Correlation of Serum IgA anti Tissue Transglutaminase Antibody levels with Histopathological grades of Celiac disease using Corazza Grading system

Anum Usman[1], Noor Khan Lakhnana[2], Ayesha Sarwar[3], Mudassira Zahid[4]

ABSTRACT

Objective: To correlate serum IgA anti-tissue transglutaminase antibody levels with the histopathological grades of celiac disease using Corazza grading system

Study Design: Descriptive Cross- sectional study

Place and Duration: At Al Nafees Medical College and Hospital Department of Pathology from April 6, 2015 to June 10, 2016.

Methodology: From all the enrolled patients, based upon inclusion and exclusion criteria, endoscopic biopsies were processed routinely for histopathological analysis. Corazza Grading system was used for grading the morphological findings. Anti-Tissue transglutaminase (tTG) IgA antibodies were measured by the ELISA (Enzyme-Linked Immunosorbent Assay) method. Both biopsy data and serological marker were correlated.

Results: 77 patients were included in this study, out of which 55 were diagnosed as celiac disease patients. Gender distribution included 38.9% males and 61.1% females. According to Corraza Grading System, there were 28.6% cases in Corraza 0 and 22% cases in Corraza A whereas Corraza B1 and B2 included 35% and 14.3% cases respectively. After correlation with anti- tTG IgA Ab titers, 27.2% patients had negative serology. Total 22% patients in Corraza A were serologically positive and had IgA tTG Ab titers between 11 to 100 units/ml whereas in Corazza B1,only 18% patients had titers greater than 100 units/ml and Corazza B2 almost all patients had titers greater than 100 units/ml.

Conclusion: Corazza Grading System significantly correlates with anti-tissue transglutaminase IgA Antibody titers

Keywords: Endoscopic biopsy, Celiac disease, Serology, Morphology, Marsch, Tissue transglutaminase, Corazza Grading System

How to Cite This:

Usman A, Lakhnana NK, Sarwar A, Zahid M. Correlation of Serum IgA anti Tissue Transglutaminase Antibody levels with Histopathological grades of Celiac disease using Corazza Grading system. Isra Med J. 2021; 13(1): 39-42.

1. Assistant Professor of Pathology, Al-Nafees Medical College and Hospital, Isra University, Islamabad Campus, Islamabad.
2. Professor of Pathology, Al-Nafees Medical College and Hospital, Isra University, Islamabad Campus, Islamabad.
3. Assistant Professor of Pathology, HBS Medical and Dental College, Islamabad
4. Associate Professor of Pathology, Mohiuddin Islamic Medical College AJK

Correspondence:
Anum Usman
Assistant Professor of Pathology, Al-Nafees Medical College and Hospital,
Isra University, Islamabad Campus, Islamabad.
Email: dranumusman@gmail.com

Received for Publication: October 19, 2020
1st Revision of Manuscript: November 11, 2020
2nd Revision of Manuscript: January 02, 2021
Accepted for Publication: January 05, 2021

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder of the small intestine triggered by the ingestion of gluten in genetically predisposed individuals carrying the HLA type II DQ2 and DQ8 haplotypes[1]. Celiac disease may present with classical gastrointestinal and extraintestinal symptoms or may be asymptomatic[2]. The classical gastrointestinal symptoms include chronic diarrhea, constipation, bloating, and weight loss due to malabsorption[3]. Extraintestinal symptoms includes dermatitis herpetiformis, anemia, osteoporosis and neurological problems[4]. Variable presentation of celiac disease depends upon several factors such as age, gender, genetics, immunology, dietary habits and extent of mucosal injury as they play a significant role in altering the clinical manifestation of the disease[5].

The prevalence of celiac disease, according to various studies, is reported as 1% throughout the world[6]. About 0.8% of the population is effected in Europe and the United States. The prevalence is high as 2% to 3% in Finland and Sweden, where as in Germany it is only 0.2%[7]. The incidence of celiac disease in Asian countries is low whereas frequency is increasing in China[8]. The histopathological features of duodenal biopsy along with serologic tests for antibodies against IgA anti tissue transglutaminase are required for the accurate diagnosis of

celiac disease in patients presenting with typical signs and symptoms[9]. Microscopy of celiac disease includes increase in number of intraepithelial lymphocytes, crypt hyperplasia and villous atrophy[10]. Corazza grading system is based on all these microscopic features for the diagnosis of the disease[11].

Corazza grading system consists of the following categories i-e Grade A includes increase intraepithelial lymphocytes along with crypt hyperplasia. Grade B1 lesions includes mild to marked atrophy of villi based on villi to crypt height ratio. Grade B2 is complete atrophy along with crypt hypoplasia[12].

The advances in serologic tests has been one of the greatest developments in diagnosis of CD. Highly sensitive and specific antibody tests are available to screen high risk or minimally symptomatic celiac patients[13]. Commonly used antibodies are antigliadin antibodies (AGA), endomysial antibodies (EMA) and tissue transglutaminase antibodies (tTG) [11]. Serological titers of immunoglobulin A (IgA) antibodies against tissue transglutaminase (tTG) have appreciable diagnostic characteristics[14,15]. In recent studies, IgA-tTG antibodies level is considered as ideal test for screening of celiac patients as it has higher sensitivity and specificity as compared to others[16,17].

The objective of my study was to establish a significant correlation between serum IgA anti Tissue transglutaminase antibody levels with histopathological grades of celiac disease using Corazza grading system because Corazza grading system allow discriminating latent celiac disease from patients with normal mucosa and also help in identifying and treating patients at an early stage with accuracy. The aim of our study is to assess the correlation between anti-tTG titers and Corazza grading system and to avoid the need for repeated biopsy sampling after finding a reliable level with acceptable specificity for predicting mucosal atrophy.

METHODOLOGY

This descriptive cross-sectional study conducted at Pathology Department, Al Nafees Medical College and Hospital, Islamabad over a period of nine months from April 6, 2015 to June 10, 2016. Seventy seven endoscopic duodenal biopsy specimens and the sera for serological testing from both males and females of all age groups having symptoms of malabsorption were included in the study. Improperly processed or oriented samples and improperly stained slides were excluded from the study.

The biopsy specimens were collected in formalin and processed in automated tissue processor. Paraffin embedded sections were stained with the hematoxylin and eosin stain. Slides were examined by consultant histopathologist under light microscope. All the macroscopic and light microscopic findings of duodenal biopsies were noted in systemic manner in the proforma. The final diagnosis was written at the end in each case. Endoscopic biopsy findings were recorded and grouped into different grades as per Corazza grading system. Serological marker of celiac disease of each patient i.e. anti-tTG antibodies was measured by the ELISA technique. SPSS 20.0 was used for the analysis of collected data. Regression analysis test and Spearman rho test was applied for statistical evaluation.

RESULTS

A total of 77 patients were enrolled in the study having a clinical diagnosis of suspected celiac disease on symptomatology. Among these there were 71.4% (n=55) cases of celiac disease confirmed both by histopathology and serology. In Corazza Grading System, Grade-0 included 28.6% (n=22) patients, Corazza A consisted of 22% (n=17) patients, Corazza B1 included 35% (n=27) patients whereas Corazza B2 included 14.3% (n=11) patients.

Serological test for celiac disease was done in all patients using serum IgA anti tissue transglutaminase antibodies. Serological IgA anti-tissue transglutaminase antibodies titers were divided into three groups according to the serological kit manufacture guidelines. Stratification of Corazza grades into quantitative anti-tissue transglutaminase tTG Ab groups (negative 0-10 units, positive 11 to 99 units, strongly positive ≥ 100 units) was done which is shown in Table -I.

Table-I: IgA anti-tTG Ab titers versus Corazza histological grades

Corazza Grades	No of pts.	IgA tTG n < 11 U/ml Negative	IgA tTG n ≥ 11 but <100U/ml Positive	IgA tTG n ≥ 100U/ml Strongly Positive
	n (%)	n (%)	n (%)	n (%)
0	22(28.6%)	21 (95%)	01 (5%)	00 (00%)
A	17(22.1%)	04 (24%)	13 (76%)	00 (00%
B1	27(35.1%)	01 (4%)	12 (44%)	14 (51%)
B2	11(14.3%)	00 (00%)	01 (9%)	10 (90%)

In Corazza grade 0, anti-tTG (IgA Ab) value <11 U/ml was identified in twenty one patients while 1 patient had IgA value between 11 to 100 units/ml. Seventeen patients in Corazza grade A were IgA tTG Ab positive but none had values greater than 100 units/ml. In Corazza B1, 12 patients had IgA tTG Ab values between 11 to 100 units/ml while 14 patients had IgA tTG Ab values greater than 100 units/ml. Eleven patients with Corazza B2 grade had serology titers greater than 100 units/ml as shown in Table -I.

Table-II: Spearman's rho correlation for Corazza grades versus Serology (N=77)

Statistical test	Parameters	Variables	Corrazza	Serology
Spearmann's rho	Corazza grades	Correlation Coefficient	1.00	0.919**
		Sig.(2-tailed)	.	0.00
	Serology	Correlation Coefficient	0.919**	1.000
		Sig.(2-tailed)	0.000	.

Analysis of IgA tTG with Corazza grades by Spearman rho correlation revealed a statistically higher probability of Celiac disease with increasing IgA anti-tissue transglutaminase antibody titers. Each unit of increase of IgA tTG titers increased the risk of having Corazza grades A, B1 or B2 lesions as evident in scatter plot in Figure-1. IgA tTG Ab titers ware significantly

correlated with Corazza grades (Spearman rho =0.919, p ≤ 0.01) as shown in Table-II.

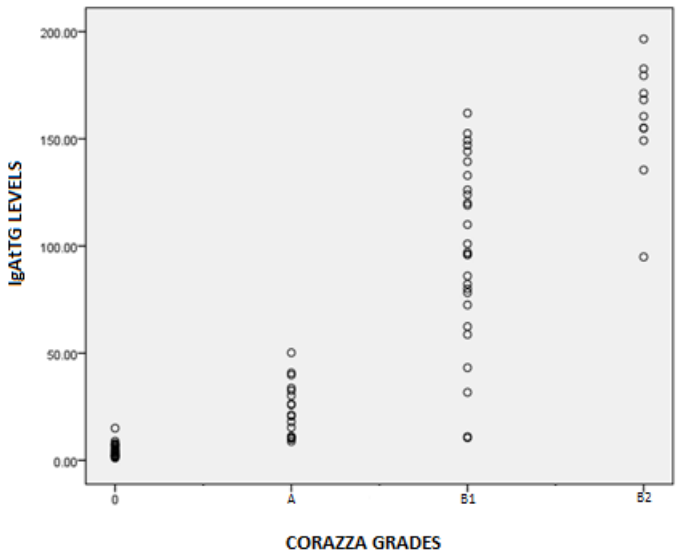

Figure-1: Scatter plot of tTG IgA Ab titers by Corazza grades

DISCUSSION

Celiac disease (CD) is an autoimmune disease characterized by a histopathological and serological changes elicited by ingestion of gluten in genetically predisposed individuals[18]. Applicable diagnostic criteria of celiac disease is required that helps the physicians in avoiding misdiagnosis and missing cases of CD[19]. Clinical features, small bowel histological features and serology specific for celiac disease are several characteristics of disease activity that can serve as potential measures of response to therapeutic intervention in patients with celiac disease[20]. Corazza grading system is actively used for diagnostic as well as for follow up of celiac disease patients[21]. Corazza grading system facilitates in minimizing disagreement between pathologists and also facilitate the comparison between serial follow-up biopsies as compared with modified Marsch grading system[22]. Anti-tTG IgA antibody titer is used to screen as well as monitor symptomatic and asymptomatic patients for celiac disease[23].

Recent studies showed that patients having celiac disease had a significant correlation between endoscopic biopsy findings and serum anti-tissue transglutaminase IgA Ab titers. On the Contrary, Makovicky showed that raised serological titers of different antibodies had lower sensitivity and specificity with the biopsy microscopic findings in celiacs[24].

In the current study, a statistically significant correlation was documented in anti-tissue transglutaminase IgA tTG Ab levels from mild grade disease to highly severe grade disease for Corazza grading system.

Macedo, in his study also showed similar results of positive correlation between serum antibodies with modified Marsch grading system. But no single study is present in the literature which shows correlation between Corazza grades and serological titres[25].

In current study, various statistical tests i-e Spearman rho and regression R2 methods are applied to verify the correlation and it revealed a significant positive correlation with Corazza grading system with p value ≤ 0.01.In 2016, Banotto in his study, had similar statistically results of positive correlation but for Modified Marsch grading system[26].

Corazza grading system correlates with serological marker because it has a simpler range of levels describing the increasing morphological severity of celiac disease in patients. Results showed that the raised positive prognostic titers of serology become more significant in Corazza grade B2 as compared to grade B1 and grade A.

IgA anti-tTG antibody has been used as a sensitive and specific ELISA based test in celiac disease and also there is a positive correlation between titers of tTG antibody and Corazza grading in current study. We propose that repeated endoscopic biopsy should be dejected in celiac patients having strongly positive tTG antibody titers.

In a study conducted by Vivas and colleagues also proposed that duodenal biopsy might be avoided in celiac patients with strongly positive tTG antibody titers. In 2013, this diagnostic approach has been reconfirmed by Mubarak and co-workers that small intestinal biopsy can be avoided in symptomatic patients of celiac disease with tTGA levels ≥100 U/ml[27].

So positive significant correlation is established between Corazza grading system and serum IgA anti-tissue transglutaminase antibodies levels which shows proportionate increase of serum antibodies levels with severity of mucosal damage of intestine. It is therefore recommended that a patient's first diagnosis should be carried out with a combination of biopsy using Corazza grading system and serology. For accurate diagnosis before the treatment plan, endoscopic biopsy should be considered as the benchmark. But in the follow up of celiac disease, repeated biopsies should be avoided as Corazza grading system provides a significant correlation with serological markers as presented in the results. This will allow minimal invasive procedures to be adopted during the course of the treatment of celiac disease, and will also save patients from unwarranted treatment costs.

CONCLUSION

Corazza Grading System significantly correlates with anti-tissue transglutaminase IgA Antibody titers

AUTHOR'S CONTRIBUTION

Usman A: Conceived idea, Designed study, Data analysis, Manuscript writing
Lakhnana NK: Final critical review of manuscript
Sarwar A: Data collection and compilation, Literature review
Zahid M: Statistical Analysis, Literature review

Disclaimer: None.
Conflict of Interest: None.
Source of Funding: None.

REFERENCES

1. Douida A, Tahiri A, Berraho M, Moustapha H, Elyousfi M, Hammas N et al. What is the most reproducible histopathological classification for celiac disease? study of the interobserver variability in a serie of 69 cases. PAMJ Clinic Med.2020;3(2):36–48
2. Singh P, Arora S, Singh A. Prevalence of celiac disease in Asia: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2016;3(1):1095–1101.
3. Dielicrimi R, Cenit C, Nunez C. The genetics of celiac disease: A comprehensive review of clinical implications. J Autoimmun. 2015;64(2):26–41.
4. Nejad RM, Romanos J, Rostami K, Ganji A, Ehsani-Ardakani J, Bakhshipour R et al. Allele and haplotype frequencies for HLA-DQ in Iranian celiac disease patients. World J Gastroenterol. 2014;20(20):6302–6308.
5. Verdu EF, Galipeau HJ, Jabri B. Novel players in celiac disease pathogenesis: the role of gut microbiota. Nat Rev Gastroenterol Hepatol. 2015;185(2):2969–2982.
6. Szakacs Z, Matrai P, Hegyi P, Szabo I, Vincze A, Balasko M, etal. Younger age at diagnosis predisposes to mucosal recovery in celiac disease on a gluten-free diet: A meta-analysis. PLoS One. 2017;12(11):8752-8756.
7. Mardini E, Westgate P, Grigorian AY. Racial Differences in the Prevalence of Celiac Disease in the US Population: National Health and Nutrition Examination Survey (NHANES) 2009-2012. Dig Dis Sci. 2015 ;60(6):1738-1742.
8. Dieli R, Cenit C, Nunez C. The genetics of celiac disease: a comprehensive review of clinical implications. J Autoimmun. 2015;64(1):26-41.
9. Caio G, Giorgio DR, Ursini F. Prevalence of celiac disease serological markers in a cohort of Italian rheumatological patients. Gastroenterol Hepatol Bed Bench. 2018;11(2):244–249.
10. Kim M, Mayassi T, Jabri B. Innate immunity: actuating the gears of celiac disease pathogenesis. Best Pract Res Clin Gastroenterol. 2015;29(1):425-435.
11. Rashid M, Lee J. Serologic testing in celiac disease: Practical guide for clinicians. Can Fam Physician. 2016;62(1):38–43.
12. Peña AS. What is the best histopathological classification for celiac disease? Does it matter? . Gastroenterol Hepatol. 2015;8(4):239-243.
13. Schumann M, Siegmund B, Schulzke D, Fromm M. Celiac disease: role of the epithelial barrier. Cell Mol Gastroenterol Hepatol. 2017;3(2):150–162.
14. Oxentenko S, Murray J. Celiac disease: ten things that every gastroenterologist should know. Clin Gastroenterol Hepatol. 2015;13(1):1396-1410.
15. Daniel C , Murray J , Wu T, Mäki M , Ciarán P. Measuring Change In Small Intestinal Histology In Patients With Celiac Disease. Am J Gastroenterol.2018; 113(1):339-347
16. Toma A. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders.UEG.2019;7(5):583-613.
17. Castillo E, Theethira G, Leffler A. The present and the future in the diagnosis and management of celiac disease. Gastroenterol Rep. 2015;3(1):3-11.
18. Caio G, Volta U, Sapone A, Leffler D, Giorgio R, Fasano A. Celiac disease: a comprehensive current review. BMC Medicine.2019;142(1):17-25.
19. Rahmati A, Shakeri R, Sohrabi M, Alipour A, Boghratian A, Setareh M, et al. Correlation of Tissue Transglutaminase Antibody with Duodenal Histologic Marsh Grading. Middle East J Dig Dis. 2014;6(3):131-136.
20. Bhattacharya M, Lomash A, Sakhuja P, Dubey AP, Kapoor S. Clinical and histopathological correlation of duodenal biopsy with IgA anti-tissue transglutaminase titers in children with celiac disease. Indian J Gastroenterol. 2014 ;33(4):350-354.
21. Rosa M, Ferrari M , Pedrosa M, Ribeiro G, Brasileiro G, Cunha DA, etal. Correlation of endoscopic and histological features in adults with suspected celiac disease in a referral center of minas gerais. Arquivos de Gastroenterologia. 2014 ;51(4) : 290–296.
22. Aldaghi M, Dehghani S, Haghighat M. Evaluation of the Correlation Between tTG-IgA Titer and Duodenal Biopsy Findings in Children With Suspected Celiac Disease. Iran J Pediatr. 2016 ;26(1):3615-3622
23. Makovicky P, Rimarova K, Boor A, Makovicky P, Vodicka P, Samasca G, etal. Correlation between antibodies and histology in celiac disease: Incidence of celiac disease is higher than expected in the pediatric population. Mol Med Reports.2013;8(4): 1079-1083.
24. Macedo R, Abreu M, Salgado M, Meirelles G. Correlation of endoscopic and histological features in adults with suspected celiac disease in a referral center of minas gerais, brazil. Arq Gastroenterol. 2014;51(4):290-296.
25. Bonatto MW, Kotze L, Orlandoski M, Tsuchyia R, Carvalho DCA, Lima D, et al. Endoscopic evaluation of celiac disease severity and its correlation with histopathological aspects of the duodenal mucosa. Endosc Int Open. 2016 ;4(7):767-777.
26. Vivas S, Vaquero L, Martín RL, Caminero A. Age-related differences in celiac disease: Specific characteristics of adult presentation. World J Gastrointest Pharmacol Ther. 2015 ;6(4):207-212.
27. Mubarak A, Spierings E, Wolters V, Otten H, Kate F, Houwen R, etal. Children with celiac disease and high tTGA are genetically and phenotypically different. World J Gastroenterol. 2013;19(41):7114-7120