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The seroprevalence of celiac disease in patients with symptoms of irritable bowel syndrome: A cross-sectional study in north of Iran

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Abstract.
BACKGROUND: Celiac disease (CD) is a common cause of malabsorption that is definitively diagnosed by abnormal bowel biopsy, symptoms and histologic changes to gluten free diet. The symptoms of irritable bowel syndrome (IBS) are common in our community as the majority of people in Guilan, north of Iran, consume rice daily. Also, a number of celiac patients are unknown, and IBS are mistakenly diagnosed.
OBJECTIVE: This study aimed to evaluate the prevalence of CD among IBS patients.
METHODS: A total of 475 consecutive patients with IBS, confirmed by Rome IV, underwent celiac serological tests antitissue transglutaminase antibodies (IgA-tTG, IgG-tTG) after obtaining a written consent form. In case of positive serological tests, biopsy was performed from small intestine after endoscopy
RESULTS: Thirty-one (6.53%, 95% CI: 4.55–9.22) patients were positive for celiac serology. Based on Marsh-Oberhuber criteria, out of 9 patients with positive pathology 77.78% (95% CI: 40.19–96.05) had marsh IIIc. In IBS patients cramp (0.009) and stomach fullness (0.021) were two statistically significant IBS symptoms.
CONCLUSIONS: We suggest physicians to consider celiac examinations for all patients with IBS symptoms, even for patients with no obvious celiac symptoms.

Keywords: Celiac disease, IgA-tTG, irritable bowel syndrome, Screening, immunocytochemistry

1. Introduction

Celiac disease (CD) is an autoimmune disease that can cause symptoms similar to irritable bowel syndrome (IBS) in the gastrointestinal (GI) tract [23,26,27]. Its prevalence is estimated at 0.7% in the western population [10,40,42] Overall; the incidence has been significantly rising in the latter half of the 20th century and into the 21st century [16,24,37]. Knowledge of CD

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has increased over the last several decades, but most patients with CD remain undiagnosed [9,18,46]. CD has a wide range of clinical manifestations and common symptoms outside the GI tract [12,18,35]. CD is increasingly recognized in the Middle Eastern and North African [1,11,35,38]. According to a systematic review and meta-analysis, a high prevalence for CD among Iranian IBS patients has been stated, which is higher than global estimates [5]. Further, it is clinically prevalent in children in North Africa [11,35], where the prevalence of positive antiendomysial antibodies (EMA-IgA) was reported to be 5.6% among 989 children. In addition, in South Asia it is presented as both typical and atypical [6,35]. Most adults with CD had symptoms of diarrhea before 1980 [32,35,39]. With the advent of serological tests in the 1980s, a wide range of clinical manifestations were identified. Among children, it has a variety of manifestations, which are characterized by factors such as age of onset and disease duration. Much younger children often develop classic CD, which is characterized by diarrhea, abdominal distension, and developmental disorder [35]. Furthermore, it is linked to other conditions, such as diabetes, herpetic dermatitis, osteoporosis, infertility, small bowel adenocarcinoma and lymphoma, but not limited to these [8,10]. It is known as small intestinal mucosal enteropathy, usually graded according to Marsh-Oberhuber criteria and can range from intra-epithelial lymphocytes (grade 1) to widespread lesions with crypt hyperplasia (grade 2) as well as varying degrees of villus atrophy (grade 3) [13,46]. In children, mucosal lesions may have a patchy distribution which are sometimes located only in the duodenal bulb [34,46]. CD occurs when a susceptible patient is genetically exposed to gluten. The vast majority of people with CD have HLA-DQ2 or HLA-DQ8 human leukocyte antigens, and these HLA haplotypes appear to be present. The center of the pathophysiological basis of CD is through presentation of gluten peptides to CD4 T cells in the small intestinal mucosa. Presentation of these peptides can activate intra-epithelial lymphocytes and eventually lead to damage to the intestinal epithelium in the form of villus atrophy. It eventually develops symptoms of the GI tract, which in many cases can mimic IBS. While much has been thought about the pathophysiology of CD, much remains to be discovered. For example, why do some people with CD develop clear clinical symptoms despite gluten intake? Although CD should be considered in the differential diagnosis of patients with IBS symptoms, it is not clear whether its prevalence in patients with IBS is sufficient to warrant routine screening [10,29]. The sensitivity and specificity of serologic tests for CD in the diagnosis of untreated disease are higher or close to 95%, which places them among the small number of first-line trials for autoimmune and inflammatory disorders [25]. In 1997, tTG was introduced as an autoimmune CD gene [14,25], which was allowed to develop an Elisa-based test that prevented major difficulties in diagnosing patients with antibody immunofluorescence [25]. The first step in the screening and diagnosis of celiac serologic markers evaluation is antitissue transglutaminase antibodies (IgA-tTG) and a possible second step of EMA. The sensitivity and specificity of both methods are high [46]. It is worth noting that the EMA test has a slightly higher specificity because low levels of IgA-tTG can occur for reasons unrelated to CD. However, this possibility is very low for EMA [41]. Numerous studies of symptomatic CD patients have shown a poor correlation between lower levels of IgA-tTG and intestinal enteropathy [36,45]. In contrast, other studies have shown that high levels of IgA-tTG ($>$ 100 U/mL) are highly specific for grade 3 Marsh lesions [15,30]. To the best of our knowledge so far, according to the recent metanalysis, prevalence of positive celiac serology and biopsy-proven CD shown to be significantly higher in subjects with symptoms suggestive of IBS in comparison to healthy controls. However, it seems that the utility of screening for CD in individuals with suspected IBS requires further studies [22]. Since IBS-like symptoms are common in the community where many people with CD consume rice in their daily diet predominantly, IBS may be misdiagnosed for IBS-like symptoms. So, we decided to do a real study of the disease. Given that the disease is a major health problem in our country, therefore our physicians should be aware of this dilemma, given the fact that early detection and its subsequent treatment may have potential complications. This study will provide a pathway for greater knowledge to correctly identify CD patients, to prevent its complications as far as possible.

2. Methods

In this cross-sectional study out of 2000 patients with IBS like symptoms, 475 IBS patients, (250 female, 20–70 years old, with mean age 40.42 $\pm$ 12.25 yr) who were confirmed by ROME IV, were enrolled during January 2018 and February 2019 at Gastrointestinal and Liver Diseases Research Center, Rasht, Iran.

2.1. Inclusion and exclusion criteria

Based on inclusion criteria (IBS-related dyspepsia symptoms based on ROME IV criteria, one of the fol-

Table 1
Determination of seroprevalence of Serum antibodies and pathology outcomes in terms of gender

Serum antibodies and pathology outcomes	Male n (%)	Female n (%)	Total n (%)	P-value
Serum antibody ttG-IgA				
Positive	6 (2.7)	8 (3.2)	14 (2.9)	0.791
Negative	219 (97.3)	242 (96.8)	461 (97.1)	
Serum antibody ttG-IgG				
Positive	11 (4.9)	8 (3.2)	19 (4)	0.360
Negative	214 (95.1)	242 (96.8)	456 (96)	
Pathology result				
Positive	4 (26.7)	5 (31.25)	9 (29)	0.990
Negative	11 (73.3)	11 (68.75)	2 (71)	

lowings in the absence of structural evidence, gastrointestinal functional symptoms, anemia, IBS-like Symptoms, osteoporosis, chronic diarrhea, weight loss, bloating, malabsorption, allergy to bread gluten) and exclusion criteria (well-known celiac disease, gastrointestinal cancers). In addition, variables such as age, gender, occupation, comorbidities (diabetes, hypertension, thyroid diseases, and autoimmune diseases), and family history of celiac disease were recorded for each patient.

2.2. Measurements

Serologic tests for celiac including IgA-tTG, IgG-tTG were requested. Both serum IgA-tTG and IgG-tTG (LIAISON,Germany) were measured by Chemiluminescent (CL) from blood samples (2cc). Other 2cc blood was taken for cell blood count differential (CBC diff). Seropositivity was defined when one or more of measured antibody tests were positive, and all patients with at least one positive serologic test (Anti IgA-tTG $\geqslant$ 8 IgG-tTG $\geqslant$ 10 DU/ML) considering cardiac and medicine conditions endoscopy was performed after 8 hours of fasting. Four biopsy specimens were collected from the second part of the duodenum and 1 specimen from the duodenum bulb. The specimens were placed in 10% formalin and delivered to a single laboratory. The biopsy findings were classified by Marsh-Oberhuber criteria [4].

2.3. Ethical consideration

The study was approved by the Ethical Committee of Guilan University of Medical Sciences, Rasht, Iran (Ethical code: IR.GUMS.REC.1396.531). Written informed consent was obtained from all subjects.

2.4. Statistical analysis

The data were analyzed by chi- square test. The calculated prevalence was presented with a 95% confidence interval (CI). Continuous data having normal distribution are presented in means $\pm$ SD, and categorical data are presented in frequency rate and percentage. For all statistical analyses, a two-tailed P value < 0.05 was considered significant. All analyzes were performed in (SPSS 18, Chicago, Ill., USA) software.

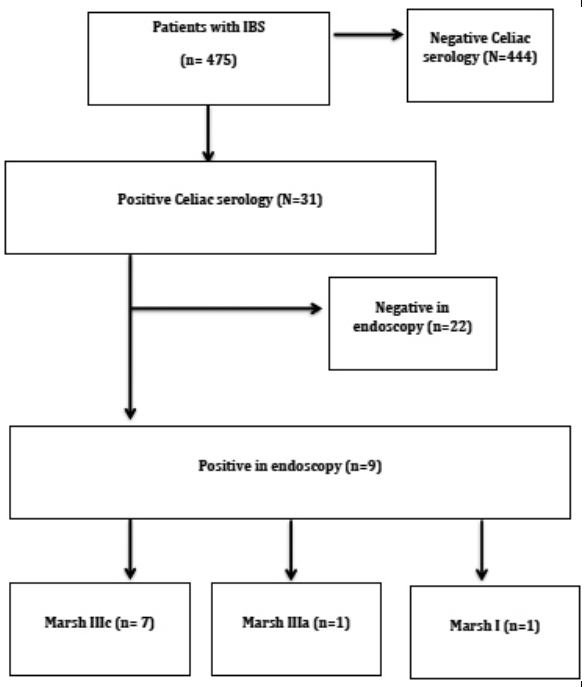

Fig. 1. Patient recruitment and examination flow-diagram.

3. Results

In this study, of 475 IBS patients, 31 patients (6.53%, 95% CI: 4.55–9.22) had positive serologic test for CD. Sixteen of them (51.6%) were female. The seroprevalence of positive IgA-tTG was 2.9% (95% CI: 1.69–5.02) in the total population. Serum prevalence of positive IgG-tTG antibody 4% just among 19 patients (Ta-

Table 2
Determination of seroprevalence of gluten sensitivity based on gender and age of patients

Variables/Serum gluten sensitivity test result	Positive n (%)	Negative n (%)	Total n (%)	P Value
Gender				
Female	16 (51.6)	209 (47.1)	225 (47.4)	0.624
Male	15 (48.4)	235 (52.9)	250 (52.6)	
Age				
20–30	6 (19.4)	103 (23.2)	109 (22.9)	0.119
31–40	9 (29)	129 (29.1)	138 (29.1)	
41–50	14 (45.2)	116 (26.1)	130 (27.4)	
51–60	1 (3.2)	64 (14.4)	65 (13.7)	
>60	1 (3.2)	32 (7.2)	33 (6.9)	

Table 3
Distribution of clinical IBS symptoms

Clinical symptoms	Gluten sensitivity status	No n (%)	Yes n (%)	Total n (%)	P value
Cramp	Yes	301 (67.8)	28 (90.3)	392 (69.3)	0.009
	No	143 (32.2)	3 (9.7)	146 (30.7)	
Stomach fullness	Yes	265 (59.7)	25 (80.6)	290 (61.1)	0.021
	No	179 (40.3)	6 (19.4)	185 (38.9)	
Constipation	Yes	77 (17.3)	7 (22.6)	84 (17.7)	0.46
	No	367 (82.7)	24 (77.4)	391 (82.3)	
Gas discharge	Yes	52 (11.7)	7 (22.6)	59 (12.4)	0.076
	No	392 (88.3)	24 (77.4)	416 (87.6)	
Diarrhea	Yes	43 (9.7)	6 (19.4)	49 (10.3)	0.087
	No	401 (90.3)	25 (80.6)	426 (89.7)	

ble 1). All of patients with positive serologic test underwent duodenal biopsy. Based on Marsh classification, out of 9 patients with positive pathology 77.8% (95% CI: 40.19–96.05) had marsh IIIc. Flow diagram of the study is seen in Fig. 1.

Specificity and negative predictive value of celiac disease serum test results compared to upper endoscopic results was zero percent. Positive predictive value of celiac disease test results was 31.6% lower than upper endoscopic results. Also, there was no significant association between the prevalence of gluten sensitivity and the gender of the patients ($P = 0.624$) (Table 2). In addition cramp (0.009) and stomach fullness (0.021) were two statistically significant IBS symptoms (Table 3).

4. Discussion

CD is a common cause of malabsorption of most nutrients and vitamins [20]. Although initially it was thought to be predominantly among the white population, especially in Europeans, recent observations have proven that it is a common disease with variable manifestations and worldwide distribution [19]. Genetics has a special place in this disease, while its prevalence in first-degree relatives of celiac patients is approximately 10%, and its concordance in homozygote twins is approximately 70% [17,19]. Gliadin bonded to HLA-DQ2 or HLA-DQ8 heterodimers are found in 90–95% and 5–10% of patients respectively [43]. HLA-DQ2 and HLA-DQ8 are present on donor cells Antigens are present in lamina propria, which bind to gliadin to release proinflammatory cytokines, which are the leading cause of complications [19].

In the study conducted by Houshiyar and colleagues, out of 105 patients with IBS 14 patients were diagnosed with CD, ranging in age from 22–55 years with a mean age of 34.93 $\pm$ 9.47 [21]. In the Akhondi et al., research among 125 patients with IBS with a mean age of 29.85 $\pm$ 9.22; IgA-tTG was positive among four of them. While after taking biopsy CD was confirmed in three of them [2]. In another study in Hormozgan, Iran; IgA-tTG was positive in 19 cases from 150 studied patients with IBS [28].

Furthermore, IgA-tTG was positive in 4 out of 200 participants in Pandav and colleagues' study [31]. Comparing the results with other studies, we conclude that the rate of celiac in our patients is approximately close to that of other studies in Iran. Given the genetic impact of celiac etiology in different regions of different ethnicities, we would expect a different prevalence in CD serum titers Many patients did not refer for biopsy despite all follow-up. Technical error and other confounding factors that may lead to false positive should be considered as a consequence of this study.

In Dieterich et al., study among 106 untreated celiac serum samples, serum samples IgA-tTG with cutoff levels greater than 15 were evaluated as positive. The sensitivity and specificity of ELISA test were 98.1% and 94.7%, respectively. Also, four serum samples that were EMA-IgA positive did not show positive IgA-tTG even after retesting. However, they suggested that IgA-tTG by ELISA could be used as a good screening test in large populations [14].

Riccardo et al. stated that both IgA and IgG titers for tTG were significantly higher in the celiac group than in the control group. It is stated that tTG is the major autogenous antigen in CD Although ELISA may be less sensitive to immunofluorescence, it has a high diagnostic potential in CD [44]. In the study of Basso et al., the sensitivity and specificity of IgA-tTG and IgG-tTG assays were different compared to the used kit. On average, the specificity of this assay was 95%. The sensitivity between the different kits was about 63% for IgG and 83% for IgA [7]. Our study showed that CD prevalence in IBS patients was 6.5% and the definitive diagnosis in seropositive individuals was 31.6% which is significantly higher than the prevalence of celiac in the normal population (about 1%). As a result, it is advisable for all IBS patients to be diagnosed with CD, even those with no clear diarrhea and other celiac symptoms. Patients with serologic titers above 2 times the normal upper limit are expected to be reported as positive in pathology [3,33]. In addition, many patients with positive serology and negative pathology may later develop CD and seropositive patients may be more likely to be followed up.

4.1. The strength and limitation of study

The strengths of this study include the novelty of the subject and importance of the studied group. This study had several limitations. This was a cross-sectional study and the temporal relationships between risk factors and health status cannot be established. Also, another limitation of our study is the small sample size.

4.2. Recommendations for future research

We recommend obtaining more accurate results by further studies with a larger serum positive sample size as well as minimizing the potential confounding factors.

5. Conclusions

We suggest physicians to consider celiac examinations for all patients with IBS symptoms, even for patients with no obvious celiac symptoms.

Author's contributions

Study conception and design: F.MG, A.S and F.J.
Acquisition of data: AM and S.Y.
Statistical analysis and interpretation of data: S.H and F.J.
Drafting of the manuscript: F.MG, A.S, A.M, S.H, L.S, S.M, S.Y and F.J.
Critical revision of the manuscript: F.J, S.Y, L.S and F. MG.

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Conflict of interest

The authors declare no conflicts of interest.

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