

Serologic celiac disease in patients with inflammatory bowel disease

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Background: There is an association of celiac disease (CD) with several gastrointestinal illnesses. We aimed to determine the prevalence of CD in patients with inflammatory bowel disease (IBD) to evaluate the value of the routine serological tests for CD in these patients. **Materials and Methods:** patients with IBD underwent screening test for CD. The screening test was based on IgA anti-tTG antibody evaluated by ELISA method and IgA EMA (endomysial antibody) measured by the indirect immunofluorescence method. Fisher exact and chi-square and t tests were used for data analysis. **Results:** the study was conducted on 100 patients, with a mean age of 34.74 ± 12.03 (SD) years. The mean simplified Crohn's disease activity index was 90 ± 17 (SE) and the mean colitis activity index was 3.46 ± 0.96 (SE). Seventeen patients (17%) had IgA anti-tTG antibody levels above the cutoff point (>20). Thirty-two patients were positive for IgA EMA. IgA EMA was positive in nine IgA anti-tTG positive patients (three patients with Crohn's Disease and six ones with ulcerative colitis). Then, the prevalence of serologic CD was 9% that was higher than that of general population. A significant correlation was found between the results of IgA EMA and those of IgA anti-tTG ($P=0.001$) whereas Fisher exact test revealed significant difference between frequency distribution of positive and negative results of IgA EMA and IgA anti-tTG in patients with ulcerative colitis and Crohn's disease ($P=0$). **Conclusion:** the prevalence of serologic CD in general population in Iran has been reported to be 0.6–0.96%. Then, its prevalence in our sample size was about ten times more than that in general population.

Key words: Celiac Disease, Inflammatory Bowel Disease

INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy, triggered by ingestion of gluten-containing grains in genetically susceptible persons.^[1] The prevalence of CD is estimated to be 1/300 to 1/500 in general population.^[2] The prevalence of CD in Iran is reported to be 1/166 to 1/104.^[3,4] CD may manifest with variety of symptoms and severities that may begin anytime during the life. Gastrointestinal symptoms may include diarrhea, abdominal pain, vomiting, bloating, anorexia, and even constipation.^[5] The classic presentation of severe malabsorption syndrome with chronic diarrhea, steatorrhea, and weight loss, however, is less common in CD that is known as the "iceberg" condition.^[6,7] The variation in clinical presentation is a major challenge for early detection of CD.^[8] Although CD is eminently treatable by the total lifelong gluten-free diet (GFD),^[9] there is often prolonged delay in diagnosis that may end up to serious complications such as intestinal malignancies.^[10-12] Therefore, timely diagnosis of CD and strict dietary treatment is important and could prevent the development of serious complications,^[9] and decrease mortality in celiac patients.^[13] Considering high proportions of CD patients with nonspecific gastrointestinal symptoms, routine screening of patients

with irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), etc. is still a debate.

IBD is comprised of two major diseases: ulcerative colitis (UC) and Crohn's disease. UC affects the colon, whereas Crohn's disease can involve any component of the gastrointestinal tract from the oral cavity to the anus.^[14] In the case of IBD, there is also an overlap between symptoms of CD and IBD that could result in misdiagnosis and delayed diagnosis of CD.

Several case reports and case series have suggested an association between CD and IBD,^[15-20] most frequently UC.^[21-26] However, the true prevalence of CD in IBD patient's and so the value of the routine serological tests for CD in these patients is not clear yet.^[27-29]

In this study, we aimed to determine the prevalence of CD in patients with IBD and to evaluate the value of the routine serological tests for CD in these patients.

MATERIALS AND METHODS

This cross-sectional study was carried out in Poursina Hakim Research Institute, Isfahan, Iran during 2008 –

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2010. Patients with IBD, who were registered in Poursina Hakim Research Institute Database, were invited to participate in this study after controlling the inclusion and exclusion criteria.

Inclusion criteria Patients with the diagnosis of IBD according to Leonard Jones criteria^[30] and those with no history of gastroduodenectomy or other upper-gastrointestinal operations were included in the study.

Exclusion criteria Patients who did not follow the protocol of study or did the serologic tests in laboratories other than those determined in the study guide were excluded from the study.

Patients with IBD who accepted to participate undergone the screening test for CD. The test was based on IgA anti-tTG antibody through an ELISA method using an *E. coli*-expressed human recombinant tTG as the coating antigen and IgA EMA by the indirect immunofluorescence method on monkey esophagus sections.

Total serum IgA was measured in patients with a tTG-Ab titer of zero and negative EMA results to exclude IgA deficiency as a cause of false-negative EMA and tTG-Ab results. Participants with positive antibodies for each test or IgA deficiency were considered to undergo D2 biopsies to confirm the possibility of CD after receiving informed consent. Four biopsy specimens were taken from the second part of duodenum with standard forceps. The biopsies were read by an expert histopathologist who was blinded to the serological results. Histopathological findings were expressed according to the revised Marsh classification.^[31] Normal mucosa with less than 30 intraepithelial lymphocytes per 100 epithelial cells was defined as the Marsh type 0; normal mucosa with more than 30 lymphocytes per 100 epithelial cells was defined as Marsh type I, infiltrative/hyperplastic lesions as Marsh II, and villous atrophy (VA) as type III. The Marsh III lesions were further subdivided into partial VA (Marsh IIIa), subtotal VA (Marsh IIIb), and total VA (Marsh IIIc).^[32]

HLA-DQ2 and DQ8 determination that is strictly associated with CD^[33] was performed on patients with negative EMA in accompany with the pathology less than marsh IIIa because increased numbers of intraepithelial lymphocytes are found not only in CD, but also in other medical conditions.^[34] In cases with "positive tTG followed by positive EMA" or "positive tTG followed by marsh higher than II in those with negative EMA" CD was considered as the appropriate diagnosis.

Statistical analysis

T test, chi square, and Fisher's exact tests were used for

data analysis and *P*-values less than 0.05 were considered significant. Data were analyzed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software.

RESULTS

This cross-sectional study consisted of 100 patients, with a mean age of 34.74 ± 12.03 (SD) years. The frequency distributions of clinical characteristics of the patients are given in [Table 1]. Of 100 patients examined, 17 (17%) had IgA anti-tTG antibody levels above the cutoff point^[20] that consisted of 12 UC and 5 Crohn's disease patients. Thirty-two patients were positive for IgA EMA that consisted of 22 UC and 10 Crohn's disease patients. IgA EMA was positive in nine IgA anti-tTG positive patients (three patients with Crohn's disease and six ones with UC); the other eight anti-tTG positive patients were all negative for IgA EMA [Table 2]. Correlation of qualitative variables by chi-square test demonstrated a significant correlation between the results of IgA EMA and those of IgA anti-tTG ($P=0.005$). Phi and Cramer's V correlation coefficient was 0.28.

All eight anti-tTG positive patients who were negative for IgA EMA were invited for duodenal biopsy. Only one patient accepted to undergo endoscopy who had no histological findings compatible with a diagnosis of celiac disease. IgA deficiency was identified in four patients (4%) and all had negative serology for celiac disease. The prevalence of serologic celiac disease was 9.5% and 10% in patients with ulcerative colitis and Crohn's disease, respectively [Table 3]. Fisher exact test revealed significant difference between frequency distribution of positive and negative results of laboratory tests in patients with IBD. Comparing IgA anti-tTG antibody levels between the two groups of patients who were positive and negative for IgA EMA was done. Comparison of mean IgA anti-tTG antibody levels between positive and negative IgA EMA patients by t test showed a significant difference (33.44 ± 14.21 versus 9.92 ± 1.6 , respectively, $P=0.015$).

Disease activity

The criteria of ulcerative colitis activity index (UCAI)^[19] was used to monitor the severity of disease in ulcerative colitis patients whereas simplified Crohn's disease activity index (SCDAI)^[20] was applied in Crohn's disease patients. Crohn's disease activity index was defined as following: score = <50, remission; 150–250, mild disease activity; 250–400, moderate disease activity and >400, severe disease activity. Two patients had moderate disease activity, seven had mild disease activity, and 14 patients were in remission.

Spearman correlation showed no significant relationship between the severity of disease in ulcerative colitis and

Table 1. Clinical and demographic characteristics of IBD patients

Mean Age	34.74 ± 12.03 (SD) (%)
Gender	
Female	42 (42)
Male	58 (58)
Disease type	
Ulcerative Colitis	70 (70)
Crohn's disease	30 (30)
Disease activity	
Ulcerative Colitis according to UCAI	3.46 ± 0.96 (SD)
Crohn's disease according to SCDAI	90 ± 17 (SD)
IgA deficiency	4 (4)
Duration of disease (months)	42.97 ± 36.36

Table 2. Correlation of distribution of qualitative variables (IgA EMA and IgA anti-tTG) by chi-square test

		IgA EMA		Total (%)
		Positive (%)	Negative (%)	
IgA anti-tTG Ab	Positive	9 (9)	8 (8)	17 (17)
	Negative	23 (23)	60 (60)	83 (83)
Cramer's V = 0.28 Total		31 (31)	68 (68)	P=0.005

EMA: Endomysial antibody

Table 3. Frequency distribution of patients according to the kind of IBD and EMA and IgA anti-tTG Ab results

		IBD		Total
		Ulcerative colitis	Crohn's disease	
EMA+TT	Negative, either or both	64	27	91
	Both positive	6	3	9
Total		70	30	

EMA: Endomysial antibody; IBD: Inflammatory bowel disease

Crohn's disease with IgA anti-tTG antibody levels and IgA EMA ($P>0.05$).

The patients who had serological findings compatible with a diagnosis of celiac disease according to our criteria and they did not complain of gastrointestinal symptoms.

DISCUSSION

We found 17 anti-tTG positive cases in 100 patients, but only nine were EMA positive, a serologic celiac disease prevalence of 9%, showing about ten times higher prevalence of serologic celiac disease in IBD patients compared with the general population in Iran. Reported prevalence of celiac disease in IBD patients varied from 0.3% to 14%.^[35-37] In Iran, the prevalence of serologic CD in general population has been reported to be 0.6–0.96%.^[3,4,7] There are considerable literatures supporting an association between celiac disease and IBD. In 1965, Salem and Truelove^[38] showed that 20% of patients with UC had villous atrophy in duodenal biopsies. Studies from the United Kingdom^[18] Sweden,^[19] and the United States^[39] have reported an increased prevalence

of UC and Crohn's disease in patients with celiac disease. These studies had shown a two to tenfold increase in the incidence of patients with both IBD and celiac disease than would be expected by chance.^[18,19] In our study, the prevalence of celiac disease was not completely confirmed because of lack of duodenal biopsy.

Other studies described moderate increase in antitissue transglutaminase antibodies in a number of autoimmune diseases, which is not always a marker of underlying celiac disease. False positive antitissue transglutaminase antibodies may be a phenomenon of autoimmunity.^[30] In addition, tissue transglutaminase is overexpressed in apoptotic tissue and is, therefore, a phenomenon related to mucosal lesions. Mucosal barrier defects are well described, such as increased tight junction permeability in both celiac disease^[40,41] and IBD.^[42] Increased intestinal permeability may lead to increased antigen presentation and therefore, generation of autoantibodies or increased bacterial translocation, which has been implicated in IBD as a pathogenic mechanism.

Leeds *et al.* corroborated this view in that 16/354 (4.5%) patients had positive antitissue transglutaminase antibodies and negative EMAs but only one patient was found to have celiac disease on biopsy.^[43] In Di Tola *et al.* study, low-positive values of antitissue transglutaminase antibodies were detectable in 22 out of 45 Celiac Sprue (49%), 32 out of 49 Crohn's Disease (65%), 20 out of 29 Ulcerative Colitis (69%), and 1 out of 27 MS patients (4%).^[44] Positive anti-tTG results have been reported in patients affected by other disorders, such as inflammatory bowel disease (IBD),^[35,45] suggesting a loss of specificity for these antibodies in celiac.

The standard test uses IgA endomysial antibody (EMA). This is based on its very high specificity, which approaches 100%. Overall, the sensitivity of the EMA is excellent with the majority of reports indicating greater than 90% sensitivity,^[46] although it is more expensive and more observer dependent than the IgA anti-tTG test.

The Di Tola *et al.* study has been suggested that antitissue transglutaminase antibodies correlate to the disease activity,^[44] although in our study there was no relationship between the activity of disease and IgA anti-tissue transglutaminase antibodies and IgA EMAs, which could be due to the small sample size.

In our study, there were no significant deference between ulcerative colitis and Crohn's disease in patients with serologic celiac disease although most of our patients had ulcerative colitis. Our experience did not confirm Snook *et al.* report of celiac disease being associated more frequently with ulcerative colitis than with Crohn's disease.^[47]

CONCLUSION

Our study identified a higher prevalence of serologic celiac disease in IBD patients than in the population at large, although not performing endoscopy in positive serologic patients and small sample size challenged our findings and further studies are needed to clarify whether or not there is an association between IBD and celiac disease.

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