Original Article

The Prevalence of Celiac Disease in Northern Iran

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ABSTRACT

Background:
Celiac disease is a small bowel disorder that occurs upon exposure to dietary gluten and is followed by reduced absorption capacity of the intestine. Serological tests are usually used to assess the prevalence of the disease; however, serological tests without pathological results cannot give a precise assessment. In this regard, we attempted to determine the prevalence of celiac disease in the northern regions of Iran by performing a biopsy among adults with positive serological tests.

Materials and Methods:
This was a population-based cross-sectional study. Serum level of tissue transglutaminase IgA (or, tTg-IgA) was assessed in 5148 individuals, and those with a positive serological test (serum anti-tTG IgA > 20 IU/mL) underwent a biopsy during upper gastrointestinal (GI) endoscopy. Symptoms and other accompanying disorders were also assessed in this study.

Results:
Among the 5148 participants, 23 patients (12 men) had positive anti-tTG IgA test (0.4%) with a mean age of 45.90 ± 12.45 years. The most common symptoms among the 23 individuals were abdominal distension (100%), abdominal pain (78.26%), chronic constipation (60.86%), and three (13.04%) of them had iron deficiency. 16 individuals out of the 23 accepted to undergo a biopsy during upper GI endoscopy. The pathology results showed that eight (four men) of them had biopsy-proven celiac disease (0.15%). The second serum IgA anti-tTG test was negative in individuals with negative pathologies.

Conclusion:
The prevalence of celiac disease in Northern Iran was 0.4% and 0.15% based on serological and pathological results, respectively. Half of the patients with positive serum IgA anti-tTG test had negative pathological results, indicating the need to rely on a pathological assessment for a definite diagnosis.

Keywords: Celiac disease, Prevalence, Serology, Pathology

Please cite this paper as:
Mehrabi S, Nikkhah M, Ajdarkosh H, Motamed N, Khoonsari M, Faraji A, et al. The prevalence of celiac disease in northern Iran. *Govaresh* 2023;28: 176-182.

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Received: 14 Apr. 2023
Revised: 11 Sep. 2023
Accepted: 12 Sep. 2023

INTRODUCTION

Celiac disease, also known as gluten-sensitive enteropathy, is an autoimmune disorder. In people who are genetically predisposed to celiac disease, eating gluten, which is part of the structure of many grains, can damage the intestinal mucosa with an unsafe immune response. In this disease, the intestinal villi are destroyed, and the absorption capacity of the intestine is reduced. The disease has a variety of clinical manifestations and may occur at any age. The average age of diagnosis is between the 4th and 6th decades of life, although 20% of patients are over the age of 60 at the time of diagnosis (1-3). Epidemiologically, until a decade ago, celiac disease was considered a rare disease. Today, various studies have shown that this disease is common and can be seen in all races (4); however, the prevalence of the disease in epidemiological estimates is lower than the actual prevalence (5). Celiac disease is similar to a floating iceberg, the peak of which is people with a classic illness, and much of the floating mountain, where patients are without obvious symptoms, is unknown (2). The highest prevalence of the disease has been reported in Western Europe (1%) (6). The prevalence of celiac disease in the United States is comparable to that in Western Europe, but epidemiological information is scarce in some parts of Asia. In Central Asia, the prevalence of celiac disease in people who are not at risk is similar to that in Western countries (7-9). In Iran, the prevalence of this disease in the general population, taking into account various studies, is about 1% (8, 10, 11). An epidemiological study on a population of healthy blood donors in Tehran, Iran, reported that one out of every 166 healthy blood donors had celiac disease (8). In a comprehensive study conducted jointly by Tehran, Kerman, and Mazandaran Universities of Medical Sciences, one in 104 people had celiac disease, and more than 52% of them had iron deficiency anemia (10).

In most of the previous studies, serological tests were used to assess the prevalence of celiac disease in Iran. However, serological tests cannot give a precise assessment of the disease prevalence. In this regard, we attempted to determine the prevalence of celiac disease in the northern region of Iran, Amol, by performing a biopsy among adults with positive serological tests.

MATERIALS AND METHODS

This population-based cross-sectional study was conducted on Amol Cohort Study regarding gastrointestinal disorders. The details of Amol Cohort Study were completely explained in another article (12), but in brief, this study was carried out in Amol, a city in the northern area of Iran, in two different periods: 2009-2010 (phase 1) and 2016-2017 (phase 2). The study subjects were selected from 25 rural and 16 urban primary health care (PHC) centers among those aged between 10-90 years old. Then, the subjects were stratified into 16 strata based on their sex and age with 10-year intervals of 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80-89. The selection of study subjects in each stratum was done using a simple randomization method proportional to the population size in the same stratum.

In the second phase of the Cohort Study, serum samples extracted from 10-hour fasting venous blood were used to measure the anti-tissue-transglutaminase antibody IgA (anti-tTG IgA) serum level of the participants, using AESKUL ELISA kit, Germany. The measurement conditions (the type of the kit and the laboratory) were the same for all samples and were done shortly after blood sampling. The cut-off point of 20 (IU/mL) was considered to detect positive anti-tTG IgA, and individuals with positive serology results were invited for endoscopic duodenal biopsy.

Participants with positive anti-tTG IgA test filled out a questionnaire containing data about concomitant diseases (DM type 1, vitiligo, herpetic dermatitis, Down syndrome, iron deficiency anemia, and other autoimmune disease), first-degree family history of celiac disease, symptoms (abdominal pain, distension of abdomen, chronic diarrhea and constipation, weight loss, nausea, and vomiting).

Ethics

Approval for the study was granted by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (approval number IR.IUMS.FMD.REC.1399.596). Written informed consent was obtained from all subjects.

Statistical analysis

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables

and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using a t-test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using the Chi-square test. P values ≤ 0.05 were considered statistically significant. For the statistical analysis, the statistical software SPSS version 23.0 for Windows (IBM, Armonk, New York) was used.

RESULTS

Among 5148 individuals included in this study (56.8% men, mean age: 46.91±15.87), 23 (52.2% men, mean age: 45.90±12.45] had positive anti-tTG IgA with the mean serum level of 58.17±51.32 (IU/mL) and the range of 20-200 IU/mL.

The most prevalent symptoms among these 23 patients were distension (100%), abdominal pain (78.26%), and chronic constipation (60.86%). Chronic diarrhea, nausea/vomiting, and weight loss were also present in 34.78%, 13.04%, and 8.69% of them, respectively. Prevalence of iron deficiency and type 1 diabetes were 13.04% and 4.34%, respectively, and 8.69% of them had a first-degree family history of celiac disease.

All 23 patients were invited for biopsy sampling and pathological evaluation, but seven patients missed their endoscopy appointment. The prevalence of abdominal pain (28.6% vs. 100%, P=0.001) was significantly less, and the prevalence of chronic constipation (100% vs. 43.8%, P=0.019) was significantly more among the seven individuals who missed the pathological test compared with those who took the test, but the prevalence of other symptoms, concomitant diseases, first-degree family history of celiac disease, mean age, anti-tTG IgA serum level, and sex distribution were not significantly different (Table 1).

Among the 16 patients who underwent biopsy, pathology classification based on the Marcs criterion showed that eight cases (50%) were negative. Anti-tTG IgA serum level was double-checked in five negative pathologies, and the serological responses were negative in all of them.

Among the eight patients with positive pathology, one patient (12.5%) was Marsh II, three patients (37.5%) were Marsh IIIA, one patient (12.5%) was Marsh IIIB, and three patients (37.5%) were Marsh IIIC (Figure 1). Sex distribution was the same in both groups with positive and negative pathologies, but the group with positive pathology was significantly younger than the group with negative pathology (40.00±11.01 vs 54.43±8.867, P=0.019). There were no significant differences in the prevalence of symptoms, concomitant diseases, first-degree family history of celiac disease, and the first mean anti-tTG IgA serum level between the positive and negative pathological tests (Table 1).

DISCUSSION

In this study, the prevalence of celiac disease in the northern regions of Iran (Amol) was assessed by performing a biopsy sample among adults with positive serological tests. According to the results, the prevalence of celiac disease based on a positive serological test (considering the cut-off point of 20 IU/mL for serum IgA anti-tTG level) was estimated to be 0.44%. In other words, one out of 227 individuals in the study population (5148 people) had celiac disease according to the positive serological test, with the ratio of men to women being 1.09. However, according to positive biopsy results, the prevalence of celiac disease was estimated to be 0.15% (approximately 1 in 667 individuals), with the same prevalence in both sexes. The most prevalent Marsh categories were IIIA and IIIC.

According to our findings, 50% of individuals with positive serological tests had negative pathological results. This indicates the lack of optimal sensitivity of serum IgA anti-tTG level (with the cut-off point of 20 IU/mL) in the definitive diagnosis of celiac disease.

In a study conducted in Sari in 2003, out of 1,438 people evaluated for celiac disease, 12 cases were positive based on pathology results. These results indicate a prevalence of 0.8% for celiac disease. The ratio of males to females was 1.0, the mean age was 37.8 years, and only one person was in Marsh III's classification. So, the prevalence of celiac disease in this study is more than five-fold higher compared with our study, who were younger, with lower stages of the disease, and with the same sex distribution (13).

Table 1. Characteristics of the 23 individuals with a positive serological test

	Pathology			*P* value Positive vs. Negative Pathology	*P* value With vs. Without Pathology
	Positive Pathology N = 8	Negative Pathology N = 8	Without Pathology (N = 7)		
Sex N (%)					
Men	4 (50)	4 (50)	4 (57.1)	1.00	1.00
Women	4 (50)	4 (50)	3 (42.9)		
Age, year (mean ± SD)	40.00 ± 11.01	54.43 ± 8.867	43.29 ± 13.561	0.019	0.51
Anti-tTG IgA serum level	73.87 ± 59.39	44.62 ± 25.24	55.71 ± 64.94	0.22	0.88
Pathological grade					
II	1 (12.5)	-	-	-	-
IIIA	3 (37.5)	-	-	-	-
IIIB	1 (12.5)	-	-	-	-
IIIC	3 (37.5)	-	-	-	-
Symptoms N (%)					
Abdominal distension	8 (100)	8 (100)	7 (100)	-	-
Abdominal pain	8 (100)	8 (100)	2 (28.5)	-	0.001
Chronic constipation	4 (50)	3 (37.5)	7 (100)	1.00	0.019
Chronic diarrhea	4 (50)	4 (50)	0 (0)	1.00	0.052
Nausea/vomiting	1 (12.5)	0 (0)	2 (28.5)	1.00	0.209
Weight loss	1 (12.5)	0 (0)	1 (14.28)	1.00	0.52
Concomitant diseases N (%)					
Iron deficiency	2 (25)	0 (0)	1 (14.28)	0.46	1.00
Down syndrome	0 (0)	0 (0)	2 (28.5)	-	0.083
Diabetes mellitus type1	1 (12.5)	0 (0)	0 (0)	1.00	1.00
Vitiligo	0 (0)	0 (0)	0 (0)	-	-
Herpetic dermatitis	0 (0)	0 (0)	0 (0)	-	-
First-degree family history of celiac disease N (%)	1 (12.5)	1 (12.5)	0 (0)	1.00	1.00

Marsh II: crypt hyperplasia increased/normal villi
Marsh IIIA: crypt hyperplasia increased/mild atrophy villi
Marsh IIIB: crypt hyperplasia increased/marked atrophy villi
Marsh IIIC: crypt hyperplasia increased /complete atrophy villi
Anti-tTG IgA: Tissue Transglutaminase antibody

Another study was performed in Golestan province in 2005 on 2547 individuals. Based on serum IgA anti-tTG level, 28 (1.1%) individuals had celiac disease. They were predominantly men (with a ratio of 5 to 1) with an average age of 30 years. The prevalence of celiac disease in this study was far above the prevalence observed in our study (more than 2.5-fold higher based on serological results), and in contrast to our findings, the disease was more prevalent in men (14).

In another research, Khoshnia and others (2005) randomly selected adult residents of Gonbad Kavous and surrounding villages. Among 1209 participants, 12 subjects (0.9%) had a positive serological test. Pathological results showed that nine (0.74%) were positive, with more prevalence in women, and about 50% of pathologies were in Marsh III's classification. Based

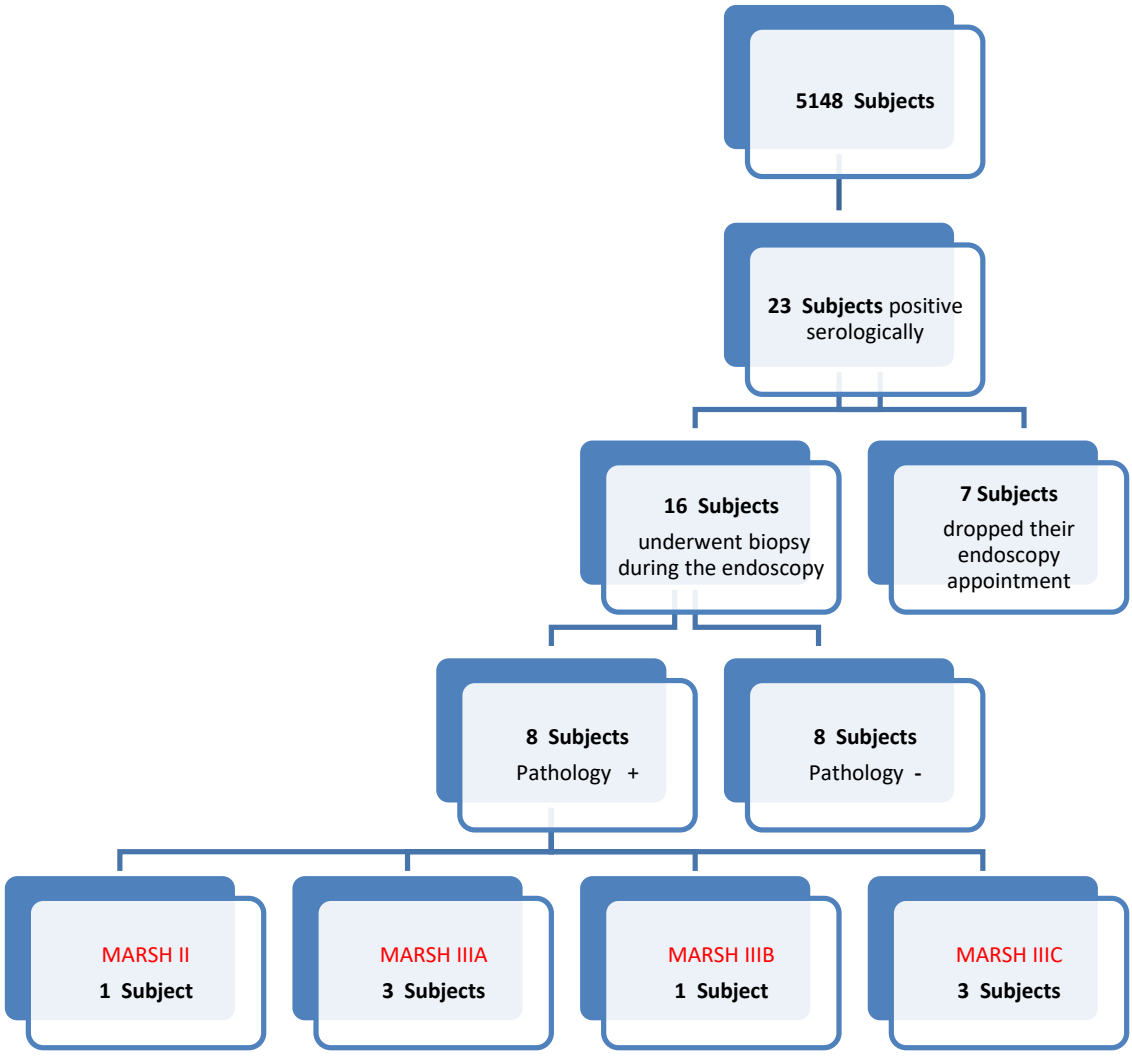

Figure 1. Enrolment of study participants

on pathological results, the prevalence of celiac disease in this study is nearly 5-fold compared with our findings and is more prevalent in women which is in contrast to our results. Most of them had gastrointestinal symptoms, and the most prevalent Marsh category was Marsh III, which is similar to our findings (11).

In a systematic review and meta-analysis of 275818 individuals worldwide, the prevalence of celiac disease based on serological and biopsy results were 1.4% and 0.7%, respectively. The prevalence values were 0.4% in South America, 0.5% in Africa and North America, 0.6% in Asia, and 0.8% in Europe and Oceania based on pathological results. The prevalence was also higher in women (15). These results are much higher than our findings, and their sex distribution (with more prevalence in women) is different. Another systematic review and meta-analysis of 4070 articles also showed a higher risk for celiac disease in women than men identified through general population screening, with the pooled prevalence of undetected celiac disease of 0.589% in women and 0.415% in men (16), while in our study the prevalence was the same in both sexes.

Another finding of this study is that all patients had gastrointestinal symptoms, and abdominal distension, abdominal pain, and chronic constipation were the most common symptoms. This is similar to the findings of

other studies in Iran. Khoshniya and others reported that 83% of patients with celiac disease in Gonbad Kavoos had gastrointestinal symptoms (11). The results were similar in Sari (13) and Kerman (10). However these results are in contrast to the findings of other countries in which most of the patients were asymptomatic or had weak symptoms (17, 18).

Altogether, according to our study, the prevalence of celiac disease in Amol and its surroundings is lower than previously reported in most of the studies. The cut-off point of 20 IU/mL for serum IgA anti-tTG level might have missed some of the cases, but on the other hand, some of the positive serological tests ended up in negative pathologies. Considering the fact that the second serum IgA anti-tTG test was negative in individuals with negative pathologies, once measurement of serum IgA anti-tTG level might not be a good marker of celiac diagnosis. The inaccuracy of the kits used in this study or the laboratory procedure may also be other reasons for these results, though.

CONCLUSION

The present study on the Northern Iranian population showed a 0.4% and 0.15% prevalence of celiac disease based on serological and pathological results, respectively. More than half of the patients with positive serum IgA anti-tTG test had negative pathological results, indicating the need to rely on a pathological assessment for a definite diagnosis.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. James MW, Scott BB. Coeliac disease: the cause of the various associated disorders? *Eur J Gastroenterol Hepatol* 2001;13(9):1119-21. doi: 10.1097/00042737-200109000-00022
2. Catassi C, Rätsch IM, Fabiani E, Rossini M, Bordicchia F, Candela F, et al. Coeliac disease in the year 2000: exploring the iceberg. *Lancet* 1994;343(8891):200-3. doi: 10.1016/s0140-6736(94)90989-x
3. Bürgin-Wolff A, Hadziselimovic F. Coeliac disease. *Lancet* 2003;362(9393):1418-9. doi: 10.1016/s0140-6736(03)14653-3
4. 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):823-36.e2. doi: 10.1016/j.cgh.2017.06.037
5. Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. *World J Gastroenterol* 2012;18(42):6036-59. doi: 10.3748/wjg.v18.i42.6036
6. Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med* 2010;42(8):587-95. doi: 10.3109/07853890.2010.505931
7. Shamir R, Lerner A, Shinar E, Lahat N, Sobel E, Bar-or R, et al. The use of a single serological marker underestimates the prevalence of celiac disease in Israel: a study of blood donors. *Am J Gastroenterol* 2002;97(10):2589-94. doi: 10.1111/j.1572-0241.2002.06028.x
8. 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. *Eur J Gastroenterol Hepatol* 2003;15(5):475-8. doi: 10.1097/01.meg.0000059118.41030.96
9. Qari FA. Clinical presentation of adult celiac disease in Western Saudi Arabia. *Saudi Med J* 2002;23(12):1514-7.
10. 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. *Eur J Gastroenterol Hepatol* 2006;18(11):1181-6. doi: 10.1097/01.meg.0000224477.51428.32
11. Khoshnia M, Pourshams A, Mohammadkhani A, Tavangar SM, Shahbazkhani B, Malekzadeh R. Celiac disease in Gonbad-Kavoos. *Govaresh* 2012;10(3):131-3. [Persian].
12. Motamed N, Faraji AH, Khonsari MR, Maadi M, Safarnezhad Tameshke F, Keyvani H, et al. Fatty liver index (FLI) and prediction of new cases of non-alcoholic fatty liver disease: a population-based study of northern Iran. *Clin Nutr* 2020;39(2):468-74. doi: 10.1016/j.clnu.2019.02.024
13. Tirgar-Fakheri H, Malekzadeh R, Akbari MR, Sotoudeh M. Prevalence of celiac disease in north of Iran: screening of an adult population in Sari. *J Gorgan Univ Med Sci* 2004;6:94-100. [Persian].
14. Joshaghani HR, Semnani S, Mirrezaei SA, Abdolahi N, Besharat S, Behnampour N, et al. Seroepidemiology of celiac disease among blood donor in Golestan province. *J Gorgan Univ Med Sci* 2006;8(3):44-7. [Persian].
15. Singh P, Arora S, Singh A, Strand TA, Makharia GK. Prevalence of celiac disease in Asia: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2016;31(6):1095-101. doi: 10.1111/jgh.13270
16. 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):1954-68.e13. doi: 10.1016/j.cgh.2018.11.013

17. Malekzadeh R, Sachdev A, Fahid Ali A. Coeliac disease in developing countries: Middle East, India and North Africa. *Best Pract Res Clin Gastroenterol* 2005;19(3):351-8. doi: 10.1016/j.bpg.2005.01.004
18. Rostami K, Malekzadeh R, Shahbazkhani B, Akbari MR, Catassi C. Coeliac disease in Middle Eastern countries: a challenge for the evolutionary history of this complex disorder? *Dig Liver Dis* 2004;36(10):694-7. doi: 10.1016/j.dld.2004.05.010