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Prevalence of IgA Anti-tissue Transglutaminase Antibody in a Cohort of Iranians Patients with Inflammatory Bowel Disease

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Abstract

Background and Aims Some studies have reported the coexistence of inflammatory bowel disease (IBD) and celiac disease (CD). However, the prevalence of anti-tissue transglutaminase antibodies (IgA and IgG) and their screening value in patients with IBD is not yet clear. This study aimed to assess the prevalence of IgA anti-tTG and its potential correlation with disease status in patients with IBD.

Materials and Methods This cross-sectional study was conducted on 110 patients with confirmed IBD diagnosis at Ghaem Hospital, Mashhad, Iran. For each patient, all demographic and clinical data including age, extra intestinal manifestations, underlying diseases, types of diseases, and surgical history were collected. IgA anti-tissue transglutaminase titers were assessed by enzyme-linked immunosorbent assay.

Results None of the patients with IBD were positive for IgA anti-tTG antibodies, with a mean titer of 3.31 ± 1.3 AU/mL. Also, the mean titers were not associated with age, gender and various disease clinical features including the disease history, underlying disease, diagnosis type, extraintestinal manifestations, and surgery history.

Conclusion No significant prevalence pattern of IgA anti-tTG antibody was observed in patients with IBD. Accordingly, serological screening for CeD is not recommended in IBD patients, unless in a relevant clinical CeD suspicion.

Keywords
- Celiac disease
- Crohn's disease
- IgA anti-tissue transglutaminase
- inflammatory bowel disease
- ulcerative colitis

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition in the gastrointestinal tract, resulting from a dysregulated immune response to host gut microflora. IBD comprises two major types including ulcerative colitis (UC), which is most common in the colonic mucosa, and Crohn's disease (CD), which can affect the entire gastrointestinal

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tract.[1] IBD is often diagnosed in early adulthood between 20 and 40 years of age and has a substantial impact on the quality of life.[2] It has been suggested that IBD develop in genetically predisposed individuals under the influence of environmental factors (e.g., intestinal microbiota), as well as the interaction between anti- and pro-inflammatory factors.[3] Most patients with intestinal malabsorption have symptoms (e.g., anemia, osteopenia, infertility, and neurological symptoms) that are not clearly associated with the condition.[4] On the other hand, a large number of people are asymptomatic and their diseases are diagnosed based on abnormalities in small bowel histology and serological tests. A possible explanation for this condition is silent celiac disease (CeD), which is about seven times more common than the classic type and its association with IBD has been reported in some cases.[5]

Celiac disease occurs when the immune system reacts permanently to gluten.[6] CeD has now been recognized as a multisystem disease affecting various organs in genetically predisposed individuals. It was reported that CeD can be associated with some autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome (SjS), primary biliary cirrohsis, eosinophilic esophagitis, systemic sclerosis (SCL), polymyositis (PM), and dermatomyositis (DM) as well as IBD. Although the coexistence of CeD and IBD have been reported in literature, the prevalence of CeD in patients with IBD remain to be cleared.[7] Some physicians believe that the IBD patients should also be screened for CeD specific anti tissue transglutaminase antibodies, followed by their symptoms' evaluation. In addition, clinical findings, histological evidence of duodenal mucosal damage, along with antibody tests against endomysial or tissue transglutaminase are all used to diagnose celiac disease.[8]

It has been determined that the anti-tissue transglutaminase (tTG) antibody assay is the best test for screening patients with suspected celiac disease.[9] Compared to anti-endomysium antibodies (EMA), anti-tTG tests using recombinant antigens have a high sensitivity and positive predictive value (PPV).[10] EMA assays are limited in their use in daily practice by their high costs and subjective interpretation, as well as the unacceptable variability among laboratories that perform this test.[11] Additionally, systematic reviews have found that anti-tTG assays have an excellent diagnostic performance for diagnosing celiac disease in adults and children older than 2 years, with a 90%-95% sensitivity and specificity.[12–14]

It is well known that celiac disease is associated with IgA deficiency and that IgA deficiency affects 1%-2% of those with celiac disease.[15] Considering that celiac disease is common in patients with IBD according to some studies, this study aimed to determine the prevalence of celiac disease based on assessing IgA anti-tTG levels and its potential correlation with disease status in patients with IBD.

Materials and Methods

A total of 100 cases with confirmed diagnosis of IBD who referred to the Gastroenterology Subspecialty Clinic of Ghaem Hospital, Mashhad, Iran, were enrolled in this cross-sectional study from 2019 to 2021. IBD diagnostic was based on the clinical, endoscopic, and histologic evaluation. Patients were eligible if they had no previous history of CeD diagnosis. Of them, anti-tTG positive patients were offered endoscopic intestinal biopsy for possible CeD diagnosis. Written informed consent was obtained from all participants and study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (No: IR.MUMS.MEDICAL.REC.1398.677). After a complete physical examination, demographic and clinical data including age, extraintestinal manifestations, underlying diseases, types of diseases, and surgical history were collected for each patient. Then a total of 5cc of whole blood were taken and stored at optimal laboratory conditions. Serological tests were done in the same laboratory and sera were thawed only once before measurements. IgA anti-human tTG antibodies were measured by enzyme-linked immunosorbent assay using a commercial ELISA kit (Generic Assays Company, Germany) according to manufacturer instructions. Antibody titers >18 (AU)/mL were considered as positive.

Statistical Analysis

Data were summarized as mean $\pm$ SD/median and percentage. One-Sample Kolmogorov-Smirnov test was used to check the data normality. The Mann-Whitney U or student's t tests were employed to compare quantitative variables. All statistical analyses were performed in SPSS software (version 25, Chicago, IL, USA), and p-value <0.05 was considered to be statistically significant.

Results

The demographic characteristics of 110 included IBD patients are presented in ►**Table 1**. Of them, 70 (64%) were females and 40 (36%) were males. The mean age and disease duration of the participants were 39.76 ± 11.56 and 6.84 ± 4.61 years, respectively. In patients stratification based on the age, 7(6.4%) persons had less than 20 years age, 19 (17.3%) of them had the age ranged between 20 to 29 years, 36 (32.7%) persons were between 30 to 39 years, 26 (23.6%) were between 40 to 49 years, 18 (16.4%) were between 50 to 59 years, and 4 (3.6%) were $\geq$60 years of age. Moreover, regarding the disease duration most patients had less than five years of disease duration (50.5%).

The clinical characteristics of the patients is shown in ►**Table 2**. About half of the patients were having proctitis which constitutes 44.5% of the total patients. Pancolities (19.1%) and Crohn's (18.2) were the other two most common types of the disease. With regard to the underlying disease and extra intestinal manifestations most patients (80%) and (92.7%) had no underlying conditions, respectively.

IgA anti-tTG antibodies were measured with a mean titer of 3.313 ± 1.3, which was less than the rate confirming the positive result for CeD. IgA anti-tTG antibodies levels were also not correlated with age categories, history of the disease, underlying disease, diagnosis type, extraintestinal

Table 1 The demographic characteristics of the IBD patients

Variable	N (%)
Gender	
Male	40 (36)
Female	70 (64)
Age (mean ± SD)	39.76 ± 11.56
Less than 20 years	7 (6.4)
20-29 years	19 (17.3)
30-39 years	36 (32.7)
40-49 years	26 (23.6)
50-59 years	18 (16.4)
60 years and more	4 (3.6)
Disease duration (mean ± SD)	6.84 ± 4.61
Less than 5 years	56 (50.5)
5-9 years	35 (31.8)
10-19 years	12 (10.9)
20 years and more	7 (6.4)

manifestations, and history of surgery ($P > 0.05$). Furthermore, only one sample was positive for IgG anti-tTG, with a titer of 85.5 AU/mL. This sample was belonged to a diabetic patient who was IgA deficient and accepted to undergo endoscopy. However, no histological findings compatible with a diagnosis of celiac disease was found in endoscopic evaluation.

Discussion

In the case of IBD, there is also an overlap between its symptoms and those of celiac disease that could result in misdiagnosis and delayed diagnosis of celiac disease.[16] Due to the fact that the IgA anti-tTG antibody assay is the best method for screening the cases suspected of celiac disease,[17] this study evaluated the IgA anti-tTG level in patients with IBD. The results cannot confirm an increase in celiac disease prevalence among patients with IBD since the IgA anti-tTG levels were lower than the standard index in the evaluated IBD patients. However, anti-tTG levels showed no significant relationships with age categories, underlying diseases, diagnosis types, extraintestinal manifestations, and surgical history.

Table 2 Frequency distribution of patients according to the diagnosis type, underlying disease, history of surgery, and extra intestinal manifestations

Variable		N (%)
Diagnosis type	Proctitis	49 (44.5)
	Proctosigmoiditis	6 (5.5)
	Ulcerative colitis on the left side	9 (8.2)
	Pancolitis	21 (19.1)
	Crohn's	20 (18.2)
	Indeterminate colitis	1 (0.9)
	Unknown	4 (3.6)
Underlying disease	Diabetes	4 (3.6)
	Blood pressure	5 (4.5)
	Other diseases	13 (11.8)
	None	88 (80)
History of surgery	Yes	4 (3.6)
	No	106 (96.4)
Extraintestinal Manifestations	Primary sclerosing cholangitis (PSC)	0 (0)
	Autoimmune hepatitis	0 (0)
	Uveitis	1 (0.9)
	Erythema nodosum	0 (0)
	Pyoderma gangrenosum	1 (0.9)
	Arthritis	6 (5.5)
	None	102 (92.7)

The association between celiac disease and IBD has been reported in several studies,[18–20] and a wide range of celiac disease prevalence (0.3%-14%) was noted among IBD patients.[21,22] The prevalence rate of celiac disease has been reported from 0.6% to 0.96% in the Iranian IBD populations.[23,24] One patient identified with celiac disease was evaluated in this study out of 100 patients with IBD. In the same direction, Leeds et al. investigated 354 patients with IBD, and only one patient was found to have celiac disease on biopsy, even though 4% of the cases had positive IgA anti-tTG but negative EMAs.[25]

Since celiac disease and IBD have similar clinical symptoms, if celiac serology is not obtained in patients with IBD, celiac disease can go undiagnosed. In patients with IBD, the evaluation of the possibility of celiac disease is of significant clinical importance because this disease is treated very differently from IBD.[19] Apoptotic tissues overexpress tissue transglutaminase; therefore, they are associated with mucosal lesions. Accordingly, both IBD and celiac disease have mucosal barrier defects, such as increased permeability of tight junctions. The increase in intestinal permeability may cause an enhancement in antigen presentation, which may result in autoantibodies or enhancement of bacterial translocation. This pathogenic mechanism can be implicated in IBD.[26] Kori et al. found that 575 out of 34,375 IBD patients (1.67%) had positive anti-tissue transglutaminase antibodies (Crohn's disease = 56%, ulcerative colitis = 44%). Among IBD patients, 0.93% of the cases had celiac disease.[20]

Nurmi et al. examined 629 newly diagnosed positive IgA anti-tTG cases between 1976 and 2012. The results indicate that IBD prevalence has increased among patients with high IgA anti-tTG from 0% to 4.4%, whereas clinically diagnosed celiac disease has declined from 2.6% to 0.6%.[27] Accordingly, a very limited number of IBD patients have celiac symptoms, which is in line with the findings of the current study. However, it is important to note that IBD and IgA anti-tTG can coexist. Further studies are required to determine whether this finding is related to the increase in the prevalence of IBD among the population or whether IgA anti-tTG and IBD share a common pathophysiology.[28]

In the same vein, Khayyat et al. found that celiac disease and IBD have a two-way relationship. In IBD patients treated with corticosteroids, 5-aminosalicylates, immunomodulators, or anti-tumor necrosis factor drugs, celiac disease was less common. Therefore, the study also confirms the findings of the present research. Additionally, in another study, Shah et al. reported that celiac disease is a risk factor for IBD although patients with IBD are prone to an increased risk of celiac disease to a lesser extent.[19]

According to a large survey conducted in the United States involving 1,647 people with IBD, 28% of the individuals had tried a gluten-free diet. Gluten exposure increased symptoms (gastrointestinal and extraintestinal) for a significant majority of patients in this study; nonetheless, for 38% of the cases, a gluten-free diet reduced flares and symptoms.[29]

The survey, however, could have been biased. There is a possibility that IBD manifests more severely in the presence of celiac disease. According to Oxford et al., 51 patients with coexisting IBD and celiac disease had a higher risk of pancolitis, compared to the control patients.[30]

In contrast, 12.8% of the Japanese patients with IBD without the biopsy-proven celiac disease had positive tTG values.[31] According to Alper et al., false-positive tTG values have been reported in patients with IBD.[32] False-positive tTG levels have been associated with apoptosis and intestinal inflammation in patients with IBD, according to Marcos et al.[33] Fecal calprotectin or video capsule endoscopy could have been useful in diagnosing false-positive tTG in our patients because of gut inflammation caused by IBD. These tests can distinguish between positive tTG due to gut inflammation and true false-positive tTG and should be performed after celiac disease is excluded in patients with persistent tTG.[32]

Tse et al. showed that IBD patients with celiac disease have unique phenotypic characteristics, compared to non-celiac IBD, as well as associated risks of colitis, extensive colitis, and primary sclerosing cholangitis, which can lead to the hospitalization of these patients.[34] Physicians may investigate comorbidities sooner if they are aware of IBD and celiac disease. Studies indicate that celiac disease is more likely to develop in IBD patients who have genetic factors, and prior detection may reduce its prevalence.[18,19,21] The present study also investigated other underlying diseases that may affect celiac disease, and based on the results, no significant relationship or difference was found between those with underlying diseases and those without. Furthermore, no differences were observed between the groups in terms of disease diagnosis and surgical history. It appears that celiac disease should be caused by other factors (e.g., genetics), and based on the findings, there was no correlation between IgA anti-tTG levels and age or history of the disease.

In this study, researchers selected a significant number of people from the studied population as samples, and their frequent follow-ups resulted in people participating in the study. Because of the possibility of testing after completing the consent form and questionnaire, as well as the location of the office and laboratory in the same place, sampling and sample attrition were reduced. There were also several indicators examined in this study that had been understudied. In spite of this, it was difficult to convince patients to participate in the research due to the COVID-19 pandemic, and researchers had limited access to the patient database. It is suggested that future research investigate the relationship between other factors, especially the genetic factors mentioned, and celiac disease. This research should also be conducted on a large scale, in a broader community, and based on comparisons.

Conclusion

The prevalence of IgA anti-tTG in patients with IBD was examined, and it was found that the IgA anti-tTG index was

not high in these patients; however, the number of patients with celiac disease was limited; therefore, this relationship cannot be considered significant. As a result, cases with both diseases can be considered rare and statistically significant. Celiac disease and IBD must be treated separately, and the two diseases cannot be considered related to each other.

Data Availability Statements

All data generated or analyzed during this study are included in this published article

Conflict of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

All authors have seen and agree with the contents of the manuscript and there is no financial interest.

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References

1 Song K, Wu D. Shared decision-making in the management of patients with inflammatory bowel disease. World J Gastroenterol 2022;28(26):3092–3100
2 Ramos GP, Papadakis KA, Eds. Mechanisms of disease: inflammatory bowel diseases. Mayo Clinic Proceedings; Elsevier; 2019
3 Chang JT. Pathophysiology of inflammatory bowel diseases. N Engl J Med 2020;383(27):2652–2664
4 Adolph TE, Meyer M, Schwärzler J, Mayr L, Grabherr F, Tilg H. The metabolic nature of inflammatory bowel diseases. Nat Rev Gastroenterol Hepatol 2022;19(12):753–767
5 Yu T, Xie Y, Yuan J, et al. The nutritional intervention of resveratrol can effectively alleviate the intestinal inflammation associated with celiac disease induced by wheat gluten. Front Immunol 2022;13:878186
6 Catassi C, Verdu EF, Bai JC, Lionetti E. Coeliac disease. Lancet 2022; 399(10344):2413–2426
7 Gobbi G, Mainardi P, Striano P, Preda A. Epilepsy, coeliac disease and other inflammatory bowel diseases. The Comorbidities of Epilepsy Elsevier; 2019:107–130
8 Bengi G, Cıvak M, Akarsu M, et al. Prevalance of celiac disease in patients with inflammatory bowel disease in Turkish population. Gastroenterol Res Pract 2019;2019:6272098
9 Donat E, Roca M, Castillejo G, et al; Coeliac Disease Working Group of the Spanish Gastroenterology, Hepatology, Paediatric Nutrition Society (SEGHNP) Correlation of Anti-Tissue Transglutaminase Antibodies With the Mucosal Changes and IgA Status of Children With Celiac Disease. J Pediatr Gastroenterol Nutr 2022;75(06): 743–748
10 Infantino M, Merone M, Manfredi M, et al. Positive tissue transglutaminase antibodies with negative endomysial antibodies: Unresolved issues in diagnosing celiac disease. J Immunol Methods 2021;489:112910
11 Savvateeva LV, Erdes SI, Antishin AS, Zamyatnin AA Jr. Current paediatric coeliac disease screening strategies and relevance of questionnaire survey. Int Arch Allergy Immunol 2018;177(04): 370–380
12 Gandini A, Gededzha MP, De Maayer T, Barrow P, Mayne E. Diagnosing coeliac disease: A literature review. Hum Immunol 2021;82(12):930–936
13 Losurdo G, Di Leo M, Santamato E, et al. Serologic diagnosis of celiac disease: May it be suitable for adults? World J Gastroenterol 2021;27(42):7233–7239
14 Elwenspoek MMC, Jackson J, O'Donnell R, et al. The accuracy of diagnostic indicators for coeliac disease: A systematic review and meta-analysis. PLoS One 2021;16(10):e0258501
15 Chourasia S, Ahirwar S. Celiac Disease. Int J Pharm Sci Med 2021; 6:42–72
16 Alkhayyat M, Abureesh M, Almomani A, et al. Patients With Inflammatory Bowel Disease on Treatment Have Lower Rates of Celiac Disease. Inflamm Bowel Dis 2022;28(03):385–392
17 Zhu X, Zhao X-H, Zhang Q, et al. How does a celiac iceberg really float? The relationship between celiac disease and gluten. Crit Rev Food Sci Nutr 2022;•••:1–29
18 Velmishi V, Kollcaku L, Cekodhima G, Dervishi E, Cullufe P. Seronegative celiac disease presented with a pronounced abdominal distention in a 4-year-old boy-Case report and review of literature. Pediatr Ther 2020;10:379
19 Shah A, Walker M, Burger D, et al. Link between celiac disease and inflammatory bowel disease. J Clin Gastroenterol 2019;53(07): 514–522
20 Kori M, Zamir Y, Yermiyahu SO, et al. The association of Inflammatory Bowel Disease with Celiac Disease and Celiac Autoimmunity in children and adults: A nationwide study from the epi-IIRN. J Crohn's Colitis 2022
21 Mak WY, Zhao M, Ng SC, Burisch J. The epidemiology of inflammatory bowel disease: East meets west. J Gastroenterol Hepatol 2020;35(03):380–389
22 Roberts SE, Thorne K, Thapar N, et al. A systematic review and meta-analysis of paediatric inflammatory bowel disease incidence and prevalence across Europe. J Crohn's Colitis 2020;14 (08):1119–1148
23 Ashtari S, Najafimehr H, Pourhoseingholi MA, et al. Prevalence of celiac disease in low and high risk population in Asia-Pacific region: a systematic review and meta-analysis. Sci Rep 2021;11 (01):2383
24 Tavakkoli H, Haghdani S, Adilipour H, et al. Serologic celiac disease in patients with inflammatory bowel disease. J Res Med Sci 2012; 17(02):154–158
25 Leeds JS, Höroldt BS, Sidhu R, et al. Is there an association between coeliac disease and inflammatory bowel diseases? A study of relative prevalence in comparison with population controls. Scand J Gastroenterol 2007;42(10):1214–1220
26 Kociszewska D, Vlajkovic SM. The association of inflammatory gut diseases with neuroinflammatory and auditory disorders. Front Biosci (Elite Ed) 2022;14(02):8
27 Nurmi R, Pohjonen J, Metso M, et al. Prevalence of inflammatory bowel disease and celiac disease in patients with IgA nephropathy over time. Nephron 2021;145(01):78–84
28 Almroth G, Axelsson T, Müssener E, Grodzinsky E, Midhagen G, Olcén P. Increased prevalence of anti-gliadin IgA-antibodies with aberrant duodenal histopathological findings in patients with IgA-nephropathy and related disorders. Ups J Med Sci 2006;111 (03):339–352
29 Herfarth HH, Martin CF, Sandler RS, Kappelman MD, Long MD. Prevalence of a gluten-free diet and improvement of clinical symptoms in patients with inflammatory bowel diseases. Inflamm Bowel Dis 2014;20(07):1194–1197
30 Oxford EC, Nguyen DD, Sauk J, et al. Impact of coexistent celiac disease on phenotype and natural history of inflammatory bowel diseases. Am J Gastroenterol 2013;108(07):1123–1129

31 Fukunaga M, Ishimura N, Fukuyama C, et al. Celiac disease in non-clinical populations of Japan. J Gastroenterol 2018;53(02): 208–214
32 Alper A, Rojas-Velasquez D, Pashankar DS. Prevalence of anti-tissue transglutaminase antibodies and celiac disease in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2018;66(06):934–936
33 Manceñido Marcos N, Pajares Villarroya R, Salinas Moreno S, Arribas López MR, Comas Redondo C. The association between de novo inflammatory bowel disease and celiac disease. Rev Esp Enferm Dig 2020;112(01):7–11 (REED)
34 Tse CS, Deepak P, De La Fuente J, et al. Phenotype and clinical course of inflammatory bowel disease with co-existent celiac disease. J Crohn's Colitis 2018;12(08):973–980

