherara M. Prevalence of celiac disease in patients with irritable bowel syndrome in Kerman. Iran J Kerman Univ Med Sci. 2015;20(3):319-27.
15. Khoshnia M, Pourshams A, Mohammadkhani A, Tavangar S, Shahbazkhani B, Malekzadeh R. Celiac disease in gonbad-kavoos. Govaresh. 2012;10(3):131-3.
16. Akbari MR, Mohammadkhani A, Fakheri H, Zahedi MJ, Shahbazkhani B, Nouraie M, et al. Screening of the adult population in Iran for coeliac disease: comparison of the tissue-transglutaminase antibody and anti-endomysial antibody tests. European journal of gastroenterology & hepatology. 2006;18(11):1181-6.
17. Tursi A, Brandimarte G, Giorgetti GM. Prevalence of antitissue transglutaminase antibodies in different degrees of intestinal damage in celiac disease. Journal of clinical gastroenterology. 2003;36(3):219-21.
18. Nejad MR, Rostami K, Emami MH, Zali MR, Malekzadeh R. Epidemiology of celiac disease in Iran: a review. Middle East Journal of Digestive Diseases. 2011;3(1):5.
19. Collin P, Kaukinen K, Välimäki M, Salmi J. Endocrinological disorders and celiac disease. Endocrine reviews. 2002;23(4):464-83.
20. Greco L, Romino R, Coto I, Di Cosmo N, Percopo S, Maglio M, et al. The first large population based twin study of coeliac disease. Gut. 2002;50(5):624-8.
21. O'leary C, Walsh C, Wieneke P, O'regan P, Buckley B, O'halloran D, et al. Coeliac disease and autoimmune Addison's disease: a clinical pitfall. Qjm. 2002;95(2):79-82.
22. Sheikholeslami H BK, Hashemipoor S, Hadjmanoochehri F, Ziaii A. COMPARING FREQUENCY OF CELIAC DISEASE IN PATIENTS WITH DIABETES MELLITUS TYPE I AND NON-DIABETIC , HEALTHY PERSONS. Iranian Journal of Diabetes and Metabolism. 2005;4(3):49-55.
23. Schuppan D, Hahn EG. Celiac disease and its link to type 1 diabetes mellitus. Journal of Pediatric Endocrinology and Metabolism. 2001;14(Supplement):597-606.
24. Al-Ashwal AA, Shabib SM, Sakati NA, Attia NA. Prevalence and characteristics of celiac disease in type 1 diabetes mellitus in Saudi Arabia. Saudi medical journal. 2003;24(10):1113-5.
25. Shahbazkhani B, Faezi T, Akbari M, Mohamadnejad M, Sotoudeh M, Rajab A, et al. Coeliac disease in Iranian type I diabetic patients. Digestive and liver disease. 2004;36(3):191-4.
26. Catassi C, Kryszak D, Louis-Jacques O, Duerksen DR, Hill I, Crowe SE, et al. Detection of celiac disease in primary care: a multicenter case-finding study in North America. American Journal of Gastroenterology. 2007;102(7):1454-60.
27. Collin P, Rasmussen M, Kyr¶npalo S, Laippala P, Kaukinen K. The hunt for coeliac disease in primary care. Qjm. 2002;95(2):75-7.
28. Hin H, Bird G, Peter F, Mahy N, Jewell D. Coeliac disease in primary care: case finding study. Bmj. 1999;318(7177):164-7.
29. Berti I, Della Vedova R, Paduano R, Devetta M, Caradonna M, Villanacci V, et al. Coeliac disease in primary care: evaluation of a case-finding strategy. Digestive and Liver Disease. 2006;38(7):461-7.
30. Sanders DS, Patel D, Stephenson TJ, Ward AM, McCloskey EV, Hadjivassiliou M, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. European journal of gastroenterology & hepatology. 2003;15(4):407-13.
31. Rawashdeh M, Khalil B, Raweily E. Celiac disease in Arabs. Journal of pediatric gastroenterology and nutrition. 1996;23(4):415-8.
32. Qari FA. Clinical presentation of adult celiac disease in Western Saudi Arabia. Saudi medical journal. 2002;23(12):1514-7.
33. Rostami K, Shahbazkhani B, Malekzadeh R. Microenteropathy; the entity of the new millennium. Overview of the second asian symposium on coeliac disease, October 18-21, 2003, Tehran. Romanian journal of gastroenterology. 2004;13(1):29.
34. Sima H, Hekmatdoost A, Ghaziani T. Seroprevalence of coelic disease among autoimmune and HBV chronic hepatitis in Tehran Iran. Govaresh. 2003;7:237.

35. Nasr K, Haghighi P, Abadi P, Lahimgarzadeh A, Hedayati H, Halstead J, et al. Idiopathic enteropathy: an evaluation in rural Iran with an appraisal of nutrient loss. The American journal of clinical nutrition. 1976;29(2):169-76.

36. Shahbazkhani B, Forootan M, Merat S, Akbari M, Nasserimoghadam S, Vahedi H, et al. Coeliac disease presenting with symptoms of irritable bowel syndrome. Alimentary pharmacology & therapeutics. 2003;18(2):231-5.

37. Shahbazkhani B, Malekzadeh R, Sotoudeh M, Moghadam KF, Farhadi M, Ansari R, et al. High prevalence of coeliac disease in apparently healthy Iranian blood donors. European journal of gastroenterology & hepatology. 2003;15(5):475-8.

38. Nikpour Sh MHE. Prevalence of Celiac Disease in Patients with Idiopathic Iron Deficiency of Referred to Gastroenterology Clinic. Journal of Isfahan Medical School.25(84):10-5.

39. Akbari MR MA, Fakheri H, Javad Zahedi, M SB, Nouraie M, et al. Screening of the adult population in Iran for coeliac disease: comparison of the tissue-transglutaminase antibody and anti-endomysial antibody tests. Eur J Gastroenterol Hepatol 2006;18(11):1181-6.