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Evaluating the Correlation between High Titers of Tissue-Transglutaminase Antibody with the Grade of Severity of Villous Atrophy in Syrian Patients with Celiac Disease

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Background. Diagnosis of celiac disease depends on the patient's history and serological tests, and is confirmed by biopsies from the duodenum. Biopsies from the small intestine could be dispensable regarding the verification of celiac disease with the presence of high levels of atissue-transglutaminase antibody.
Aim. The objective of this investigation is to substantiate the correlation between titers of anti-tissue transglutaminase type IgA (anti-tTG IgA) and the severity of histological alterations in Syrian patients with celiac disease and to determine the diagnostic level of anti-tTG to previse celiac disease in adults and children without the necessity of a biopsy sampling.
Materials and methods. The study was conducted as a prospective cohort study with the participation of 100 symptomatic patients between the age group of 6–65 years. All participants underwent upper gastrointestinal endoscopy. Two samples were taken from the duodenum and were evaluated by an expert pathologist according to Marsh grading. Serum anti-tTG Ig A levels were measured as well to determine any association between the levels of serum anti-tTG Ig A and Marsh grading.
Results. The mean age of the patients was (18.55 ± 12.92). Anemia was the most frequent non-gastrointestinal finding as it was found among 35 % of the participant, but no remarkable association was found between Marsh grading and hemoglobin levels ($r = 0.36$, $p > 0.05$). However, serum tTGA levels were positively correlated with Marsh grading ($r = 0.718$, $p < 0.001$). Receiver-operator curve (ROC) analysis cut-off value of serum anti-tTGA for speculating villous atrophy was 270 IU/ml of cut-off value with a sensitivity of 100 % and a specificity of 89 %.
Conclusion. Duodenal biopsies could be foregone during the diagnosis of susceptible patients for celiac disease with high anti-tTG Ig A.
Keywords: celiac disease, duodenal biopsy**,** anti-tissue transglutaminase IgA, histology, March grading
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Оценка корреляции между титром антител к тканевой трансглутаминазе и выраженностью атрофии ворсин тонкой кишки при целиакии в сирийской популяции

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Введение. Диагноз целиакии заподозривают на основании анализа клинической картины заболевания и серологических тестов и подтверждают данными биопсии двенадцатиперстной кишки. Однако при высоком титре антител против тканевой трансглутаминазы верификацию данного диагноза возможно провести и без выполнения биопсии.
Цель. Целью данного исследования является оценка корреляции между титром антител против тканевой трансглутаминазы (анти-tTG) IgA и степенью выраженности гистологических изменений при целиакии

в сирийской популяции, а также установление диагностического титра данных антител для верификации диагноза «целиакия» у детей и взрослых без проведения биопсии.
Материалы и методы. В проспективном когортном исследовании приняли участие 100 больных с целиакией в возрасте от 6 до 65 лет. Всем им была выполнена эзофагогастродуоденоскопия с проведением биопсии слизистой оболочки двенадцатиперстной кишки (взято 2 биоптата) и определение титра анти-tTG IgA. Оценка гистологических изменений в биоптатах была проведена в соответствии со шкалой Марша патоморфологом-экспертом.
Результаты. Средний возраст пациентов составил 18,55 ± 12,92 года. Анемия была выявлена у 35 % из них и оказалась самым частым внекишечным проявлением целиакии. При этом не было значимой корреляции между стадией гистологических изменений по Маршу и уровнем гемоглобина в крови (r = 0,36, p > 0,05). Однако уровень анти-tTG IgA значимо позитивно коррелировал со стадией гистологический изменений по Маршу (r = 0,718, p < 0,001). ROC-анализ установил, что использование 270 МЕ/мл в качестве точки отсечения значения содержания анти-tTG IgA в крови позволяет предсказать выявление атрофии ворсин при проведении биопсии двенадцатиперстной кишки с чувствительностью 100 % и специфичностью 89 %.
Выводы. Диагноз целиакии может быть поставлен без проведения биопсии слизистой оболочки двенадцатиперстной кишки на основании высоких титров антител против тканевой трансглутаминазы.
Ключевые слова: целиакия, биопсия двенадцатиперстной кишки, антитела против тканевой трансглутаминазы, гистология, шкала Марша
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Introduction

Celiac disease (CD) results from an autoimmune disorder caused by consuming gluten in people who are genetically vulnerable. It affects about 1–3 % of individuals worldwide [1]. The manifestations of the disease differ greatly between the affected persons, ranging from malabsorption to extraintestinal complaints [2]. The classical symptoms and signs incorporate: diarrhea, weight loss, failure to thrive, anemia, bloating, chronic fatigue, headache and abdominal pain; the latter being the most common [3, 4]. Most patients with celiac disease have tissues transglutaminase antibodies (anti-tTG) and endomysial antibodies (EMA) type IgA which are sensitive and specific [5, 6]. The diagnosis of the Celiac disease requires upper endoscopy of the duodenum, taking biopsies, and evaluating the presence of any villous dystrophy depending on the classification of Marsh [7] (Table 1). Finally, scalloping of the gut layers can also be noted during endoscopy [8]. The recent recommendations of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) explained that the diagnoses of the Celiac disease in children can be done without a biopsy from the duodenum if the titer of the anti-tTG antibodies is ≥10 times greater than the upper limit value with positive EMA test in a separate sample of blood. Moreover, the recent recommendations have forsaken the presence symptoms as a diagnostic requirement and indicated that high serum titer of anti-tTG antibodies is by itself enough for celiac disease diagnoses [9, 10].

Some studies have suggested the presence of an association between serum antibody levels and villous dystrophy in the guts of affected children and adults [11–16]. There is little evidence regarding the correlation between the levels of serum antibody and the levels of iron [16, 17].

The past studies reported a high prevalence of CD amongst the Syria population (1/62 of healthy individuals) [18, 19]. As a huge ratio of CD patients in this region are not diagnosed, studying the relationship between anti-tTG antibody titer and the severity of villous pathological changes in these patients will be useful. These data will make CD identification easier in low-income regions such as Syria, where there are many CD patients and insufficient number of gastroenterologists, endoscopic facilities, and qualified pathologists. The goal of this study is to find a correlation between the titers of anti-tTG IgA and the severity of villous changes in Syrians diagnosed with CD according to Marsh scale. We also attempted to identify anti-tTG sensitivity and specificity regarding the diagnosis of celiac disease so that it can be used in CD diagnosis in susceptible cases instead of duodenal biopsies.

Materials and Methods

The presented study has been carried out between July 2019 to January 2020. A total of 110 patients

Table 1. Marsh Classification for Celiac Disease

Таблица 1. Классификация гистологических изменений в слизистой двенадцатиперстной кишки по Маршу

	Marsh 0	Marsh 1	Marsh 2	Marsh 3		
				3a	3b	3c
IEL Count*	<30/100	>30/100	>30/100	>30/100	>30/100	>30/100
Crypt Hyperplasia	Normal	Normal	Increased	+	+	+
Villous atrophy	Normal	Normal	Normal	Mild	Moderate	Total
	Pre-infiltrative	Infiltrative	Infiltrative-hyperplastic	Flat destructive		
IEL — intraepithelial lymphocytes. * Number of intraepithelial lymphocytes per 100 enterocytes.						

of the University hospitals and gastroenterological centers who had a high probability of having CD depending on their clinical symptoms and features (anemia, diarrhea, bloating, abdominal pain, weight loss, short stature, anorexia, vomiting, constipation) were screened for inclusion in the study. Patients with positive stool for giardiasis (n = 4), Ig A deficiency (n = 2) and those already diagnosed with CD and maintained a diet free from gluten (n = 4) were excluded from the study. As a result, 100 patients were included in the study. Laboratory data including complete blood count, liver and thyroid function tests, iron profile tests and calcium levels as well as demographic information and symptoms data were extracted from the hospital records of the patients.

Five milliliters of venous blood were gathered from all patients under aseptic safety measures. All specimens were labeled by a serial number and the person's name, and then were immediately frozen at -20 °C.

All patients were tested for anti-tTG IgA using the ELISA technique (Diametra/Italy), and the cut-off value > 20 IU/ml was considered as positive value according to the manufacturer's instructions.

Ethical approval was procured from the Research Ethics Committee of the University of Damascus. Each patient signed a consent form after fully explaining to them the objectives of the study and the expected benefits from participating in it. A parental approval was obtained for participated children.

Statistical analysis

Data are expressed as mean ± standard deviation. All study variables were tested for normality using the Kolmogorov — Smirnov test. Comparisons between groups were obtained using the Mann-Whitney and Kruskal-Wallis tests. Spearman rank test was used to evaluate the correlation between villous atrophy and serum anti-tTG Ig A. Specificity, sensitivity, and area under were calculated. Optimal cut-off points and relative sensitivity and specificities were calculated according to Youden index (J) = maximum {sensitivity — specificity — 1} after the receiver operating characteristic (ROC) analysis. Statistical tests were conducted utilizing GraphPad Prism (GraphPad Software, Inc., San Diego, CA). A p-value < 0.05 was noted as a significant result.

Results

The study population included 52 (52 %) males and 48 (48 %) females. The age of the patients was 18.6 ± 12.9 years (range: 6–65 years).

Modified Marsh scale was used for the classification of duodenal biopsies [4, 5, 14, 15]. The demographic attributes of the included patients in various Marsh staging are shown in Table 2.

As shown in Table 2, anemia prevalence in patients with villous atrophy was 35 % making it the most frequent non-gastrointestinal finding. Nevertheless, no significant interrelation between Marsh grading and hemoglobin levels (r = 0.36) was found, Thus, there is no relationship between the severity of iron deficiency anemia and the severity of histological changes in celiac disease.

Although the frequency of most gastrointestinal (GI) symptoms was higher in Marsh II group compared to the other Marsh groups, there were no statistically significant differences in them among different Marsh grading.

Our results showed that the range of anti-tTG IgA values among CD patients was 343.7 ± 278.4 IU/ml (range 56–890 IU/ml). There was no meaningful difference in value of anti-tTG IgA between males and females (392.26 ± 292.19 vs. 293.00 ± 255.39 IU/ml; p = 0.3).

A significant association between the increased levels of anti-tTG IgA and elevated score of modified Marsh scale (i.e. severity of villous atrophy) was found (Table 3; Figure 1).

The average fold-increase of anti-tTG IgA was 2.9 ± 0.5 in patients with Marsh grade 2, 4.7 ± 0.5 in grade 3A, 12.4 ± 5.0 in grade 3B was and 33.0 ± 7.3 in grade 3C (Figure 2; Table 4). There was significant difference in anti-tTG IgA between atrophic (3) and non-atrophic (0-2) Marsh grades (p < 0.001).

A strong positive correlation between Marsh grade of villous atrophy and serum levels of anti-tTG was found (r = 0,718; p < 0.001).

Table 2. The descriptive features of patients in various Marsh staging

Таблица 2. Характеристики пациентов, классифицированных по разным стадиям гистологических изменений в биоптатах слизистой оболочки двенадцатиперстной кишки по модифицированной шкале Марша

Variable		Modified Marsh Classification					
			Normal & Marsh I	II	IIIa	IIIb	IIIc
Frequency (%)			9	19	17	25	30
Mean ± SD age (year)		19.1 ± 13.7	15.8 ± 18.3	21.5 ± 14.6	22.2 ± 18	18.0 ± 13.2	17.7 ± 8.7
Sex (%)	Female	49	0	11	9	14	15
	Male	51	9	8	8	11	15
Anemia	Total (%)	35 (35 %)	10	8	5	2	7
Bloating		16 (16 %)	3	6	2	1	4
Abdominal pain		12 (12 %)	4	5	1	1	1
Diarrhea		22 (22 %)	5	9	4	2	2
Weight loss		16 (16 %)	4	7	1	2	2
Short stature		6 (6 %)	2	0	1	1	2
Anorexia		11 (11 %)	1	2	1	2	5
Constipation		10 (10 %)	1	4	1	2	2

Table 3. The levels tissues transglutaminase antibodies (anti-tTG) IgA in the patients with different Marsh grade.

Таблица 3. Уровень антител против тканевой трансглутаминазы у пациентов, классифицированных по разным стадиям гистологических изменений в биоптатах слизистой оболочки двенадцатиперстной кишки по шкале Марша

Marsh grade	Anti-tTG IgA, IU/ml	Number of patients (%)
Grade 1	70.6 ± 34.9	9 (9)
Grade 2	97.56 ± 39.7	19 (19)
Grade 3A	158.1 ± 46.7	17 (17)
Grade 3B	224.1 ± 82.0	25 (25)
Grade 3c	497.6 ± 221.4	30 (30)

Table 4. Significance of differences in the serum level of antibodies against tissue transglutaminase between groups of patients with different values of the Marsh scale

Таблица 4. Значимость разниц в содержании антител против тканевой трансглутаминазы в крови между группами пациентов с разными значениями шкалы Марша

Marsh Grades	1–2	1–3A	1–3B	1–3C	2–3A	2–3B	2–3C	3A–3B	3A–3C	3B–3C
p-value	0.048	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.005	<0.001	<0.001

ROC-analysis was used to determine a cut-off point for anti-tTG IgA to distinguish atrophic (Marsh 3a–c) and non-atrophic (Marsh 0–2) villous lesions accurately. Area under the curve (AUC) was 0.97 (95 % CI 0.94–0.99). Cut-off value of serum anti-tTG IgA for predicting villous atrophy was 270 IU/ml (13.5 times of the upper limit of normal range) with sensitivity of 100 % and specificity of 89 %.

Discussion

New evidence supporting the positive correlation between serum anti-tTG IgA level and duodenal damage has been building up in the last few years, and biopsy is no longer a requirement for confirming the diagnosis of CD, as elevated titers of anti-tTG IgA strongly suggest the presence of the disease presence. In addition, recent ESPGHAN guidelines regarding the diagnosis of CD in pediatric settings

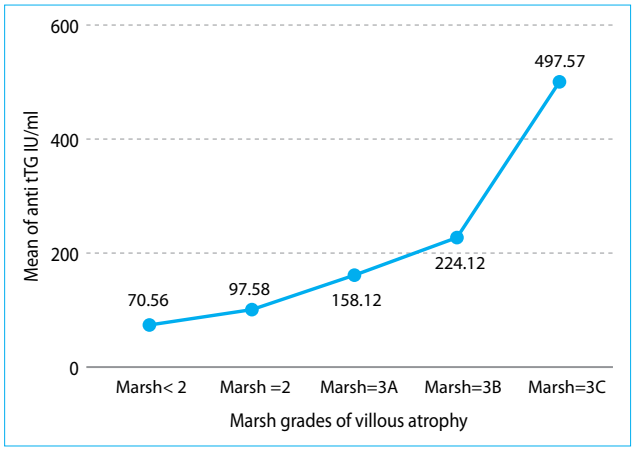

Fig. 1. Correlation between levels of anti-tTG IgA and score of Marsh scale
Рис. 1. Корреляция между уровнем антител к тканевой трансглутаминазе в крови и степенью выраженности гистологических изменений в биоптатах слизистой оболочки двенадцатиперстной кишки по шкале Марша

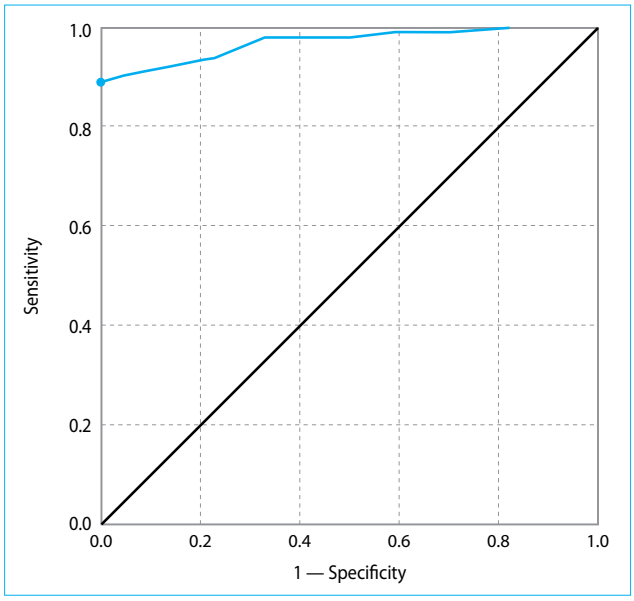

Fig. 3. Receiver operating characteristic (ROC) curve between anti-tissue transglutaminase IgA and atrophic/non-atrophic Marsh staging
Рис. 3. ROC-анализ предсказательной ценности значений содержания антител против тканевой трансглутаминазы в крови в отношении выявления атрофии ворсин слизистой оболочки двенадцатиперстной кишки

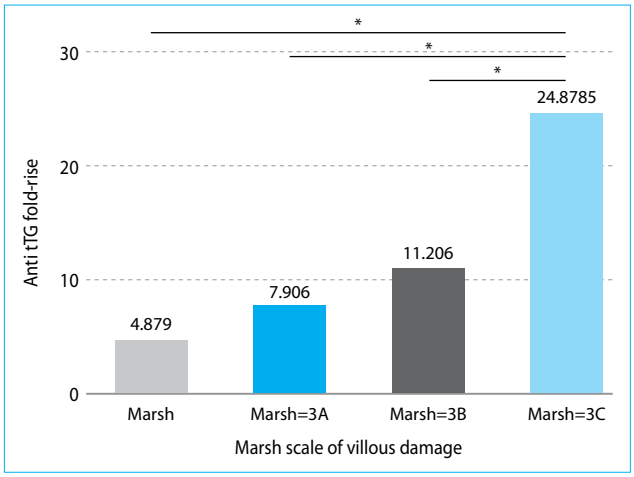

Fig. 2. Mean anti-tTG fold-rise in celiac patients with various grades of villous atrophy (Marsh scale).
* $p < 0.05$
Рис. 2. Средняя кратность увеличения содержания в крови антител против тканевой трансглутаминазы у пациентов с разной степенью атрофии ворсинок двенадцатиперстной кишки по шкале Марша. * $p < 0.05$

have discarded the need for histological confirmation in patients who are symptomatic and have at least 10 times anti-tTG IgA levels of the upper limit of normal range and whose symptoms resolve with the gluten free diet [8,9].

Our study showed a correlation between anti-tTG IgA levels and extent of duodenal damage. Our findings were as follow: anti-tTG IgA levels more than 13.5 times a manufacturers' recommended cut-off value (anti-tTG IgA ≥ 270 IU/ml) had a sensitivity of 100 % and specificity of 89 % for Marsh 3 and correlated with more duodenal damage. These results are in agreement with recent findings in similar studies [20–22].

Scientists in Iran have shown that anti-tTG titers in CD patients that were 9 times higher than the normal kit's cut-off value had sensitivity of 97.2 % for Marsh 2 and more extensive duodenal injury [23]. The study concluded that in this case, it is possible to avoid duodenal biopsy for diagnosing those patients. However, small intestinal biopsy is always necessary when there is a doubt about the diagnosis regardless of serological tests results [23]. An Italian study at Brescia University College revealed that it is possible to diagnose CD and to predict the degree of villous atrophy without a biopsy when the patient has elevated value (5-fold higher than the cut-off value) of anti-tTG [22].

A study in the USA has found that anti-tTG IgA ≥ 100 IU/ml was associated with villous atrophy (Marsh 3 duodenal histopathology) in children and adults with CD. Despite the high specificity of this value, some cases did not demonstrate any villous atrophy. The researchers suggested that these serological tests are very useful for CD diagnosis, but they cannot entirely replace duodenal biopsy [14]. Other results from Indian investigations have demonstrated that when anti-tTG IgA titer are ≥ 14-fold higher than the normal kit's cut-off value, the positive predictive value was 100 % for the diagnosis of CD. So the severity of duodenal atrophy can be presumed by measuring the high titer of anti-tTG IgA. However, the study found that more than 40 % of CD patients with anti-tTG IgA titer <20 IU/ml had severe

villous atrophy. That is why it is of high importance to perform endoscopy and take mucosal biopsy even with titers <20 IU/ml, according to this study [16]. Outcomes from the Italian group at the University of Brescia speculated that elevated titer of anti-tTG IgA >5-fold of normal kit's cut-off value can predict villous atrophy of small intestine in adults who have an increased risk for CD. The study concluded that in 1/3 of the duodenal biopsy could be avoided [24].

Prospective data gathered by Onyeador et al. in 126 symptomatic children who had CD that was histologically confirmed that 98.3 % of them had anti-tTG > 100 U/ml (>10 ULN). However, total villous atrophy was encountered in greater frequency with anti-tTG level >200 U/ml [25]. In an another study by Vivas et al. a comparison between adult and pediatric CD population found less severe histopathological manifestations (26 % vs. 63 %, $p < 0.001$) and lower anti-tTG antibody titers in the adult group compared with the children's group. Thus, it could be concluded that anti-tTG >30 U/ml can replace biopsy usage for CD diagnosis in children, but this cannot be applied in adults cases due to dissimilarity in the model of presentation and monitoring between the two groups [26]. Similar comparable results have been observed in previous retrospective studies: high levels of anti-tTG IgA are interrelated with histological damage pathognomonic for CD [27, 28]. Barker et al. reported that 48 of 49 children with CD symptoms and anti-tTG level ≥ 100 U/ml had positive biopsy findings [29].

In a comparable manner, Donaldson et al. found that all of the 38 pediatric patients in with anti-tTG IgA ≥100 U/ml had Marsh 3 grade [30]. Lately, another retrospective study in pediatric settings supported the utilization of a biopsy sparing protocol as it reasonable and easy to apply in both symptomatic and asymptomatic patients when anti-tTG titer was ≥10 times ULN [31].

Moreover, the results of our study also showed anemia to be the most common laboratory finding among celiac disease patients and that the three most common complaints were bloating, abdominal pain, and diarrhea respectively. These results are in agreement with the results of a recent study [32].

Considering the high prevalence of celiac disease in Syria, reported to be 1:62 and similar to western countries [33, 34], it seems that anti-tTG test can be applied for the diagnosis of celiac disease without the need for duodenal biopsy, at least in patients with very high titers of serum antibody, approximately between 5 to 14 folds higher than normal values.

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