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Research Paper

Diagnostic and Predictive value of Serum Anti C1q Antibody in a Sample of Patients with Systemic Lupus Erythematous

Israa Sabah Sukkar [1], Faiq Isho Gorial [2], Aida Rashid M. Al-Derzi [3]

ABSTRACT:

BACKGROUND:

Background: SLE is characterized by overproduction of numerous types of autoantibodies. Anti C1q antibody is the most studied between antibodies directed against a component of the complement system. AntiC1q antibodies are present in patients with lupus who frequently show high clinical disease activity.

OBJECTIVE:

The aim is to assess Diagnostic and predictive value of serum anti C1q antibody in patients with SLE, to evaluate the correlation between serum anti C1q antibody with sociodemographic and clinical characteristic of SLE patients.

PATIENTS AND METHODS:

A total of 35 SLE patients and 35 apparently healthy individuals were selected as control group in the current study. Serum level of anti C1q antibody was detected by ELISA technique. This case control study was conducted at the Rheumatology Consultation Clinic of Baghdad Teaching Hospital, kidney Diseases and Transplant Center/ Medical City from January 2020 to September 2020.

RESULTS:

There was a significant association between Anti C1q antibody and Systemic Lupus Erythematous Disease Activity Index Score. There was no significant association between Anti C1q antibody among patients or controls. There was no significant association between sociodemographic characteristics and anti C1q antibody. For laboratory investigations, there was no significant association with anti C1q antibody. There was no significant association between organ involvement and anti C1q antibody.

CONCLUSION:

Anti C1q antibody could play as an important, reliable serology marker for monitoring or predicting disease activity among SLE patients. As associated with SLE disease activity score suggesting its potential usefulness in assessment of disease activity, but not as accurate diagnostic marker, which is still need further elucidation and interpretation.

KEYWORDS: Anti-C1q, Autoantibody, Diagnostic, Predictive value, Systemic lupus erythematosus.

[1] Al Yarmouk Teaching Hospital-Baghdad, Baghdad, Iraq.

[2] Department of Rheumatology, College of Medicine, University of Baghdad, Baghdad, Iraq.

[3] Department of Immunology, College of Medicine, University of Baghdad, Baghdad, Iraq.

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INTRODUCTION:

Systemic lupus erythematosus is a debilitating autoimmune disease that develops progressively. It is characterized by the production of numerous autoantibodies against various nuclear and cytoplasmic components, which results in the formation of immune complexes, inflammation, and irreversible tissue damage [(1)].

The first component of the classical complement pathway is C1q. Complement C1q is a cationic glycoprotein that is produced by fibroblasts, epithelial cells, and immune cells (dendritic cells, macrophages, and monocytes). Its primary role is to eliminate autoantigens from tissues that are generated during cell death and immune complexes [(2)].To eliminate dying cells, C1q selectively attaches to early apoptotic cells and starts complement activation [(3)]. Anti-C1q IgG antibody binds to the collagen-like region of C1, where neo epitopes are exposed due to impaired clearance of apoptotic cells [(4)].

The characteristic autoantibodies can arise many years before the illness' initial clinical signs and

symptoms [5]. Some of these autoantibodies have been regarded pathogenic due to their strong correlation with disease activity and the fact that their target is implicated in the etiology of SLE. Thus, autoantibodies directed against C1q (anti-C1q), the initiator molecule of the classical complement pathway, are particularly interest. Anti-C1q antibodies do, on the one hand, correlate with overall disease activity [6] and the manifestation of severe lupus nephritis [7], making them an essential marker for diagnosis. On the other hand, C1q accumulates in inflammatory tissues and has been associated to complement activation and immune complex deposition [8]. Thus, Anti-C1q may consequently accelerate the progression of the disease (9). The "waste disposal" theory provides an important explanation for the involvement of C1q and anti-C1q in SLE. According to this theory, SLE results from an inefficient removal of dying cells, which could turn into antigenic and trigger autoimmunity. Furthermore, macrophages from C1qdeficient mice and humans reveal an inadequate clearance of apoptotic cells in vitro. It has been reported that C1q accelerates the clearance of self-antigens generated during apoptosis [10,11]. The physiological role of C1q in patients with SLE may be affected by the binding of anti-C1q antibodies [12]. In order to assess the diagnostic and predictive value of serum anti-C1q antibody levels in SLE patients as well as the correlation between these levels and the sociodemographic and clinical characteristics of SLE patients, the current study aimed to measure serum anti-C1q antibody levels in SLE patients and healthy controls.

PATIENTS AND METHODS:

Study design

This comparative cross sectional study was conducted at the Rheumatology Consultation Clinic of Baghdad Teaching Hospital, kidney Diseases and Transplant Center/ Medical City from January 2020 to September 2020. Ethical approval has been obtained from the Medical Department, College of Medicine, University of Bagdad. Participants obtained informed consent before participating in this study.

Subjects

A total of thirty-five systemic lupus erythematosus female patients were included in the study. They were among patients attending the Rheumatology Clinic, kidney Diseases and Transplant Center in Baghdad Medical City. All the patients in the study fulfill the American College of Rheumatology (ACR) 1997 SLE diagnostic criteria, Disease activity was assessed according to the disease activity index for lupus patients (SLEDAI) [13], Patients having acute or chronic infection, pregnancy, surgery within 4 weeks, malignant tumour or other autoimmune disease were excluded from the study. Thirty-five apparently healthy individual females were selected as control group in the current study, their age and sex matched to the patients group. Data were collected by direct interview with the patients using a questionnaire form (including demographic data, disease manifestations, disease duration, drug history, laboratory investigations, smoking history)

Specimen processing

Whole blood specimens were collected using acceptable medical techniques to avoid hemolysis, Blood were evacuated into gel tubes. Serum was separated by centrifugation. The supernatant was carefully transferred by using a plastic pipette to Eppendorf tubes and immediately frozen in aliquots at -80 °C till use.

Enzyme-linked Immunosorbent Assay (ELISA)

Anti C1q antibody in the serum were determined according to the manufacturer's instructions using a commercial specific ELISA kit (My BioSource, USA).

Complement (C3) &Complement (C4) determination

The complement (C3) and complement (C4) are both protein fractions synthesized in the liver and give an indication about SLE disease activity. according to SLE Disease Activity Index (SLEDAI) (Mancini et al., 1965). In this study both complements were determined by Radial Immunodiffusion (RID) technique.

CRP Latex Agglutination Slide Test

The test is based on the immunological reaction between human c-reactive protein of a patient sample or control serum and the corresponding antihuman CRP antibody attached to latex particles. A distinctly visible agglutination of the latex particle in the slide's test cell indicated a positive reaction.

Statistical Analysis

Data were translated into a computerized database structure. The descriptive statistical analysis was performed using mean and standard deviation for numerical variables, Frequency and percentage for categorical variables. The association between Anti

C1q and SLEDAI score was examined using Pearson correlation. A Multiple linear regression analysis was conducted to determine the factors affecting or associated with Anti C1q.
antibody using enter method. All analyses were performed using SPSS version 24 (Statistical Package for Social Sciences) in association with Microsoft Excel 2016.

RESULTS:

Table 1 shows the demographic and clinical characteristics of patients and controls. There was no statistical significant difference regarding age and BMI between patients and controls (P=0.441, P=0.067, respectively). The mean age among patients was 30.63±10.17 years while among control was 32.49±9.88 years and mean BMI among patients which was 26.77±5.38 kg/m2 while among control was 24.87±2.52 kg/m2. Regarding the clinical characteristics patients, the mean disease duration which was 8.77±7.13 years. All patients had negative smoking history and majority having mild to moderate disease severity (45.7%). Regarding medications, 22.9% on NSAIDS, 94.3% on steroids, 17.1% on Azathioprine, 91.4% on Hydroxychloroquine, 91.4% on Mycophenolate, only 2.9% on Sandimmune syrup and Cyclophosphamide, 11.4% on Tracrolimus. Regarding Laboratory investigations, 5.7% had leucopenia, 14.3% had thrombocytopenia, 51.4% with anemia, 40% had positive CRP, 20% presented with hematuria and 17.1% with urinary cast, 60% with proteinuria and only 22.9% presented with pyuria. The mean serum creatinine was 1.26±1.14 mg/dl, blood urea was 40.87±30.11 mg/dl, C3 was 110.12±34.95 and C4 was 27.05±11.52.

Table 1: Demographic and clinical characteristics of SLE patients and controls.

Variables	Patients N=35	Control N=35	P value
Age,mean±SD(years)	30.63±10.17	32.49±9.88	0.441
BMI,mean±SD(kg/m2)	26.77±5.38	24.87±2.52	0.067
Diseaseduration,mean±SD(years)	8.77±7.13		
SLEDI Score, mean±SD	7.46 ±6.25		
	Number (%)		
Disease activity			
Inactive	11 (31.4)		
Mild to moderate	16 (45.7)		
Severe	8 (22.9)		
NSAIDs	30(94,3)		
Steroid)	33 (94.3		
Azathioprine	6 (17.1)		
Hydroxychloroquine	32 (91.4)		
Mycophenolate	32 (91.4)		
Sandimmune syrup	1 (2.9)		
Cyclophosphamide	1 (2.9)		
Tracrolimus	4 (11.4)		
Leucopenia	2 (5.7)		
Thrombocytopenia	5 (14.3)		
Anemia	18 (51.4)		
CRP positive	14 (40.0)		
Hematuria	7 (20.0)		
Urinary cast	6 (17.1)		
Proteinuria	21 (60.0)		
Pyuria	8 (22.9)		
S.Creatinine (mg/dl) (mean±SD)	1.26 ±1.14		
Blood urea (mg/dl) (mean±SD))	40.87 ±30.11		
eGFR (mean±SD))	92.6±6 50.24		
C3 (mg/dl) (mean±SD))	110.12 ±34.95		
C4 (mg/dl) (mean±SD))	27.05 ±11.5		

SD, standard deviation, BMI, Body mass index; NSAID: non-steroidal anti-inflammatory drugs; CRP:C-reactive protein; eGFR: estimated glomerular filtration rate; C3: complement 3; C4: complement 4.

Table 2 represents organ involvement with SLE patients, 88.6% had musculoskeletal involvement, 85.7% had renal, 34.3% Mucocutaneus, 31.4% had hematological and Neuropsychiatric while only 5.7% had cardiovascular.

Table 2: Organ involvement in SLE patients .

Organ involved	Number	Percentage%
Mucocutaneus	12	34.3
Musculoskeletal	31	88.6
Renal	30	85.7
Cardiovascular	2	5.7
Hematological	11	31.4
Serositis	0	0
Neuropsychiatric	11	31.4

Table 3 represents Anti C1q antibody mean level in patients and controls that showed no significant association with P value 0.457. The mean Anti C1q antibody among patients was 1.20±0.23 ng/ml and among controls 1.17±0.21 ng/ml.

Table 3: Anti C1q antibody in patients and controls.

	Patients		Control		P-value
	Mean	SD	Mean	SD	
Anti C1q (ng/ml)	1.20	0.23	1.17	0.21	0.457

*Independent t test was performed

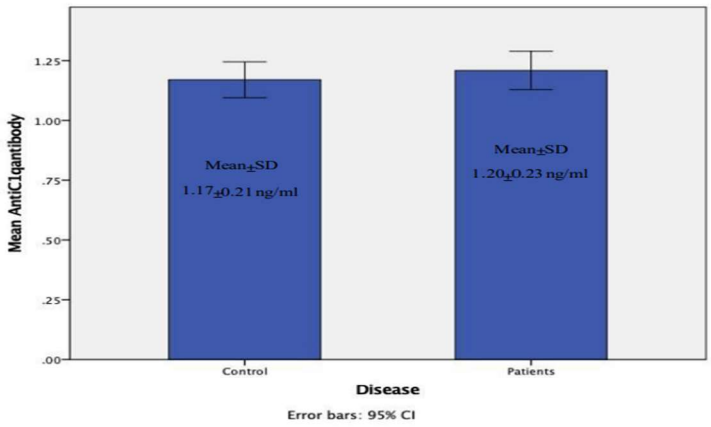

Figure 1: Anti C1q antibody in patients and controls.

Figure 1 represents the association between Anti C1q antibody among patients and controls. There was no significant association between Anti C1q antibody level among patient and control with P value 0.457. The mean Anti C1q antibody among patients was 1.20±0.23 ng/ml and among controls 1.17±0.21 ng/ml. The effect size (Cohen's d) was 0.13.

Table 4 represents the association between Anti C1q antibody and SLEDAI Score. There was a significant association between Anti C1q antibody and SLEDAI Score with P value 0.03. The Pearson correlation was 0.36 which represent weak positive correlation.

Table 4: Correlation between antiC1q antibody and SLEDAI score .

Variable	SLEDAI Score	
Anti C1q antibody (ng/ml)	Pearson's r	0.36
	p-value	0.03
	Upper 95% CI	0.62
	Lower 95% CI	0.03

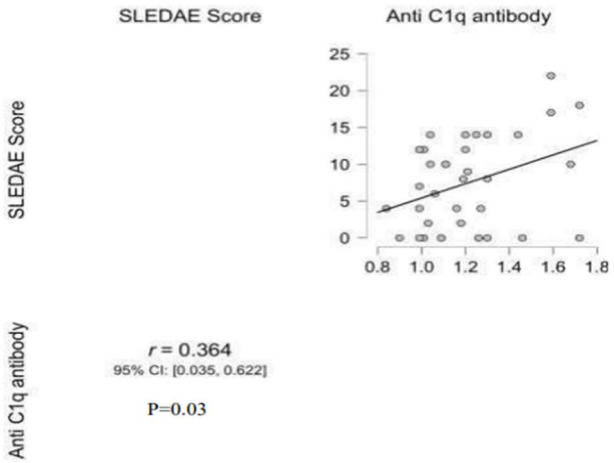

Figure 2: Correlation matrix.

DISCUSSION:

Systemic lupus erythematosus is a diverse disease affected by a variety of genetic and environmental factors. Autoimmune dysfunction in SLE leads to autoantibodies production with formation of immune complexes that drive target organ inflammation. The presence of autoantibodies in patients, including anti-dsDNA, anti-SSA (Ro), anti-SSB (La), anti-Sm and anti-RNPs, and anti-C1q which is also considered to be involved in the pathogenesis of SLE [14] Assessing the value of C1q among Iraqi patients will help to establish a diagnostic panel for these patients.

Regarding the socio-demographic characteristics, the mean age among patients was 30.63 ± 10.17 years which was comparable to other local Iraqi studies that showed the mean age of the SLE patients was (33.6 ± 11, 30.23 ± 10.25, 31.91 ± 7.49 years respectively) [15,16,17]. Also, the mean age was comparable to a pooled analysis of 3,273 patients among Arabic countries (Egypt, Iraq, UAE, Saudi Arabia, Jordan, Kuwait, Lebanon, Oman, Sudan, Tunisia, and Yemen), [18] of which showed the mean age to be 28.9 years at diagnosis, while in the UK the mean age was (48.5 years) higher than the results of present study [19].

Concerning gender, all the patients included in the present study were female, this result was compatible with other studies conducted in Iraq [20, 21,22]. This female predominance is mainly due to estrogen influence [23].

On the other hand, psychological stress at any age leads to the depletion of estrogen store in the body, leading to the loss of expansion of T regulatory cells and making the immature B cells evade the negative selection at the germinal center, Psychological stress, regardless of age, causes the body's estrogen reserves to be depleted, which stops T regulatory cells from proliferating and allows immature B cells to evade the germinal center's negative selection. This, in turn, results in the loss of central tolerance, which is a trigger for autoimmune diseases. It is presumed that the stress-triggered neuroendocrine

hormones followed by immune dysregulation, which ultimately results in autoimmune disease, by altering or amplifying cytokine production [24]. Additionally, Iraqi women have faced years of political and social hardship, which may explain the study's findings.

Regarding BMI among patients was 26.77 ± 5.38 kg/m2 which indicates that patients with SLE were overweight, and the obesity has been proven as a risk factor for developing and aggravating SLE and thromboembolic effect which showed an increase in thickness of intima-media. [25, 26].

Concerning hematological laboratory investigations of the patients in the present study, it was in correlation with other studies that showed a 20- 80% of SLE patients had hematological manifestations throughout their disease course [27,28,29]. They usually result from an immune mediated bone marrow failure, excessive peripheral cells destruction due to certain drugs and infections [30].

Concerning renal function test, the mean serum creatinine was 1.26 ± 1.14 mg/dl, blood urea was 40.87±30.11 mg/dl, as most patients of the present study show renal involvement, they did not have renal impairment which indicates a good control for the disease. However, about 28% of patients had elevated serum creatinine and blood urea. Chapter Four: Discussion 46 More than 88% of the patients in the current study had organ involvement, with musculoskeletal and renal involvements being the most common organ. These results represented very high organ involvement in comparison to a study conducted by Rahman [31] which showed that 40% of patients have organ involvement and the kidney was the most common organ, also same results (40%) have been demonstrated by El-Gazzar a study that conduct in Egypt [32], while it was lower (26%) in Sjowall study [33]. This disparity in organ involvement could rely on that the present sample has been selected from a highly specialized center for SLE. Also, a high dose of medication could play an important role in increasing organ involvement [34].

Regarding the Anti C1q, the mean Anti C1q among patients was 1.20±0.23 ng/ml and among controls was 1.17±0.21 ng/ml, despite this difference, the association was statistically insignificant with P-value 0.457. This result was different from other studies that showed a significant association between anti C1q antibody in SLE patients and healthy controls [35]. Despite the majority of the patients in the present study had renal involvement and many studies demonstrating the diagnostic value of anti C1q antibody in lupus nephritis [36], patients did not demonstrate the relation of anti C1q antibody and SLE. This could be due to that all of the patients in the present study were on immunosuppressant medication for at least 6 months and this medication could suppress the anti C1q production, this relation has been investigated an approved by Grootsholten [37] and Orbai [35] who noted that anti C1q antibody to be increased before symptoms flares up, specifically for lupus nephritis, and the level of antibody decrease or disappears with immunosuppressive treatments. In addition, Yasuhiro demonstrated the relation between the treatment and decreased anti C1q antibody level, they went further and retest the anti C1q antibody level after treatment which found that anti C1q antibody level decreased significantly after treatment in about 84% decrease in the level of anti C1q antibody [38]. There was a significant association between Anti C1q antibody and SLEDAI Score with P value 0.03, however, the Pearson correlation was 0.36 which represents a weak positive correlation. This correlation is also approved by ElHewala study which has a strong association between SLEDAI and anti C1q antibody [39]. Also, a recent study by Emad showed a strong association between lupus nephritis and disease activity. These results demonstrated that anti C1q antibody could play as an important marker for monitoring or predicting disease activity among SLE patients [40]. A large-scale longitudinal studies are still needed to rigorously validate many promising biomarkers and also identify better biomarkers not only for lupus diagnosis but also for monitoring and predicting upcoming flares and response to treatment. An important strength of this study is a well-established diagnosis of SLE patients in a specialized center for SLE. In addition to that, the data of single center gave us the uniformity characteristic for this study. Furthermore, the detection of anti C1q antibody level was measured by same lab and assess to reduce the fraction of error which could be related to inadequate standardization for anti C1q antibody level. On the other prospective, there are limitations impacting this study, firstly sample size in addition to short period for the study. The second limitation was related to the recruiting of newly diagnosed SLE patients which was very limited in highly specialized

centers, due to lack of awareness and delay in seeking of medical consultation among our society. Furthermore, all the included patients had no baseline anti C1q antibody measurement and therefore the measured anti C1q antibody is the only available data for each patient in this study.

CONCLUSION:

In accordance with the results of the present study, the subsequent points are concluded: 1. The results of this study showed no significant association between Anti C1q antibody in the serum of SLE patients in comparison to controls, suggesting that the measurement of anti C1q antibody as ′individual ′biomarker is not diagnostically useful. 2. The results of this study revealed a significant association between Anti C1q antibody and SLE disease activity index among SLE patients, which may suggest that anti C1q antibody was shown to be a non–invasive useful marker for monitoring disease activity. 3. There was no significant association between socio-demographic characteristics, laboratory investigations, and anti C1q antibody level. 4. Concerning organ involvement, there was no significant association between musculoskeletal involvement, renal, mucocutaneous, hematological, Neuropsychiatric, cardiovascular, and anti C1q antibody.**Acknowledgment** The authors are thankful to the staff of the immunology department – teaching laboratories-medical city for their consistent help in this study.

Author's Declaration Conflicts of Interest: None.
Ethical Clearance: The project was approved by the Iraqi Board for Medical Specialization.

Authors' Contribution Statement

Conception and study design, data collection, manuscript drafting, manuscript revision: Israa Sabah Sukkar, Faiq Isho Gorial and Aida Rashid M.Al-Derzi. Data analysis and interpretation: Israa Sabah Sukkar, Faiq Isho Gorial and Aida Rashid M. Al-Derzi. All authors have read and approved the final version of the manuscript.

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