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ORIGINAL ARTICLE

Serum Anti-Tissue Transglutaminase IgA Antibodies in Patients with Psoriasis Vulgaris and Relation to its Severity

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ABSTRACT

Background: Psoriasis is a common skin disease associated with different co-morbidities. High serum levels of anti-tissue transglutaminase-2 IgA (TTG-IgA), produced and deposited in the intestine, characterizes celiac disease. Recently, an elevation in TTG-IgA antibodies in psoriatic cases was reported, compared to non-psoriatics.

The aim of the current study was to compare the level of anti-tissue transglutaminase IgA in psoriatic patients versus non-psoriatic control group and to find a possible relation with disease severity.

Methods: This was a case-control study conducted on 45 patients with psoriasis who attended the outpatient clinic of Dermatology, Andrology & STDs Department of Mansoura University Hospitals, and 45 age and sex matched completely healthy people.

Results: Psoriatic cases demonstrated a significant increase in TTG-IgA serum levels compared to non-psoriatic controls. GIT manifestations were prevalent among psoriatic cases and were related positively to the degree of psoriasis activity (PASI score). TTG-IgA concentration showed excellent value in differentiating psoriatic cases from controls. TTG-IgA demonstrated as a significant positive correlation with PASI score among psoriatic cases.

Conclusions: TTG-IgA concentration could be used as a significant predictor for psoriasis as well as its severity.

Keywords: Anti-tissue transglutaminase IgA antibodies; Celiac disease; PASI score;Psoriasis.

INTRODUCTION

Psoriasis is a common skin disease with a prevalence of 2% of general population. Various comorbidities have been linked with psoriasis, some examples are: psoriatic arthritis (PsA), Crohn's disease, psychological/psychiatric disorders (DPP), uveitis, and metabolic syndrome [1, 2].

Coeliac disease (CD) is characterized by inflammatory process involving the mucosa of the small intestine in response to dietary gluten, leading to villous atrophy and crypt hyperplasia [3].

The association between psoriasis and CD has been studied thoroughly in the past decade [4, 5]. It was demonstrated that the prevalence of celiac disease in psoriatic patients was 0.29% versus 0.11% in controls. Other two studies suggested that antibodies related to CD showed elevated values that correlated with psoriasis and psoriatic arthritis severity [6, 7]. Acharya and Mathur, found that the likelihood of patients with psoriasis to be diagnosed with CD were 2.16-folds and that of patients with CD to have psoriasis were 1.8-folds higher [4]. Interestingly, psoriatic skin lesions were proved to be evoked by some genetic and common immunlogic mechanisms of CD-associated enteropathy occurring in patients who were not still diagnosed or have not receive treatment [8]. This can be explained by the fact that both CD and psoriasis are T cell-mediated disorders. Furthermore, the inflammatory response of the mucosa of the small intestine in CD is mainly a T helper 1 immune response with the prominent role of of Th17 [9]. Therefore, no wonder that antibodies

that characterize CD such as antigliadin IgA, IgG, anti-endomysium IgA and anti- transglutaminase IgA rise concomitantly in patients with psoriasis [5,10].

Increased gluten sensitivity prevalence was observed in patients with psoriasis. Although gluten-sensitive enteropathy can be asymptomatic, it can manifest with gastric pain, diarrhea, gas, heart burn, nausea, tiredness, lactose intolerance and weight loss [11]. Gluten protein is mainly composed of two subgroups called glutenin and gliadin. Gluten-free diet was found to have a therapeutic effect on psoriatic lesions of patients with positive CD antibodies even in the absence of clinical symptoms [12, 13].

Tissue transglutaminase IgA antibodies (TTG-IgA) are sensitive and specific marker of CD. According to the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines, TGA-IgA should be considered as the first serological test when CD is suspected in symptomatic patients with normal IgA levels [14]. Four studies in Turkey, Egypt, Poland, and India also found elevated AGA- IgA levels in psoriasis patients compared to controls, and also elevated TTGA-IgA levels in the latter two studies [6, 7, 15, 16].

The aim of the current study was to compare the level of anti-tissue transglutaminase IgA in psoriatic patients versus non-psoriatic control group, and to find a possible relation with disease severity.

METHODS

This was a case control study conducted on a total of 90 subjects and approved by IRB of Mansoura Faculty of Medicine (MS.19.03.548). Written informed consent was obtained from all participants. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Psoriatic patients were selected from those attending the outpatient clinic, inpatient of Dermatology, Andrology & STDs Department at Mansoura University Hospitals. Entire subjects were divided into two equal groups: Group A (psoriasis group): 45 patients complaining of psoriasis, and Group B (Control group): 45 Age and sex matched completely healthy people. Patients included in the study were clinically diagnosed as psoriasis vulgaris confirmed by dermoscopy and biopsy in doubtful cases. Patients with other autoimmune disease, patients with renal and hepatic diseases and patients with a history of systemic treatment as acitretin or potent topical steroids (in the last 3 months) were excluded. Controls were free from any skin or systemic disease and with no drug history.

All psoriasis patients were subjected to detailed history taking including family history and duration of psoriasis, full clinical examination including the measurement of Body mass index, Waist/Hip ratio, and Psoriasis Area and Severity Index (PASI) score. A PASI Score below 10 defined psoriasis as mild, between 10 and 20 as moderate and above 20 as severe [17]. All patients were asked about possible symptoms of gluten sensitivity such as diarrhoea, flatulence, fatigue and history of iron deficiency anaemia. All participants of the study were subjected to measurement of stool analysis. Complete blood count, and serum level of antitissue transglutaminase IgA antibodies by enzyme-linked immunosorbent assay (ELISA) using Human (tTG-IgA) ELISA Kits, Cat no: 201-12-0488, supplied By Shanghai Sunredbio (SRB) Technology co., Ltd., China.

STATISTICAL ANALYSIS:

Data were analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data expressed in number and percentages. Chi-Square test was used for comparison of 2 or more groups. Fischer Exact test was used as correction for Chi-Square test when more than 25% of cells have count less than 5 in 2*2tables Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Student t-test was used to compare 2 independent groups. One Way ANOVA test was used to compare more than 2 independent groups with Post Hoc Tukey test to detect pair-wise comparison. Significance of the obtained results was judged at the (0.05) level. The Spearman's rank-order correlation was used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables .The point-biserial correlation was used to determine the strength of a linear relationship between one continuous variable and one nominal variable with two categories (i.e., a dichotomous variable). Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from non-diseased cases. Sensitivity and Specificity were detected from the curve and PPV, NPV and accuracy were calculated through cross tabulation.

Binary stepwise logistic regression analysis was used for prediction of independent variables of binary outcome. Significant predictors in the Univariate analysis were entered into regression model using forward Wald method /Enter. Adjusted odds ratios and their 95% confidence interval were calculated.

RESULTS

There was no statistically significant difference between cases and control groups regarding their age and sex, body mass index and waist/ hip ratio. There was a statistically significant higher mean RBCS count among control group than cases (4.74 versus 4.52, respectively). Mean WBCS was significantly higher among cases than control group (7.01 versus 6.57, respectively). There was statistically significant difference between cases and control groups regarding presence of undigested food in their stool analysis , abdominal distension, constipation and fatigue with higher frequency among cases than control (97.8 % , 44.4% , 40% and 33.3% versus 17.8% , 11.1% , 6.7% &4.4% , respectively). There was a statistically significant difference between cases and control groups regarding TTG-IgA with high mean optical density (OD) and concentration (CONCN) among cases than control group (Table 1).

The median duration of psoriasis among studied cases was 3 years ranging from 2 months to 35 years. Median PASI score was 13.4 ranging from 4.8 to 26 which was distributed as following (57.8% were moderate, 24.4% mild and 17.8% severe) (Table 2). There was statistically significant higher mean TTG-IgA optical density and concentration among cases with severe Psoriasis than mild and moderate cases based on PASI score classification (Table 3). Moreover, there was statistically significant higher frequency of abdominal distension and constipation among severe cases than mild and moderate cases (Table 4).

The area under ROC curve for TTG-IgA OD and CONCN was excellent (0.993) with the best detected cut off point was 0.196 for OD and 79.5 for CONCN yielding accuracy of 94.4% & 95.6%, respectively in differentiating psoriatic cases from control group. The area under ROC curve for TTG-IgA OD and CONCN was excellent (0.898) with the best detected cut off point was 0.3235 for OD and 146.5 for CONCN yielding accuracy of 89.5% each in differentiating severe psoriatic cases from mild cases. The area under ROC curve for TTG-IgA OD and CONCN was good (0.769) with the best detected cut off point was 0.3265 for OD and 149.5 for CONCN yielding accuracy of 76.5% each in differentiating moderate psoriatic cases from mild cases (Table 5). The TTG-IgA concentration showed to be a significant predictor of psoriasis, as with every increase one unit in its concentration there was an increased risk of psoriasis by 1.26 (Odds ratio) with the overall % predicted is 95.6% (Table 6).

Table 1: Demographic characteristics, anthropometric measurement, laboratory results, GIT symptoms and TTG-IgA of the studied groups:

	Control n=45(%) Mean± SD N (%)	Cases n=45(%) Mean± SD N (%)	Test of significance
Age (years)	36.78±7.22	40.67±12.14	t=1.85 p=0.07
Sex			
Male	18(40.0)	16(35.6)	χ^2=0.189
Female	27(60.0)	29(64.4)	p=0.664
Anthropometric measurement			
BMI(Kg/m2)	31.28±5.28	30.56±5.54	t=0.632 p=0.529
Waist / hip ratio	0.853±0.058	0.846±0.053	t=0.581 p=0.563
Laboratory results:			
Hb (gm/dl)	11.89±0.87	11.81±1.37	t=0.340 p=0.734

	Control n=45(%) Mean± SD N (%)	Cases n=45(%) Mean± SD N (%)	Test of significance
RBCs	4.74±0.298	4.52±0.467	t=2.60 p=0.01*
WBCs	6.57±0.824	7.01±1.20	t=2.02 p=0.04*
PLT	289.29±28.94	277.64±47.72	t=1.40 p=0.165
GIT symptoms:			
Stool analysis (Undigested food) **Absent** **Present**	37(82.2) 8(17.8)	1(2.2) 44(97.8)	χ^2=59.03 P<0.001*
Abdominal distention	5(11.1)	20(44.4%)	χ^2=12.46 p=0.004*
Constipation	3(6.7)	18(40%)	χ^2=13.98 p=0.001*
Fatigue	2(4.4)	15(33.3%)	χ^2=12.26 p=0.004*
TTG-IgA:			
OD	0.137±0.041	0.304±0.064	t=14.65 P<0.001*
CONCN	47.02±19.25	130.11±41.85	t=12.09 P<0.001*

t:Student t test χ^2:Chi-Square test ,OD: Optical Density CONCN: concentration

Table 2: Disease duration and severity distribution among studied cases:

Parameter Mean± SD	Total cases n=45	%
Duration of psoriasis /years **Median (Range)**	3.0 years (2 months-35.0 years)	-----
PASI score **Mean±SD** **Median (Range)**	13.86±5.38 13.4(4.8-26.0)	-----
Mild **Moderate** **Severe**	11 26 8	24.4 57.8 17.8

Table 3: TTG-IgA distribution according to disease severity among studied cases:

	PASI score <10 Mild	10-20 Moderate	>20 Severe	test of significance
TTG-IgA OD mean±SD	0.275±0.04[a]	0.297±0.057[b]	0.366±0.072[ab]	F=6.24 P=0.004*

	PASI score			
	<10 Mild	10-20 Moderate	>20 Severe	test of significance
TTG-IgA CONCN mean±SD	109.64±27.46[a]	126.08±38.57[b]	171.38±44.19[ab]	F=6.71 P=0.003*

F: One Way ANOVA test *statistically significant (if P<0.05) .Similar superscripted letters denote significant difference between groups by Post Hoc Tukey test OD: Optical Density CONCN: concentration

Table 4: Association between PASI score and GIT symptoms among studied cases:

	PASI			Test of significance
	<10 Mild	10-20 Moderate	>20 Severe	
Stool analysis (Undigested food)				
Absent	1(9.1)	0(0.0)	0(0.0)	MC
Present	10(90.9)	26(100.0)	8(100.0)	P=0.206
Abdominal distention	0(0.0)	14(53.8)	6(75.0)	MC P=0.002*
Constipation	0(0.0)	11(42.3)	7(87.5)	MC P=0.001*
Fatigue	1(9.1)	11(42.3)	3(37.5)	MC P=0.141

MC:Monte Carlo test , *statistically significant (if P<0.05)

Table 5: Validity of TTG-IgA in differentiating psoriatic, severe from mild psoriatic and moderate psoriatic cases:

		AUC (95% CI)	P	Cut off point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Psoriatic cases	TTG-IgA OD	0.993 (0.983-1.0)	<0.001*	0.1960	97.8	91.1	91.7	97.6	94.4
	TTG-IgA CONCN	0.993 (0.983-1.0)	<0.001*	79.5	95.6	95.6	95.6	95.6	95.6
Severe From Mild psoriatic cases	TTG-IGA OD	0.898 (0.746-1.0)	<0.001*	0.3235	87.5	90.9	87.5	90.9	89.5
	TTG-IGA CONCN	0.898 (0.746-1.0)	<0.001*	146.5	87.5	90.9	87.5	90.9	89.5
Moderate psoriatic cases	TTG-IGA OD	0.769 (0.580-0.959)	0.02*	0.3265	87.5	73.1	50.0	95.0	76.5
	TTG-IGA CONCN	0.769 (0.580-0.959)	0.02*	149.5	87.5	73.1	50.0	95.0	76.5

AUC: Area Under curve, NPV: Negative predictive value, PPV: Positive predictive value. OD: Optical Density CONCN: concentration

Table 6: Predictors of psoriatic cases among different laboratory parameters:

Predictors	B	P	Odds ratio	95.0% C.I. for odds ratio	
				Lower	Upper
RBC	-1.928	.078	.145	.017	1.238
WBC	.298	.464	1.347	.607	2.990
PLT	-.007	.379	.993	.977	1.009
TTG-IgA conc	0.229	0.002*	1.26	1.09	1.45
Overall % predicted=95.6%					

DISCUSSION

The present work was conducted as a case-control study on 45 patients with psoriasis who attended the outpatient clinic of Dermatology, Andrology & STDs Department, Mansoura University Hospitals and 45 age and sex matched controls. The aim of the current study was to compare the level of anti-tissue transglutaminase IgA in psoriatic patients versus non-psoriatic control group in Egyptian population in Delta region.

The current study choice was based on two important findings; firstly that TTG-IgA was demonstrated to be an important marker for celiac disease development and secondly, CD seemed to have frequent occurrence in patients with psoriasis than in normal individuals [8, 18, 19]. Furthermore, to the best of our knowledge, there were very limited researches that discussed the level of anti-tissue transglutaminase IgA in psoriatic patients. The majority of prior researches mainly emphasized the role of anti-gliadin only in psoriatic patients [15, 16, 18, 20].

The current study demonstrated that, there was a statistically significant difference between cases and control groups regarding presence of undigested food in their stool analysis, abdominal distension, constipation and fatigue with higher frequency among cases than controls. This could be explained by the theory of cross reactivity to a common antigen (could be gluten) that is present in both the intestinal mucosa and skin [21].

Regarding TTG-IgA among studied groups, there was statistically significant difference between cases and control groups with high mean OD and concentration among cases than control group. In accordance, Dhattarwal et al., demonstrated significantly elevated serum anti-transglutaminase and anti-gliadin antibodies levels in 80 patients of psoriasis versus matched controls [18]. In the same line, Nagui et al. demonstrated that, there was a significantly higher prevalence of anti-gliadin, and tissue transgliutaminase (tTG) antibodies in the psoriatic cases compared to controls [15]. Torii et al., confirmed the same findings of the previous study. Additionally, they suggested that tissue anti-transglutaminase antibodies (tTG) are highly sensitive and specific to CD, and hence considered pathognomonic [22]. In a study by Woo et al., More than 16% of psoriatic patients have positive AGA-IgA and IgG, TTG-IgA and anti-endomysial IgA antibodies [23].

In the present study, psoriasis severity affect significantly TTG-IGA as there was statistically significant higher mean TTG-IgA optical density and concentration among cases with severe psoraisis than mild and moderate cases based on PASI score classification. Michaëlsson et al. demonstrated that PASI score of patients with psoriasis was significantly lowered after 3 months of abstinence from gluten, while PASI score re-increased when gluten was re-allowed. They measured AGA IgA which were elevated in psoriatic patients [20], but didn't measure TTG-IgA. With regard to validity of TTG-IgA in differentiating psoriatic cases, the current study demonstrated that, concentration was excellent (0.993) with the best detected cut off point was 0.196 for OD and 79.5 for concentration yielding accuracy of 94.4% & 95.6% , respectively in differentiating psoriatic cases from control group.

The current study demonstrated that, there was a statistically significant positive correlation between TTG-IgA and PASI score among studied psoriatic cases with no significant relation between TTG-IgA and both age and sex. In addition, TTG-IgA concentration could be used as a significant predictor of psoriasis as with every increase one unit in its concentration increase risk of psoriasis by 1.26 (Odds ratio) with the overall % predicted is 95.6%. Thus, the present study demonstrated that, TTG-IgA could also be used as a marker for psoriatic disease association with coeliac disease

(depending on the positive correlation between PASI score and TTG-IgA).

CONCLUSIONS

The anti-tissue transglutaminase IgA level demonstrated significant elevation among psoriatic cases and correlated positively with the disease activity (as revealed by PASI score). In addition, it could be used as a predictor for psoriasis diagnosis and severity. This also, raises the awareness about the potential association between psoriasis and celiac disease (as revealed by GIT manifestations). Lastly, we recommended testing for anti TTG-IGA in psoriatic patients especially those with GIT symptoms, as early diagnosis of CD must carry better prognosis, in such cases, gluten free diet may serve to decrease severity of psoriasis with no need for aggressive therapy and its hazardous effects.

Conflict of Interest: None

Financial Disclosures: None

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