

Is the Prevalence of Celiac Disease Higher than the General Population in Inflammatory Bowel Disease?

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ABSTRACT

BACKGROUND

In some studies inflammatory bowel disease (IBD) and celiac disease were considered to be associated and some believe that this association may influence the prognosis of IBD. However, there is a considerable controversy regarding this association. Therefore, we aimed to assess the association of these two common digestive diseases and evaluate the complications of this association.

METHODS

In this comparative study, 200 patients with ulcerative colitis (UC) and 206 patients with Crohn's disease (CD) were evaluated for celiac disease using relevant diagnostic tests and pathologic studies. Total IgA, IgA tissue transglutaminase antibody and specific IgA anti endomysial antibody were assayed. In cases of IgA deficiency, total IgG and IgG tissue TG and IgG anti endomysial Ab were measured. Patients with increased specific IgA and IgG antibodies for celiac disease, underwent endoscopy and 4 standard samples were obtained. Our results were compared with the results of the prevalence study of celiac disease in the general population. Data were analyzed using analytic and descriptive statistics at a significance level of 5%.

RESULTS

Among the studied patients, 1 patient with UC had elevated IgA anti tTG antibody and IgA anti-endomysial antibody who underwent endoscopy and celiac was confirmed on pathology. Hence, of the 200 patients with UC, the diagnosis of celiac disease was confirmed in 1 patient (1:200) with no significant difference with the prevalence of celiac disease in the general population (1:166). However, none of our patients with Crohn's disease had celiac disease (0:206).

CONCLUSION

We found no significant difference in the prevalence of celiac disease between patients with UC and the general population. Since most of our participants had a mild level of Crohn's activation, none of those with Crohn's disease had celiac disease. Complications of IBD including sclerosing cholangitis, may be more common in patients with concurrent celiac disease. Therefore, it is recommended that celiac disease be considered in patients with severe and complicated IBD.

KEYWORDS

Celiac disease; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Anti tTG antibody; Anti endomysial specific antibody

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INTRODUCTION

Celiac disease is a common cause of one or more nutrient malabsorption. It is a common disorder with variable presentation and global distribution with an approximate incidence of 1 in 113 in the US.¹ Prevalence of celiac disease in Iran is estimated to be 1 in 166.² The age of the onset of symptoms in these patients may vary from first year up to 8th decade of life. The definitive diagnosis of celiac disease can be made based upon an abnormal small bowel biopsy and clinical and histopathological response to elimination of gluten from the diet.¹

Etiology of celiac disease is unknown but environmental, genetical and immunological factors are contributed in its development. The role of immune system in pathogenesis of celiac disease is cardinal and both innate and acquired immune responses contribute to the development of this disease. Anti-gliadin, anti-endomysium and anti-tTG IgA antibodies are present in the serum of these patients but whether these anti-bodies are primary or secondary to tissue damage is not known. Indeed, these antibodies are extremely useful for determining the prevalence of celiac sprue in populations.^{1,3}

Celiac disease is widely associated with other disorders causing chronic mucosal immune dysfunction such as inflammatory bowel diseases (ulcerative colitis and Crohn's disease).¹

Both Crohn's disease and celiac disease are related to T helper type 1 pathway, characterized by a decreased cellular apoptosis, which provoke a chronic inflammation especially in the lamina propria.⁴ Moreover, other cytokines involved in cell-mediated immuno-pathogenesis such as TNF-alpha or IL-8 are increased in both diseases.⁵ All these data confirm the possible common immuno-pathogenesis of both diseases. Besides, dissociation between the two diseases is also related to different HLA susceptibility and the increased gut permeability in these diseases.⁶ According to previous studies, the incidence of celiac disease increased in patients with lymphocytic colitis and varied between 9-27%.³ However, in recent studies this association has not been shown.⁷⁻⁹ Therefore, celiac

disease should be suspected in all patients with lymphocytic colitis especially in those who are not responsive to therapy which includes a gluten free diet similar to patients with celiac.¹

However, as mentioned previously, there are considerable controversy in different studies.⁸⁻¹¹ In some studies, this association was prognostically important¹² and from another aspect, recognition of patients with concurrent celiac disease in addition to its symptomatic control role can also prevent the development of serious complications of celiac disease.^{13,14} Hence, we aimed to recognise the association of these two common digestive disorders and evaluate the role of this association on patients prognosis.

MATERIALS AND METHODS

In this study, 200 patients with biopsy proven ulcerative colitis and 206 patients with biopsy proven crohn's disease were included sequentially using convenience sampling out of patients attending Shariati Hospital Referral Clinic, Tehran, Iran. Patients with other immunological diseases and those who were lost to follow-up were excluded from the study.

After obtaining informed consent from the patients, their demographic data, complications of IBD, drug history, and disease severity were collected and recorded.

Total IgA levels measured by IM-Tbido methods in all cases. In those cases with normal IgA levels, IgA tissue transglutaminase antibody (tTG) were assayed by ELISA method and specific anti-endomysial IgA level were determined by immunofluorescent assay. In those with abnormal IgA levels, total IgG level and IgG tissue TG were measured by ELISA method and IgG anti-endomysial level was determined by immunofluorescent assay. Those cases with increased IgA and/or IgG levels underwent endoscopy and 4 standard biopsies were obtained from duodenum. These biopsies were evaluated by a pathologist who was not aware of the serology and pathology results which were ultimately reported based on the Marsh classification.^{10,11} Crohn's disease activity index and UCDAI activity criteria was

used to determine the severity of Crohn's disease and ulcerative colitis.¹¹ Our results were compared with the results of the prevalence study of celiac disease in the general population, which was performed previously.²

Statistical analysis was performed using SPSS software, version 17.0. Analysis of variance (ANOVA) and t test were used as appropriated. The significance level was set as 5%. The study was approved by the Ethics Committee of Digestive & Liver Diseases Research Institute of Tehran University of Medical Sciences.

RESULTS

The mean±SD age of the 200 patients with ulcerative colitis was 41.15±12.91 years. The mean±SD age at diagnosis of ulcerative colitis was 28.92±11.51 years. Forty eight percent of patients were men and the remaining 52% were women.

The mean±SD age of the 206 patients with Crohn's disease was 38.88±12.88 years and 58.3% were men and 41.7% were women. The mean±SD duration of disease symptoms was 20.60±20.62 months.

In patients with ulcerative colitis, rheumatic complication was the most common complication observed in 36(18%) patients and arthralgia was the most common symptom observed in 26 (13%) followed by nephrolithiasis (5.5%,n=11), arthritis (3%,n=6), sclerosing cholangitis (2.5%,n=5), respectively. With respect to major complications, two(1%) patients underwent colectomy due to colon cancer and liver transplantation was performed in one of the patients with sclerosing cholangitis.

In patients with Crohn's disease, history of gastrointestinal surgeries was seen in 76 (36.9%) patients, anal fistula in 48 (23.3%), and arthritis in 18(8.7%). None of the patients had history of cholangitis. The occurrence of severe changes in defecation behaviors was seen in 106 (51.5%) patients, abdominal pain in 106 (51.5%), and inappropriate general well-being in 43(21.1%). In terms of extra-gastrointestinal manifestations, arthritis or arthralgia was found in 58(28.2%) patients, anal fissure or fistula in 28(13.6%), and skin or mouth lesions

Table 1: Severity of ulcerative colitis based on the UCAI criteria

Disease severity	Frequency	Percent
Mild	123	61.5
Moderate	62	31
Sever	15	7.5
Total	200	100

Table 2: Severity of Crohn's disease based on the CDAI criteria

Disease severity	Frequency	Percent
Mild	168	81.6
Moderate	26	12.6
Moderate to severe	10	4.9
Total	206	100

in 16(7.8%). Abdominal mass was not detected in any patient.

Disease severity based on UCDAI and CDAI severity criteria is presented in tables 1 and 2.

Anti-tTG level in patients with ulcerative colitis was 1.09±4.58 and in only one patient it was higher than normal (NI level: <10 Unit/ml). In patients suffering from Crohn's disease, the mean level of Anti-tTG was also 0.57 ± 0.11. The mean±SD IgA level was 216.96±95.01 and there were 3 patients (1.5%) with decreased IgA levels. In patients suffering from Crohn's disease the mean±SD serum level of total IgA was 247.84±100.21. Total IgG level, anti-tTG IgG level and anti-endomysial IgG level were all normal in the studied patients. Therefore, only one patient with ulcerative colitis required endoscopy and duodenal biopsy based on these workups.

Among all studied patients, only one patient(0.5%) suffering from ulcerative colitis had high titer of anti-tTG IgA (65 Unit/ml) and positive anti-endomysial in whom duodenal biopsy revealed chronic duodenal inflammation corresponding to MARCH 3b celiac disease.

He was a 26-year-old single worker born in Ilam, Iran. His blood group was O and his disease had presented since the age of 14 with bloody diarrhea (average of 6 times daily), abdominal pain and weight loss. Eight years following disease recognition he stopped his medications and subsequently

developed icterus, itching, weight loss, and aggravated bloody diarrhea. He underwent colonoscopy, MRCP and laboratory investigations. Work-ups revealed severe ulcerative colitis on colonoscopy, sclerosing cholangitis on MRCP and normal IgG4 level and he had been treated with Urso Deoxy Cholic Acid (UDCA) and mesalamin. He underwent ERCP and stenting at the stricture site due to persistent icterus and cholestasis and was candidate for liver transplantation. He had lactose intolerance, steatorrhea, bloating and abdominal distension for many years but never experienced herpetic dermatitis, spontaneous bleeding and neurological impairment. After pathologic confirmation of celiac disease, a gluten free diet was initiated for him and this resulted in decreasing symptoms of bloating, distention and diarrhea. Now he defecates non-bloody stool once a day and he is not experiencing abdominal pain.

Because of finding only one patient with celiac disease in this study, it was not possible to compare the celiac group with the control group.

DISCUSSION

In the current study which is performed on 406 patients with IBD (ulcerative colitis and Crohn's disease), the prevalence of celiac disease in ulcerative colitis was 1 in 200 which was not statistically significant compared with the prevalence of disease in the normal population from a previous study on blood donors (1 in 166)² (table 3). Although it should be mentioned that blood donors are not representative of the "normal" population.

However, none of our patients suffering from Crohn's disease had celiac disease because most of our participant had a mild level of Crohn's activation. The prevalence of serologic CD in the general population in Iran, has been reported to be 0.6–0.96%. in this study (table 3). However, this association has been found in some previous studies. Tavakkoli et al. found that the prevalence of serologic celiac disease in Crohn's group was 9% that was higher than that of general population.¹⁰

During recent years, several studies have been performed to determine the prevalence of ce-

Table 3: prevalence of celiac disease in IBD (UC & CD) comparison with the prevalence of disease in the normal population

Group	Number	Percent
Ulcerative Colitis†	1/200	0.5
Crohn disease	0/206	0
IBD	1/406	0.25
Control*	1/166	0.6

†there is no statistically significant difference $p > 0.05$

* prevalence of celiac disease in normal population from blood donors study which studied recently (2)

liac disease in patients with ulcerative colitis and Crohn's disease in Iran. The results of these studies are inconsistent; in the study performed in Golestan province, the prevalence of celiac disease was equal to the normal population⁸ and in the study of Isfahan seroprevalence of the celiac disease was 10 times higher than the general population.¹⁰ In another study in Shiraz, the prevalence of celiac disease in the general population was 0.5%.⁹

There were no significant differences regarding this prevalence between this study and other Mediterranean and Middle-Eastern studies.^{15,16} Therefore, there seems to be no significant difference in the prevalence of celiac disease between patients with IBD and the general population.

In a study in Isfahan by Tavakoli and colleagues during 2008–2010 on 100 patients with IBD, the seroprevalence of celiac disease based on anti tTG and anti-endomysial levels, was 10 times higher than the general population. In 17 patients with elevated anti tTG levels, 12 patients had ulcerative colitis and the remaining 5 patients had Crohn's disease. In these patients, increased anti-endomysial level was evident in only 9 cases; furthermore, in this study only one patient underwent intestinal biopsy in whom histopathological results was not compatible with celiac disease. There was no association between disease severity and presence of celiac disease.¹⁰

In Gorgan study on 102 patients with IBD, there was only one patient with ulcerative colitis in whom tTG level was elevated.⁸ This association was also uncommon in other studies including studies of Kitis et al.¹⁷ Bulger et al.¹⁸ and Kull et al.¹⁹ How-

ever, findings of some other studies are inconsistent with our findings. In some studies on patients with celiac disease, the prevalence of Crohn's disease was high.^{20,21}

Tursi et.al., in 2005 reported that synchronous celiac disease in patients with IBD results in poor prognosis.¹² In another study relative risk of ulcerative colitis in first degree relatives of patients with celiac disease was 5 in comparison with the general population.¹³

In another study in Italy which was carried out in 22 centers, 1711 patients with IBD were evaluated during 2002-2004. Among all studied cases, celiac disease was documented in 9 patients based on serological and duodenal biopsy results. Celiac disease was more common in UC but overall disease frequency was not higher in patients with IBD in comparison with the general population (0.5% in IBD vs. 1-2% in general population).¹¹

Yang and colleagues in Collombia university evaluated pathological samples of 455 patients with celiac disease and they found IBD in 10 patients concurrently. Findings of this study suggested that prevalence of IBD in patients with celiac disease was significantly higher than the general population.³

In our study the patients with UC and celiac disease also suffered from sclerosing cholangitis. This finding was observed in other studies by Bulger,¹⁸ Habior,¹³ and Wurm¹⁴ and colleagues; which found that sclerosing cholangitis was more common in celiac disease.

In some studies a significant association was observed between severity of IBD and presence of celiac disease. Although the sample size of our study was low and therefore only 1 patient had celiac disease, but this patient also had severe and complicated disease and a gluten free diet resulted in symptomomatic relief.

Results of our study suggests that there was no significant difference in celiac disease prevalence between patients with UC and the general population. However, in patients with concurrent celiac disease, disease may be more severe and complications of IBD including sclerosing cholangitis, may

be more common. None of our patients suffering from Crohn's disease had celiac disease because most of our participants had a mild level of Crohn's activation. We recommend that celiac disease be considered in patients with severe and complicated IBD (Ulcerative colitis and Crohn's disease).

CONFLICT OF INTEREST

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

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