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Assessment of serum levels of anti-gliadin (IgA and IgG) antibodies in patients with lichen planus: A pilot study

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Abstract

Despite the fact that anti-gliadin antibodies (AGA) play a key role in coeliac disease (CD) screening, elevated AGA levels have been reported in several immune-mediated cutaneous conditions even in the absence of gastrointestinal disease clinical manifestations. A gluten-free diet led to improvements in some of these disorders. The link between oral lichen planus (LP) and CD was revealed, but there is currently no information available regarding the association between cutaneous LP and gluten sensitivity. This study aimed to assess the AGA (IgA and IgG) serum levels in LP patients compared to controls and to determine their correlation with LP severity. The study included 20 patients with cutaneous LP and 20 age- and sex-matched controls, both free of CD manifestations. The enzyme-linked immunosorbent assay (ELISA) technique was utilized for the evaluation of AGA (IgA and IgG) serum levels. Hepatitis C virus (HCV) antibodies in LP patients were evaluated qualitatively using a chromatographic immunoassay. In LP patients, AGA (IgA and IgG) serum levels were significantly elevated compared to controls (p = 0.015 and p=0.016, respectively). A significant positive correlation between AGA (IgG) serum levels and the age of patients (p= 0.024), duration of disease (p= 0.02), and LP severity index (p< 0.0001) was found. AGA serum levels were insignificantly different between HCV-positive and HCV-negative LP patients (p= 0.054). In conclusion, the significant elevation of serum AGA levels in LP patients reflects a possible link between LP and occult CD. Serum AGA (IgG) levels can be used as a marker of LP severity..

Keywords: lichen planus, anti-gliadin antibodies, celiac disease

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Introduction

Lichen planus (LP) is a chronic inflammatory disorder that influences the oral and vaginal mucosa, as well as the skin.[1] Depending on the study population, geographical distribution, and clinical subtypes of the disease, the prevalence of LP varies. According to the results of a meta-analysis conducted by Li et al., 2020, that included 46 studies, LP in the general population showed a prevalence of 0.89%, while in patients searching for dermatological care,

the prevalence was 0.98%.[2] Cutaneous LP showed a reported prevalence ranging from 0.2 to 1.0% worldwide in the adult population.[3] The highest prevalence of mucosal LP (0.89%) was reported in South America.[4]

The etiology of LP is unknown; however, the interplay of genetic, environmental, and immunological factors has been reported to be essential for its initiation and progression.[5] The T-cell-mediated immune response is central to LP pathogenesis, dominated by cytotoxic CD8+ T-cells. Other subsets of T-cells involving CD45RO+ T-cells, T helper (TH) 17 cells, and CD4+ TH cells may play a key role.[3, 5] The associated cytokine alterations involve transforming growth factor-β, interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, IL-17, IL-22, tumor necrosis factor-α (TNF-α), and interferon gamma (IFN)-γ. Autoreactive T-cells and associated cytokines result in damage to the attached basal keratinocytes.[3, 5]

Gliadin is the predominant protein portion of gluten present in wheat, rye, and other cereal grains.[6] Celiac disease (CD) is caused by an aberrant immune reaction to gluten and associated proteins in genetically susceptible individuals. In the intestinal submucosa, a T-cell-mediated autoimmune response is generated and associated with autoantibody production, resulting in damage to the mucosal enterocytes.[7] Gastrointestinal (GIT) manifestations may be subtle or absent more often in adult patients, resulting in non-classic or atypical CD. Extra-intestinal associations that include cutaneous disorders may raise clinical suspicion.[8] Anti-gliadin antibodies (AGA), both IgA and IgG classes, are induced in response to gliadin in genetically predisposed individuals.[9] These antibodies have a significant role in CD screening and allow the discovery of large numbers of silent CD cases.[10, 11] Additionally, AGA (IgG) was used as a test for gluten sensitivity unrelated to CD.[12]

Several immune-mediated skin disorders, for example psoriasis, vitiligo, and atopic dermatitis, have been reported to affect CD patients, and a gluten-free diet led to good improvement.[13–15] Other cutaneous lesions that resembled psoriasis and eczema were observed in non-celiac gluten-sensitive individuals who showed quick recovery after gluten free diet (GFD) submission.[16] Cigic et al., 2015,[9] reported an increased CD prevalence in oral LP, indicated by higher levels of AGA and tissue transglutaminase antibodies as well as by endoscopic biopsy. To the best of our knowledge, no previous research has examined the association between cutaneous LP and gluten sensitivity. Several T-cell-mediated cutaneous disorders, such as psoriasis, were reported to be associated with gluten sensitivity.[15] Gluten is frequently proposed as a trigger that contributes to the expression of auto-immune disorders, irrespective of its association with CD.[17] A previous research study reported a higher incidence of AGA in psoriatic patients in comparison to normal individuals, and a gluten-free diet led to good improvement of the disease.[17] Similar to psoriasis, LP is another T-cell-mediated inflammatory disorder in which genetic, environmental, and immunological factors play a key role in its pathogenesis.[3] Therefore, we hypothesized a possible association between gluten sensitivity and cutaneous LP.

Early detection of gluten sensitivity in LP patients could be beneficial in decreasing disease severity or morbidity through the introduction of a gluten-free diet for AGA-positive patients. Patients with LP were found to have a higher incidence of hepatitis C virus (HCV) infection, with some regional variations. It has been proposed that HCV infection could play a role in the development of LP. So, patients with LP should be screened for associated HCV infection.[18] Assessment of AGA serum levels using an enzyme-linked immunosorbent assay (ELISA) is a rapid and non-invasive screening test, and it has a significantly lower cost as compared to other methods used in the detection of gluten sensitivity. In the present study, we intended to assess the AGA (IgA and IgG) serum levels in LP cases compared to controls and to correlate these levels with LP severity.

Subjects and Methods

The sample size was determined using EpiData version 7, based on the assumption that the prevalence was around 1% of the general

population (3) and the hospital's annual flow ranged from 30 to 50 cases. Accordingly, using a 5% margin of error and a 95% confidence level, the minimum estimated sample size was 15 cases and 15 apparently healthy controls.

This case-control research included 40 participants: 20 LP cases and 20 sex- and age-matched control individuals. Participants were selected randomly three days per week from the outpatient clinic at Al Zahraa University Hospital during the period from September 2021 to February 2022. Using a simple random technique, cases who fulfilled the inclusion criteria and accepted to participate in the study were included. Patients with LP, aged 18–65, of both sexes, were enrolled in the research.

Exclusion criteria included subjects previously diagnosed with celiac disease or having a history of chronic GIT manifestations, and those on GFD. Patients with other autoimmune diseases such as alopecia areata, psoriasis, vitiligo as well as dermatitis herpetiformis were excluded. We also excluded patients with chronic liver or kidney diseases and pregnant women. Patients on lichenoid drug eruption diagnosed clinically and based on histopathological examination were also excluded.

Clinical assessment

All participants were subjected to complete history-taking. General and dermatological examinations of the nails, mucous membranes, and scalp were performed. The diagnosis of LP was established using its distinctive clinical characteristics, dermoscopy examination, and histopathological examination for confirmation.

The severity of LP was assessed by the LP severity index (LPSI) (19), which is a validated tool used according to the following formula:

LPSI Formula: A (AIF Ep × MF Ep) + B (AIF Vp × MF Vp) + C (AIF Vpl × MF Vpl) + D (AIF Hp × MF HHp) + E (AIF PIH × MF PIH) ×BSA factor. The final LPSI may range from 0 to 80 (19).

(ALF: area involvement factor; PIH: post-inflammatory hyperpigmentation; HHP: hyper pigmented hypertrophic papules and plaques; Vp: violaceous papules; Vpl: violaceous plaques; Ep: erythematous papules; MF: multiplication factor; BSA: body surface area).

Laboratory assessment

From each study participant, a venous blood sample (5 ml) was collected, and serum separated after centrifugation at 1300 xg for 10 minutes. The serum was divided into two portions, placed in two Eppendorf tubes for the AGA (IgA and IgG) assay and HCV antibody detection, samples were kept at -20º C until used.

We used commercial ELISA kits to assess the AGA serum levels quantitatively (ORG 534A for IgA and ORG 534G for IgG, from ORGENTEC Diagnostica GmbH, Mainz, Germany), according to the manufacturer's instructions. The optical density of the final ELISA product was measured by using a microtiter reader (AS 1851 Das, Italy). Positive values were considered if both AGA (IgA and IgG) were equal to or greater than 12 U/Ml, according to the manufacturer guidelines.

Antibodies to HCV in LP patients were evaluated by a one-step rapid test. It is a lateral flow chromatographic immunoassay (ABON Biopharm, China) for the qualitative detection of HCV antibodies based on double antigen sandwich technique. The membrane is coated with recombinant HCV antigen in the test line region of the device. During testing, the serum or plasma specimen reacts with HCV antigen-coated particles.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS), IBM version 23 was used for data entry after they were compiled, adjusted, and coded. The Mean, standard deviation, and ranges were used to describe the quantitative parametric data, but for non-parametric data, the median range and interquartile range (IQR) were used. Similarly, numbers and percentage representations of qualitative data were provided. When the predicted number of cases in any given cell was < 5, the Chi-square test or Fisher exact test was used to compare the groups' qualitative data. An independent t-test was used to compare the two groups based on quantitative parametric data, while the Mann-Whitney U test was employed for nonparametric data. For estimating r values, Spearman's correlation coefficient test was

used. To determine the best cutoff point for this marker, we calculated its sensitivity, specificity, PPV, NPV, and area under the curve (AUC) using a receiver operating characteristic (ROC) curve. A 95% confidence level was used, and a 5% tolerance for error was allowed. A value of p< 0.05 indicated statistical significance.

Results

The participants in both groups were age and sex matched, with ages ranged from 18 to 65 years. The disease duration in the LP group ranged from 1–24 months, median (IQR) = 8 (3.5–30 months). Table 1 provides a summary of the demographic data for all participants as well as the clinical characteristics of the LP group.

Table 1. Demographic and clinical data of the patient and control groups.

		Patient group	Control group	*p*-value
		No.=20	No.=20	
Sex	Females	15 (75.0%)	15 (75%)	NS
	Males	5 (25.0%)	5 (25.0%)	
Age (years)	Mean ± SD	49.00±12.29	47.60±12.21	NS
	Range	18 – 65	18 – 65	
Duration of disease (months)	Median (IQR)	8 (3.5 – 30)		
	Range	1 – 24		
Type of LP	Classic	16 (80.0%)		
	Hypertrophic	2 (10.0%)		
	Actinic	2 (10.0%)		
LPSI	Median (IQR)	13 (11 – 17)	-	
	Range	4 – 34		
Oral LP	Negative	6 (30.0%)	-	
	Positive	14 (70.0%)		
Type of oral LP	Ulcerative	5 (35.7%)		
	Reticular	4 (28.6%)	-	
	Plaque	5 (35.7%)		
HCV antibodies	Negative	12 (60.0%)	Negative	
	Positive	8 (40.0%)		

P > 0.05 is not significant (NS). ; LPSI: Lichen Planus Severity Index, LP: lichen planus, IQR: Inter-quartile range *: Chi-square test; ≠: Independent t-test.

The patient group had significantly higher AGA (IgA and IgG) levels compared to the control group (p= 0.015 and p=0.016, respectively). The median [IQR] values of AGA (IgA and IgG) were 26.75 U/ml (19.3–57 U/ml) and 24.4 U/ml (14.75–40.8 U/ml), respectively in the patient group, compared to 14.15 U/ml (7.46–29.5 U/ml) and 17.2 U/ml (6.03–24.5 U/ml), respectively in the control group. A positive AGA (IgA) test was observed in 18 (90.0%) cases in the patient group compared to 11 (55.0%) subjects in the control group (*p*= 0.013). AGA (IgG) was positive in 17 (85.0%) cases in the patient group compared to 11 (55.0%) subjects in the control group (*p*= 0.038) (Table 2).

Table 2. Serum levels of AGA (Ig A and Ig G) in the patient and control groups.

		Patient group	Control group	*p*-value
		No. = 20	No. = 20	
AGA IgA (U/ml)	Median (IQR)	26.75 (19.3 – 57)	14.15 (7.46 – 29.5)	0.015≠
	Range	7.76 – 136.16	1.17 – 96.3	
	Negative	2 (10.0%)	9 (45.0%)	0.013*
	Positive	18 (90.0%)	11 (55.0%)	
AGA IgG (U/ml)	Median (IQR)	24.4 (14.75 – 40.8)	17.2 (6.03 – 24.5)	0.016≠
	Range	7.98 – 60.5	1.91 – 27.4	
	Negative	3 (15.0%)	9 (45.0%)	0.038*
	Positive	17 (85.0%)	11 (55.0%)	

p-value < 0.05: Significant; AGA; Antigliadin antibodies *: Chi-square test; ≠: Mann-Whitney test.

A significant positive correlation between AGA (IgG) serum levels and LP patients' age, duration of the disease, and LPSI was observed (*p*= 0240, *p* = 020, and *p*<0.0001, respectively). While AGA (IgA) serum levels did not show a significant correlation with age, duration of the disease, or LPSI (*p*> 0.05) (Table 3 and Figures 1, 2, and 3).

Table 3. Correlation between serum levels of AGA (Ig A and Ig G) and age, duration of disease, and LPSI in the patient group.

	AGA IgA antibodies		AGA IgG antibodies	
	r	*p*-value	r	*p*-value
Age (years)	-0.028	NS	0.502	0.024
Duration of disease (months)	0.022	NS	0.517	0.020
LPSI	0.327	NS	0.751	<0.0001

P > 0.05 is not significant (NS). ; LP: lichen planus. LPSI: Lichen planus severity index. r: Spearman correlation coefficient.

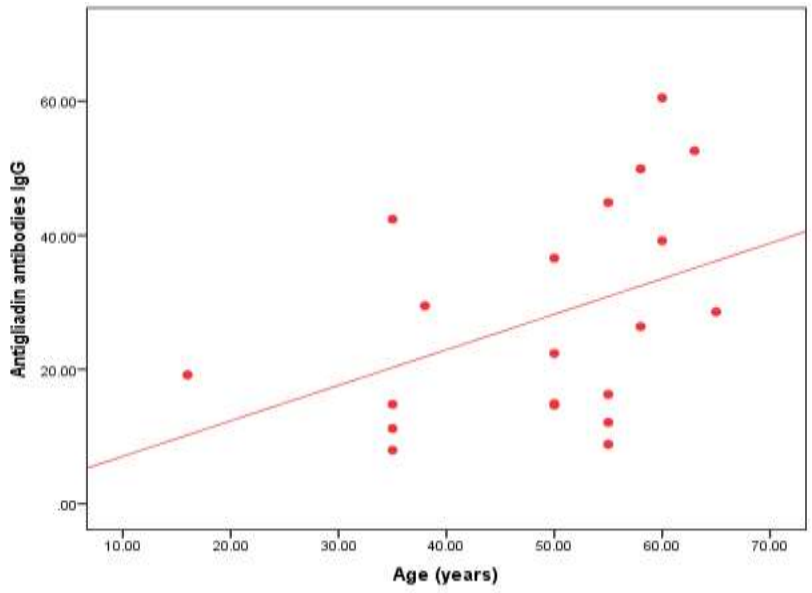

Figure 1. Correlation between serum AGA (IgG) levels and age in the patient group.

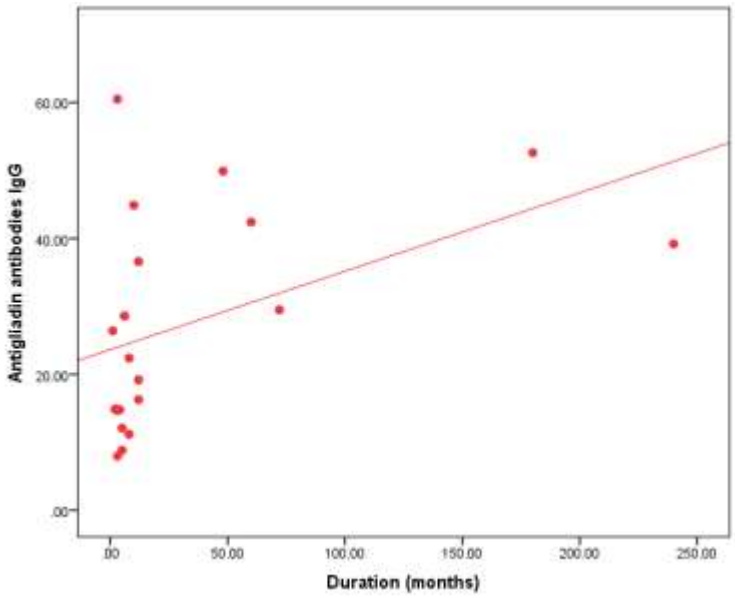

Figure 2. Correlation between serum AGA (IgG) levels and duration of disease in the patient group.

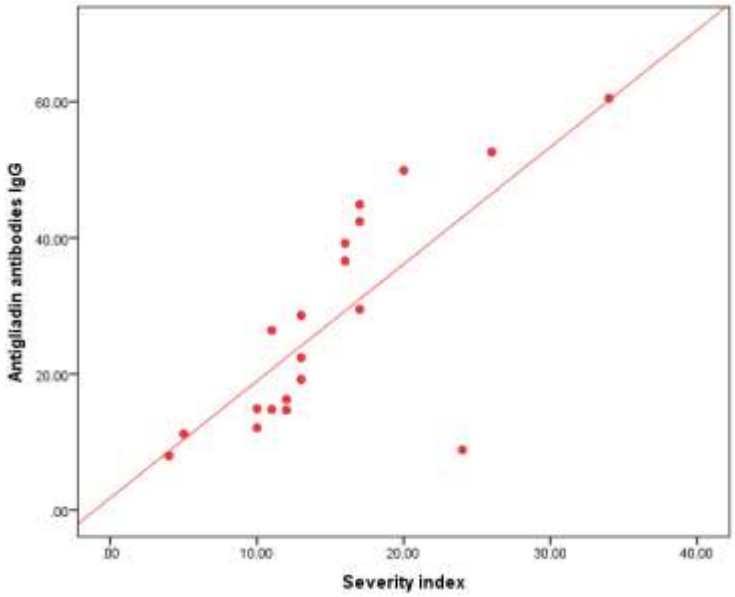

Figure 3. Correlation between serum AGA (IgG) levels and lichen planus severity index (LPSI) in the patient group.

The accuracy of AGA (IgA and IgG) in predicting CD in LP patients was evaluated using the ROC curve analysis. At a cutoff point of >17.5, AGA (IgA) showed 80% sensitivity and 65% specificity, while AGA (IgG) at a cutoff point of >27.4 showed 45% sensitivity and 100% specificity (Table 4 and Figure 4).

No significant relations were found between AGA (IgA and IgG) serum levels and the patient's sex, as well as the types of cutaneous and oral LP (p >0.05). There was no difference in AGA (IgA and IgG) serum levels between HCV-positive and HCV-negative LP patients (p> 0.05).

Table 4. Receiver operative characteristic data for AGA (IgA and IgG) in LP patients.

Variables	Cut off point	AUC	Sensitivity	Specificity	PPV	NPV
IgA	>17.5	0.725	80.00	65.00	69.6	76.5
IgG	>27.4	0.722	45.00	100.00	100.0	64.5

AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value.

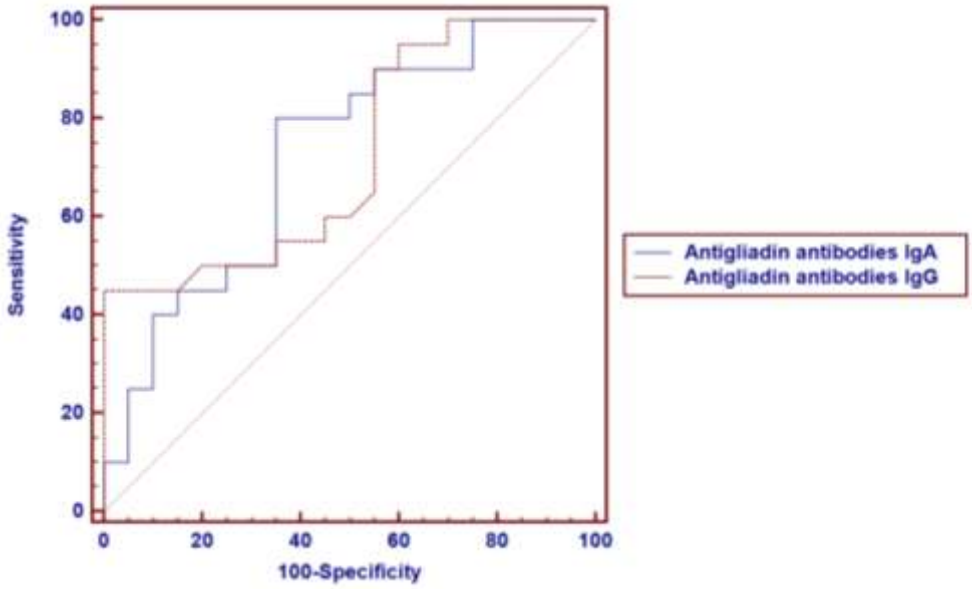

Figure 4. Receiver operating characteristic curve for AGA (IgA and IgG) in lichen planus patients.

Discussion

The current research aimed to detect gluten sensitivity early in LP patients by assessing the serum levels of AGA (IgA and IgG) in LP cases compared to controls and to correlate these levels with LP severity. Data of the present study revealed a significantly higher AGA (IgA and IgG) serum level in LP patients with absent clinical parameters of either CD or non-celiac gluten enteropathy compared to controls. Our finding was compatible with earlier studies that revealed increased AGA levels in other autoimmune cutaneous diseases such as psoriasis[15] and alopecia areata.[20]

In our research, the elevated AGA serum levels in LP cases appeared to be significant in light of the potential role of gluten in the expression of LP. Gluten is widely thought to play a role in the development of autoimmune disorders, which may be through T-cell sensitization.[17] In our research, AGA serum levels were not different between patients with concomitant cutaneous and oral LP and those without oral LP. Cigic et al., 2015,[9] found higher AGA and anti-IgA tissue transglutaminase serum levels in oral LP patients compared to the controls. They found a high CD prevalence in oral LP patients. They reported cutaneous LP in only 2 out of 8 oral LP patients with confirmed CD.

We observed no relation between AGA (IgA and IgG) levels and the clinical types of cutaneous and oral LP. In contrast to our results, Cigic et al., 2015,[9] found significantly elevated AGA (IgA) values in erosive oral LP patients and higher values of AGA (IgG) in patients with reticular variants. This may be due to the inclusion of a larger sample size of oral LP patients in their study (56 patients in their study versus 14 patients in our study).

We observed a significant positive correlation between AGA (IgG) serum levels and

both disease duration and the LP severity index. This observation may suggest that variations in AGA (IgG) serum levels over time could be valuable for disease severity monitoring and that a GFD could be beneficial for those patients. Findings of a study by Michaëlsson et al., 2007,[21] could explain the association between elevated AGA serum levels and increased disease severity. They reported an association between elevated serum AGA levels in patients with palmoplantar pustulosis and increased lymphocytic infiltration in the duodenal mucosa. This finding was relevant to the increased palmoplantar pustulosis activity and improvement of disease severity after GFD.

In the current research, there was a significant positive correlation between AGA (IgG) serum levels and the age of LP patients. We proposed that unintended, chronic, and continuous exposure to gluten in the diet could explain this finding. Such finding suggested that a higher level of AGA (IgG) (> 27.4 U/ml) could represent a marker of chronic gluten exposure and may be valuable, especially in elderly LP patients.

Our results detected no difference in AGA serum levels between HCV-positive and HCV-negative LP patients. This finding revealed that HCV infection could not be a trigger for an autoimmune response against gluten. Our findings agreed with those reported by Algam et al., 2019,[22] who observed no association between CD and HCV infection.

In the present study, results of the ROC curve analysis in LP patients showed that AGA (IgA) had relatively higher sensitivity and AGA (IgG) showed relatively higher specificity. However, due to the small numbers of patients and controls such findings are inconclusive.

In conclusion, based on the present research results, the significant elevation of serum AGA levels in LP patients compared to the controls may reflect a possible link between LP and gluten intolerance. Further studies, with large sample sizes and including diet questionnaire, would be necessary to verify our hypothesis of a possible association between gluten sensitivity and cutaneous LP.

Author Contributions

RAE; designed and approved the whole research protocol, contributed to the protocol design, revised laboratory work, and approved the final paper version to be published, monitored data collection process and the laboratory work, interpreted the data, and critically revised the paper. MSA; contributed to the protocol design, revised laboratory work, approved the final paper version to be published, monitored data collection process and the laboratory work, interpreted the data, carried out statistical analysis, drafted the paper and critically revised the paper. SMA; contributed to the protocol design, supervised sample collection according to inclusion criteria, revised clinical data, diagnosis, and patient classification, collected the samples and patient's clinical data, monitored data collection process and the laboratory work carried out statistical analysis, drafted the paper and critically revised the paper. SYA, carried out the laboratory work and analyzed it, approved the final paper version to be published and critically revised the paper. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine (for girls), Al-Azhar University, Egypt. (Dated October 2020).

Informed consent

A written informed consent was obtained from each study participant, after explanation of the study procedure and before being included in the study.

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