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Correlation Between Anti TTG(IgA) Assay and Duodenal Histology Grading in Patients with Celiac Disease

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Abstract

Background: To document the relationship between anti tissue transglutaminase assay in celiac disease patients with the histopathology grading of duodenal biopsy.

Materials & Methods: All patients with clinical suspicion of celiac disease were enrolled for study. Patients included in the study have anti TTG assay more than 07 U/mL. All patient included in study with TTG(IgA) positive assay underwent esophagogastroduodenoscopy with duodenal biopsy for histopathology grading.

Results: Total 97 patients included in the study. 50 adult patients with mean age 28.76±13.21 and 47 pediatric patients with mean age 5.99±3.43. There were significant difference in anti TTG assay with relation to histology grades. A statistically significant direct increase in TTG(IgA) titers in patients with celiac disease, according to marsh classification from low to high grade with TTG titer.

Conclusion: There is a strong direct correlation between Anti-tTG (IgA) levels and histological Marsh grades in clinically suspected celiac disease patients.

Keywords: Celiac Disease; TTG; Histology

Abbreviations: CD: Celiac Disease; HLA: Human Leucocyte Antigen; EMA: Endomysial Antibodies; ELISA: Enzyme Linked Immunosorbent Assay

Introduction

Celiac disease (CD), an autoimmune disorder also known as non-tropical sprue, gluten-sensitive enteropathy and endemic sprue is triggered in genetically susceptible individuals by the ingestion of wheat gluten and related proteins of barley and rye [1]. Clinical presentation of CD vary according to the age of patient and disease duration [2]. 90% of celiac disease patients have the human leucocyte antigen (HLA) DQ2, and 10% carry HLA DQ8 haplotype [3,4]. Although celiac disease mainly affects the GIT, it can have many extra intestinal signs and symptoms, and thus the patients are seen by different specialists like Pediatricians, Gastroenterologists, Dermatologists, Endocrinologists, Rheumatologists, Neurologist and Dentists [5]. It is now accepted that absence of chronic diarrhea, malabsorption features or weight loss does not exclude celiac disease as the patient might feel well or can be even overweight [6-8]. Because of inconsistency in clinical signs and symptoms, a substantial proportion of patients have been diagnosed to have irritable bowel syndrome [9]. For definitive diagnosis correlation between clinical features, serologic assays, and histological findings is essential [7]. Serological tests include anti- tissue transglutaminase antibodies (tTG) and anti-endomysial antibodies (EMA).

The diagnostic criteria for coeliac disease are currently based on the finding of small-bowel mucosal villous atrophy and crypt hyperplasia, together with extensive inflammation in both the epithelium and lamina propria as well as clinical and/or histological improvement on a gluten-free diet [9,10]. The duodenal biopsy for CD diagnosis, although still considered gold standard, has many limitations. Endoscopy is an invasive procedure with a number of complications including anxiety and fear related to procedure, local discomfort, bleeding, perforation, infection and anesthesia related complications. Moreover the gross endoscopic findings featuring duodenal folds and mucosal architecture might

be normal and the patchy distribution of intestinal mucosal damage and incorrect biopsy orientation for villous morphology evaluation further limits the biopsy value [11-13]. Nevertheless villous atrophy is not specific to celiac disease and can be present in number of other conditions including infectious diseases (Tropical sprue, Giardiasis) ,Whipple's disease, AIDS enteropathy, Autoimmune enteropathy, Drugs (MMF, Olmesartan, Colchicine, Chemotherapy, Immunotherapy), Nutritional Deficiency, EATL [14].The European Society of Pediatric Gastroenterology and Nutrition in its recent guidelines considered the diagnosis of CD in children without any biopsies and only by clinical manifestations and serological tests [15]. The aim of this study was to document the correlation that carefully selected patients with high clinical suspicion of celiac disease and raised titer of anti tTG(IgA) have significant histopathological findings on duodenal biopsy.

Methodology

It was a prospective observational study including 97 patients, 50 adult and 47 from pediatric age group. Patients were enrolled by consecutive, non-probability sampling technique. Study was carried out in medical and pediatric department of Benazir Bhutto hospital from January 2018 to June 2022.

Inclusion Criteria

a. Adult male and females patients with age > 14 years.

b. Patients in pediatric group from 2-13yrs.

c. Patients having intestinal and extra intestinal symptoms like diarrhea, abdominal distension, abdominal pain, malabsorption features, malnutrition. short stature, anemia, mouth ulcers, dermatitis herpetiformis, Type I diabetes mellitus and infertility.

Exclusion Criteria

i. Patients already diagnosed celiac disease on GFD.

ii. Patients with chronic diarrhea due to other diseases.

iii. Patients with immunoglobulin A (IgA) Deficiency.

Data collection procedure

After informed consent, detailed history was taken regarding symptoms and associated autoimmune diseases. 3 ml venous blood was drawn and sent for Anti-tTG (IgA) titers, which was analyzed by enzyme linked immunosorbent assay (ELISA). Endoscopy was performed in Benazir Bhutto Hospital; Endoscopy Department and six biopsies were taken from the duodenum by consultant Gastroenterologist .Biopsies were sent for histopathological analysis which was done by single histopathologist. Histological grading was performed as per Modified Marsh System. Data was entered and analyzed using SPSS V22.0 Shapiro Wilk test was applied to determine normality of distribution of age and serum Anti tTG IgA levels. Descriptive statistics were applied for quantitative variables.

Mean and Standard Deviation were determined for age and serum anti tTG IgA levels. Pearson's correlation test was applied to determine association between age and serum anti tTG IgA levels. Frequencies and Percentages were determined for qualitative variables like presence or absence of villous atrophy and distribution as per modified marsh criteria. Fischer's Exact Test was applied to determine association of age group and gender with severity as per modified Marsh criteria. One Way ANOVA was applied to compare mean serum anti tTG IgA levels between grades as per modified Marsh Criteria. $P < 0.05$ was considered significant. A value of 7 U/ml was considered as upper limit for serum anti tTG IgA levels. Sensitivity, Specificity, PPV and NPV were determined for positive or negative tTG with presence or absence of villous atrophy.

Results

A total of 97 participants, 50 adult and 47 from pediatric age group, were included in this study. Mean age of participants from adult age group was 28.76±13.21 while in pediatric age group it was 5.99±3.43 while mean serum anti tTG IgA levels were 191.04±38.99 and 130.38±233.58 respectively. Shapiro Wilk test was applied to determine normality of distribution of Age and IgA levels. The data was normally distributed. ($p<0.000$) (Graph 1 & 2) . Although age and IgA levels were normally distributed, yet correlation between these was statistically insignificant as per Pearson's correlation test. ($p=0.179$). It was observed that villous atrophy was present in 74 (76.3%) while absent in 23 (23.7%) of the patients. 75 (77.3%) patients were graded as Marsh 3, 5 (5.2%) as Marsh 2, 2 (2.1%) as Marsh I while 15 (15.5%) were graded as Marsh 0. The difference in distribution of severity by Modified Marsh Criteria as per gender was statistically insignificant. (Fischer's Exact Test=2.540, $p=0.545$) while as per age group was statistically significant. (Fischer's Exact Test =22.420, $p<0.000$) (Table 1). It was observed that most of the patients with Marsh III had villous atrophy present. (Fischer's Exact=87.77, $p<0.000$) (Table 2). However, difference in mean anti tTG IgA levels as per severity by Modified Marsh Criteria was very highly statistically significant as per One Way ANOVA test. ($p<0.000$) (Figure I, Table 3).

ROC curve was plotted to determine predictive value of anti tTG IgA levels for presence of villous atrophy in both age groups. A value of 7 U/ml was considered upper limit for anti tTG IgA. Association between villous atrophy on histopathology and anti tTG value was established along with Modified Marsh Criteria .Area Under the Curve was 0.996 with $p<0.000$ for adult population. It was observed that serum IgA levels of 87.50 had 100% sensitivity and 80% specificity to predict presence of villous atrophy in adult population (Figure 2). However, for pediatric population, Area Under the Curve was 0.852 with $p<0.000$ for Anti tTG IgA levels as predictor of presence of villous atrophy. A value of 70 U/ml had 93.1% sensitivity and 77.8% specificity (Figure 3).

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Table 1: Distribution of Severity as per Modified Marsh Criteria with Respect to age and Gender.

		Modified Marsh Criteria							
		Marsh 0		Marsh I		Marsh II		Marsh III	
		Total Patients	Percentage	Total Patient	Percentage	Total Patient	Percentage	Total Patient	Percentge
Age Group	Pediatric	15	31.91	0	0	2	4.26	30	63.83
	Adult	0	0	2	4	3	6	45	90
Gender	Male	9	20.45	1	2.27	3	6.82	31	70.45
	Female	6	11-.32	1	1.89	2	3.77	44	83.02

Table 2: Distribution of Marsh Criteria as per presence of Villous Atrophy.

Age Group	Modified Marsh Criteria	Villous Atrophy	
		No	Yes
Pediatric	Marsh 0	15	0
	Marsh I	0	0
	Marsh II	2	0
	Marsh III	1	29
Adult	Marsh 0	0	0
	Marsh I	2	0
	Marsh II	3	0
	Marsh III	0	45

Table 3: Mean anti tTG IgA levels as per Modified Marsh Criteria in different age groups.

Modified Marsh Criteria	Age Group			
	Pediatric		Adult	
	Mean	SD	Mean	SD
Marsh 0	6.29	5.99	-	-
Marsh 1	-	-	87.5	9.19
Marsh 2	13.05	10.82	151.33	1.15
Marsh 3	200.25	269.37	198.29	32.28

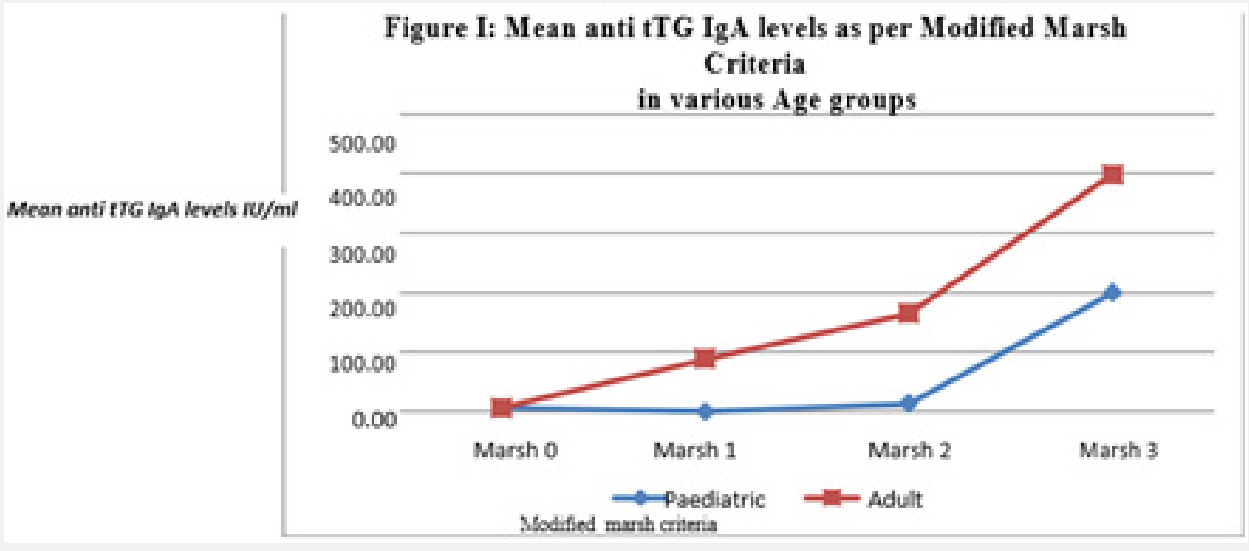

Figure 1: Mean anti tTG IgA levels as per Modified Marsh Criteria in various Age groups.

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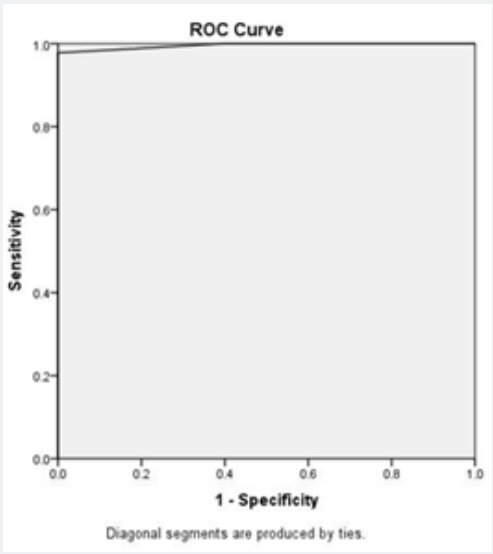

Figure 2: ROC curve for serum IgA levels as predictor of presence of villous atrophy in Adult population.

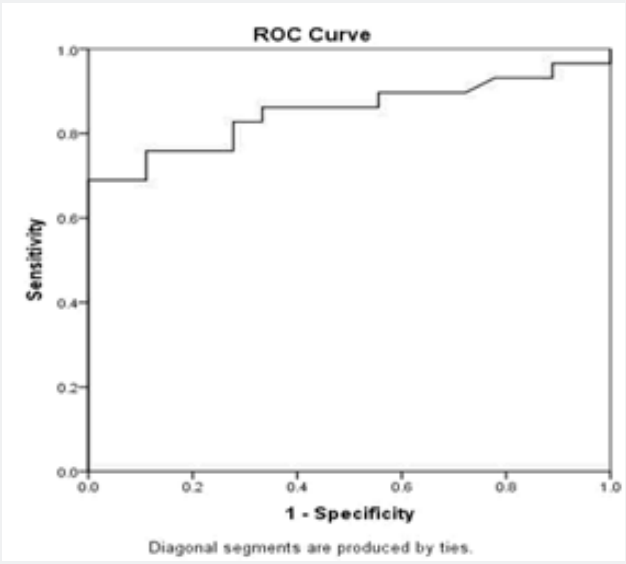

Figure 3: ROC curve for serum IgA levels as predictors of presence of villous atrophy in Pediatric Population.

Discussion

Celiac disease can present with intestinal, extraintestinal or malabsorption features. The prevalence of CD is around 1% globally but disparity between different regions. Celiac disease is a condition which is under diagnosed and undiagnosed cases are more as compared to diagnosed. It is now accepted as a more complex disease, so a multidisciplinary approach is required for correct diagnosis and management of celiac disease [16]. The purpose of our study was to see the correlation between anti-tTG levels and histological Marsh grades in pediatric and adult patients with high index of celiac disease. Among the 97 participants, 50 adult and 47 from pediatric age group were included for the data analysis. Patients who had intestinal, extraintestinal and malabsorption features were enrolled in the study. Mean age of participants from adult age group was 28.76±13.21 (mean ± SD) while in pediatric age group it was 5.99±3.43 while mean Anti tTG IgA levels were 191.04±38.99 and 130.38±233.58 respectively. 75 (77.3%) patients were graded as Marsh 3, 5 (5.2%) Marsh 2, 2 (2.1%) Marsh I while 15 (15.5%) were graded as Marsh 0. Villous atrophy was present in 74 (76.3%) while absent in 23 (23.7%) of the patients.

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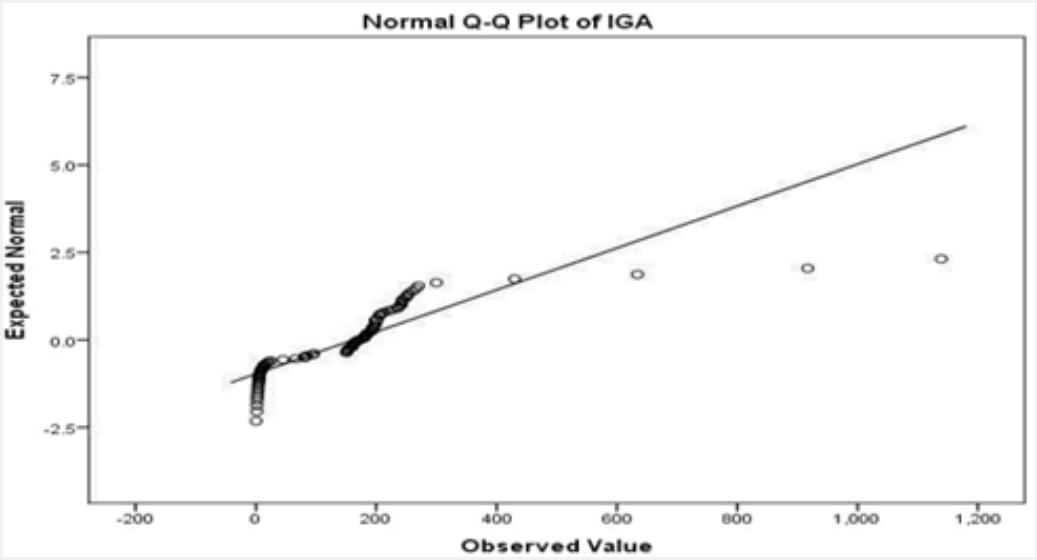
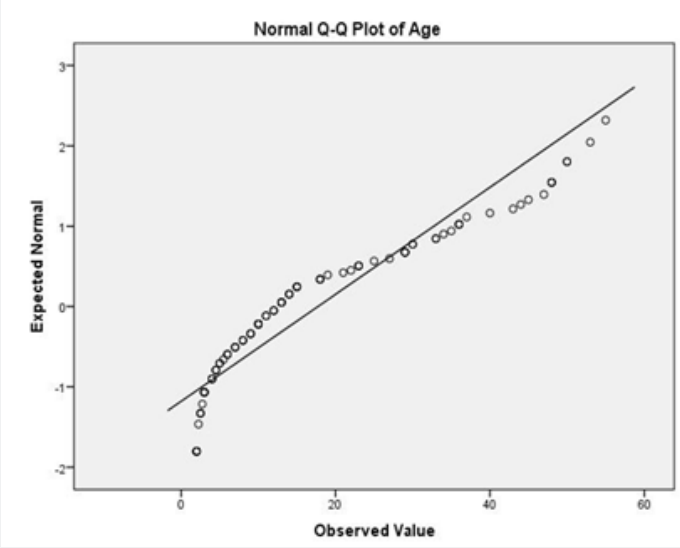


Graph 1: Normal Q-Q plot of IGA.



Graph 2: Normal Q-Q plot of Age.

It was observed that most of the patients with Marsh III had villous atrophy on histology. Our study revealed that there were significant differences in anti tTG (IgA) levels in celiac disease patients across different Marsh groups.. It was observed that serum IgA levels of 87.50 U/ml had 100% sensitivity and 80% specificity to predict presence of villous atrophy in adult population and value of 70 U/ml had 93.1% sensitivity and 77.8% specificity in pediatric group. There was a statistically significant increase in titres of anti tTG from low to high grades of histological Marsh classification. No adult patient has grade 0 histology, while 15 (31.9%) pediatric patients have Marsh 0 grade. This may be due to low thresh hold to conduct duodenal biopsy in our team. Kalhan et al, in his study found maximum patient with Marsh grade 3 histology and all have significant increasing trend in anti tTG levels from histology lower to higher Marsh grade [17].

Rahmati et al, also observed statistically increase tTG antibody levels from normal to complete villous atrophy in Marsh histology grade in his study [18]. Vivas S et al. [18], studied both adults and children and revealed that there was a significant progressive increase in mean tissue transglutaminase antibody titers with higher Marsh histology grades in both population [19].

In our study, we also found that there is a statistically significant increase in tTG antibody levels with relation to duodenal damage

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according to modified Marsh histology grades and it was also observed in many previous studies. Intestinal biopsy for diagnosis of celiac disease, although is a gold standard but has many limitations. Atleast four different portions of duodenal mucosa, biopsy should be taken [20] due to patchy damage of intestinal mucosa in celiac disease [21]. Proper orientation and positioning of sampling is must as incorrect sample preparation can give false diagnosis of disease due to false villi atrophy and increased lymphocyte count in lamina propria and epithelium [22-25]. Thirdly biopsy material for histopatholgy is often insufficient to make a diagnosis, a multicenter study concluded that more than 10% of biopsy specimens were insufficient to reach the diagnosis of celiac disease [2]. Interobserver variability in histological examination and availability of endoscopic facility especially pediatric endoscopy are the other limiting factors.

Due to high performance of available screening tests and above mentioned limitations of duodenal biopsy, many experts thought that the biopsy is not needed for celiac disease diagnosis when there were high levels of anti tTG(IgA) [9,22-24]. In patients where celiac disease is suspected or in high risk patients such as first degree relatives of diagnosed celiac disease patients , type 1 diabetics, thyroid dysfunction, patients of Down syndrome; for celiac disease diagnosis serology can be the first line investigation [1] regardless of the presence or absence of clinical features of celiac disease. Limitations of our study include small sample size, single center study and our study does not represent whole population as in pediatric age group, patients who were less than 2 years of age were not included. Our histopathologist was not blind to anti-tTG level of every patient [26-28]. This could lead to a biased reporting of duodenal biopsy. Therefore for further validation we suggest studies at large scale where histopathologist should be blind to anti-tTG level. Therefore, we propose endoscopic duodenal mucosal biopsy should not be carried out in patients where anti tTG levels were >70 U/ml (both adults & children) or should be performed where the serology is negative and patient has strong clinical suspicion of celiac disease.

Conclusion

Our study showed that there is a strong correlation between anti tTG (IgA) levels and histological Marsh classification, higher titers were found in advanced Marsh grades eliminating the need for duodenal biopsy for the diagnosis of celiac disease in both adult and pediatric age groups. This study would be helpful in the diagnosis of the celiac disease in areas and institutions where endoscopic biopsy cannot be performed due to availability of endoscopy facility and experienced endoscopist & histopathologist.

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