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Evaluating the clinical significance of Anti-C1q and Anti-C3b antibodies in systemic lupus erythematosus patients

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ABSTRACT

Objective(s). *Systemic Lupus Erythematosus (SLE) is a multifaceted autoimmune disorder that is marked by a variety of autoantibodies. This study aimed to evaluate the association of anti-C1q IgG, anti-C3b IgG, and anti-dsDNA antibodies with disease activity in patients with SLE.*

Materials and methods. *A cross-sectional case-control study was conducted including 120 SLE patients and 30 age- and sex-matched healthy controls. Serum anti-C1q and anti-dsDNA IgG levels were measured by ELISA using manufacturer-defined positivity cutoffs (>10 U/mL and >18 IU/mL, respectively), anti-C3b IgG was quantified using a commercial ELISA kit without a predefined diagnostic threshold, while complement C3 and C4 were measured by nephelometry. This study used the independent samples t-test and the Pearson correlation coefficient to compare groups and assess associations between variables.*

Results. *Anti-dsDNA antibodies were detected in 80% of SLE patients, compared with 51.6% for anti-C1q and 30% for anti-C3b ($p < 0.01$). Serum concentrations of both anti-C1q and anti-dsDNA were significantly higher in patients with active disease than in those with inactive SLE (anti-C1q: 61.4 ± 10.9 vs. 7.54 ± 3.2 AU/mL; anti-dsDNA: 70.5 ± 21.5 vs. 12.6 ± 8.0 IU/mL). Complement levels (C3 and C4) were significantly lower in active SLE ($p < 0.05$). Anti-C1q showed strong positive correlations with anti-dsDNA ($r = 0.824$) and with SLEDAI scores, and a negative correlation with C3 ($r = –0.651$). Anti-C3b was also positively correlated with anti-dsDNA ($r = 0.608$) and with disease activity ($r = 0.613$).*

Conclusion. *Anti-C1q, anti-C3b, and anti-dsDNA antibodies are significantly associated with disease activity in SLE and may supplement complement measurements in clinical assessment. These findings reflect cross-sectional associations and highlight the potential utility of these markers in evaluating disease status, while longitudinal studies are required to establish prognostic value.*

Keywords: systemic lupus erythematosus, anti-C1q, anti-C3b, anti-dsDNA, complements, SLEDAI

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder, whereby there is the generation of several autoantibodies directed to the self-antigens, especially the nuclear constituents [1]. Moreover, SLE patients have been defined as having over 160 autoantibodies, such as to double-stranded DNA (dsDNA),

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histones, chromatin, and to the components of the complement system, like C1q and C3b [2]. An important part of SLE pathogenesis is the complement system [3]. Complement synthesis, activation, and consumption are, in general, related to disease activity because complement is activated during disease exacerbations [4]. In this regard, reduced serum concentrations of C3 and C4 components of complement are widely employed in marking disease activity [5,6].

Autoantibodies to complement proteins might also play a role in the development of SLE by enhancing the complement cascade or causing functional impairment of the complement cascade [4,7,8]. Different autoantibodies have diagnostic usefulness, such as anti-dsDNA, anti-C1q, and anti-C3b, in SLE, where it has been studied by a number of studies [8]. Anti-double-stranded DNA (anti-dsDNA) antibodies are among the most widely used biomarkers in SLE and are strongly associated with disease activity. In recent years, attention has shifted toward complement-related autoantibodies, including anti-C1q and anti-C3b IgG, due to their potential role in reflecting complement activation and consumption.

The clinical relevance of anti-dsDNA is appropriately tested with a positive outcome, as it is directly added to the index of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) 2000 with a positive result and is commonly taken as one of the disease activity signs [9,10]. The anti-dsDNA can vary with the progression of the disease and treatment, and in certain instances, they may even vanish with proper therapy [11-13].

Nevertheless, the clinical role of anti-C1q and anti-C3b autoantibodies and their association with disease activity indicators and complement consumption is not well explained yet, although there is mounting evidence of the role of complement in SLE. The past research has not provided a consistent result, and their collective diagnostic or prognostic importance in connection with anti-dsDNA and SLEDAI has not been well defined. Therefore, this study analysis is to identify the correlation between the serum levels of anti-C1q and anti-C3b autoantibodies, in addition to the components of complement (C3 and C4), and the disease activity in SLE patients.

This study hypothesized that the anti-C1q and anti-C3b levels have a positive correlation with the SLE disease activity indices (SLEDAI) and a negative correlation with the complement components (C3 and C4), which indicate the use of complement in active disease.

To test these associations, we conducted a cross-sectional case-control study comparing antibody levels and complement markers in active and inactive SLE.

MATERIALS AND METHODS

Study design and population

This cross-sectional case-control study included 120 patients (108 females, 12 males) diagnosed with systemic lupus erythematosus (SLE) according to the 1997 American College of Rheumatology (ACR) classification criteria [9], along with 30 age- and sex-matched healthy controls, recruited among the relatives of patients without autoimmune diseases. Patients were recruited from the Rheumatology Clinic of the Al-Sayyab Teaching Hospital, Basrah, as outpatients between December 2023 and July 2024. All participants were between 18 and 55 years of age (mean age 34.8 ± 5.02 years). Table 1 shows demographic and clinical characteristics.

TABLE 1. *Demographic criteria of patients with systemic lupus erythematosus (SLE) (N = 120) and healthy controls (N = 30)*

Demographic criteria	SLE	Healthy control
Age (mean ± SD) (range, years old)	35.25 ± 11.57 (16-58)	34.8± 5.02 (18-57)
Sex (male/female) (% female)	12/108 (90)	3/30 (90)
Disease duration (mean ± SD) (range, years)	4.92 ± 3.54 (0.08 - 17)	-
SLEDAI score (range)	11± 0.5 (2-35)	-
C3, mg/dl	0.57 (0.23-1.1)	-
C4, mg/dl	0.15 (0.05-0.258)	-
Anti-dsDNA (positive/negative)	96/24	2/28

Ethical approval and Informed consent

The study was carried out with a protocol authorized by the Review Board Committee in the performance of Human Research at Al-Zahraa College of Medicine (RT-Number-0045) and along with the Declaration of Helsinki 1975, which was revised in 2013. All persons who visited the outpatient clinic and participated in this study have been provided with a written informed consent, and in case of participants less than 18 years old, the consents were obtained by their parents or legal guardians.

Inclusion criteria

The patients were analyzed based on at least three frequent visits to the outpatient rheumatology centers. The mean age of SLE patients at the time of drawing the sample was 35.25 +11.57 years (16 to 58 years), and the mean disease duration was 4.92 +3.54 years (0.08-17 years). Disease activity was measured by the SLE Disease Activity Index (SLEDAI), and SLEDAI 10 was consid-

ered an active disease [9,14]. The attending physician ensured the type and dose of prescribed treatment during the time of sampling. Therefore, only patients who had been taking their medications (such as hydroxychloroquine or prednisolone) steadily for at least three months before the sampling were included.

Although all patients had been on stable medication doses for at least three months prior to sampling to minimize short-term fluctuations, treatment was not included as an adjusted variable in the statistical analysis and therefore represents a potential confounder.

Exclusion criteria

Individuals with liver cirrhosis, end-stage renal failure, blood-borne infections, or pregnancy, were excluded.

Sample collection

Each participant provided a sample (5 mL) of venous blood that was placed in gel tubes, clotted, and centrifuged at 3000 rpm for 5 minutes to isolate serum. The samples were aliquoted in Eppendorf tubes and kept at -80 °C before analysis.

Autoantibodies and complement components measurement

The anti-dsDNA, anti-C1q IgG, and anti-C3b IgG serum levels were determined using commercial ELISA kits according to the workflow of the manufacturers:

- Anti-C1q IgG: Elabscience, E-EL-H0123, USA.
- Anti-C3b IgG: Elabscience, Cat. No. E-EL-H0125, USA.
- Anti-dsDNA IgG: Elabscience, Cat. No. E-EL-H0127, USA.

Anti-C1q and anti-dsDNA cutoff values were >10 U/mL and >18 IU/mL, respectively, as stipulated by the manufacturer, the Anti-C3b kit had no specified diagnostic positivity cutoff. Cut-off for anti-C3b positivity was determined as values greater the mean + 2 SD of 30 healthy controls with results expressed as normalized units (fold change), with the healthy control mean was set to one.

To determine the amount of C3 and C4 complement components (Siemens BN II System, Germany), this study used nephelometry. Although the analysis of even kits targeting the same marker can give different numerical values because of differing ranges; therefore, all samples were analyzed with kits by the same manufacturer to ensure that the results would be consistent.

Statistical analysis

Analysis of the data was done using SPSS version 29 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to test data distribution for the normality test. Mean, SD, frequencies, and percentages were used to represent continuous and categorical variables, respectively.

Independent samples t-test data were compared by group based on the normally distributed data, and the Mann-Whitney U test data based on non-parametric data, respectively. Pearson correlation coefficient of normally distributed variables and the rho of non-normally distributed variables were used to determine the relationships between continuous variables. The relationship between SLE disease activity and biochemical markers was studied by multiple logistic regression analysis. A p-value <0.05 was considered statistically significant.

RESULTS

To compare serum levels of anti-C1q, anti-C3b, and anti-dsDNA IgG in SLE patients and healthy individuals, this study used a cross-sectional approach. Anti-dsDNA was positive in 80 percent of the SLE patients as opposed to 51.6 percent of anti-C1q and 30 percent of anti-C3b ($p < 0.01$). Anti-C1q titer (107.6 ± 18.1 AU/mL) was found in SLE patients, whereas anti-C3b titer (4.79 ± 1.30 AU/mL) was the lowest. Of healthy controls, 3.3% were anti-C1q positive, but none were anti-C3b positive (Table 2).

Figure 1 includes the percentage of positive findings for each antibody in patients with SLE and the healthy group, whereas Figure 2 shows the average concentration (with standard deviation as error bars) for all groups.

Anti-C1q autoantibodies serum level was more significant in active SLE patients (61.4 + 10.9 AU/ mL),

TABLE 2. *Difference in serum levels of anti-C3b, anti-C1q, and anti-dsDNA antibodies in SLE patients compared to healthy controls (HC)*

Group	Anti-C1q			Anti-C3b			Anti-dsDNA		
	Positive[a] N / %	Conc.[b]	P[c] value	Positive[a] N / %	Conc.[b]	P[c] value	Positive[a] N / %	Conc.[b]	P[c] value
SLE (120)	62 / (51.6)	107.6 ± 18.1	<0.01	36/ (30)	4.79 ± 1.30	<0.01	96/ (80)	72.5 ± 23.1	<0.01
Healthy (30)	1/ (3.3)	7.3	<0.01	0	_	<0.01	2 / (6.6)	5.3 ± 1.8	<0.01

Anti-C1q = autoantibodies to complement C1q; Anti-C3b = autoantibodies to complement C3b; [a]Number of samples in every cohort which affirmative for anti-C1q, anti-C3b, or anti-dsDNA IgG; [b]Concentration of anti-C1q, anti-C3b, or anti-dsDNA IgG in serum samples of each participant in both cohorts; [c]Anti-C1q, anti-C3b, or anti-dsDNA IgG prevalence in each pair of cohorts was compared in the analysis

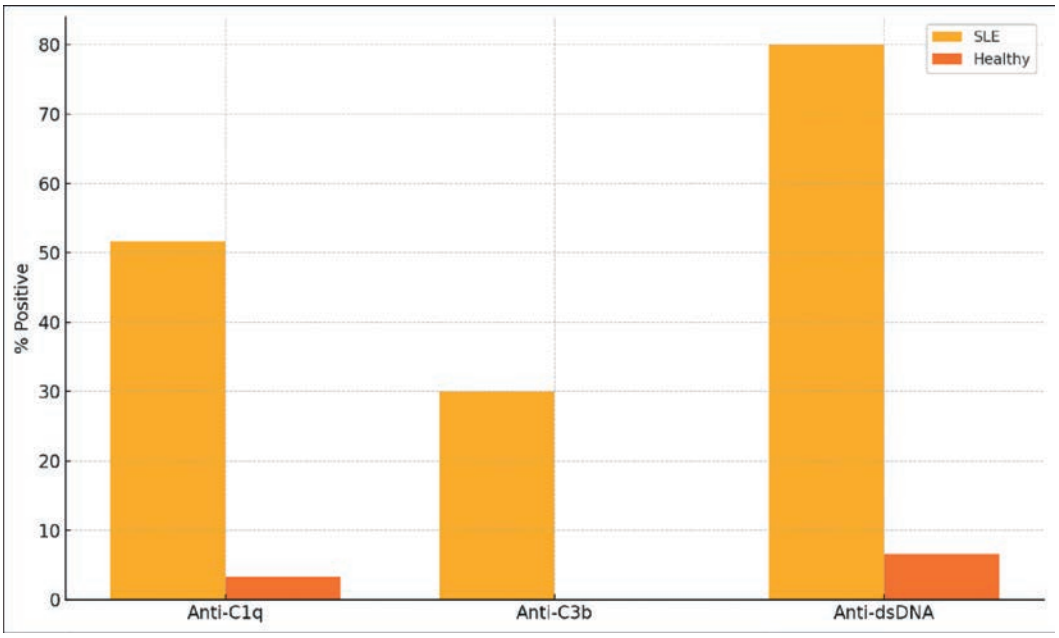

FIGURE 1. *Prevalence of Anti-C1q, anti-C3b, anti-dsDNA between SLE group and HC group (% positive)*

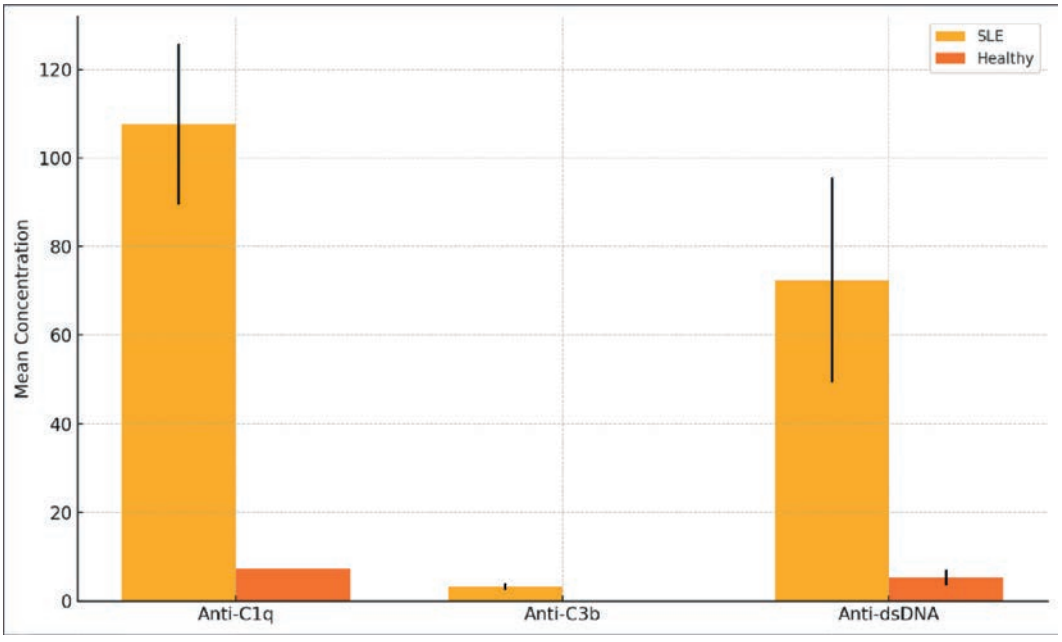

FIGURE 2. *Comparison of mean concentration difference of anti-C1q, anti-C3b, and anti-dsDNA between SLE and HC groups*

compared to inactive SLE patients (7.54 + 3.2 AU/ mL, p = 0.000). On the same note, anti-dsDNA antibodies were significantly greater in active SLE (70.50 + 21.51 IU/mL) than in inactive SLE (12.58 + 7.98 IU/mL, p = 0.000). There were lower levels of C3 and C4 (both in mg/dL), C3 = 0.60 ± 0.12 and C4 = 0.12 ± 0.07 in active SLE versus C3 = 0.95 ± 0.17 and C4 = 0.16 ± 0.05 in inactive SLE, p = 0.047 and p = 0.142, respectively. Anemia of chronic disease was also an ancillary clinical marker since hemoglobin (g/dL) was lower in active (11.8 ± 0.79 g/dL) than inactive (13.4 ± 0.8 g/dL) SLE (p = 0.008). These data are shown in Table 3 and presented in Figures 3 and 4.

TABLE 3. *Laboratory parameters among active and inactive SLE patients*

Parameter	Active SLE (61)	Inactive SLE (59)	P value
Anti-C1q (AU/mL)	61.4 ± 10.9	7.54 ± 3.2	0.000
Anti-C3b (AU/mL)	8.44 ± 1.78	1.04 ± 0.11	0.005
C3 (g/L)	0.60 ± 0.12	0.95 ± 0.17	0.047
C4 (g/L)	0.12 ± 0.07	0.16 ± 0.05	0.142
Anti-dsNDA (IU/mL)	70.50 ± 21.51	12.58 ± 7.98	0.000
Hemoglobin (g/dL)	11.8 ± 0.79	13.4 ± 0.80	0.008
Urine protein (g/24 h)	1.20 ± 0.64	0.13 ± 0.02	0.003

Active SLE: disease was defined by SLEDAI score ≥10

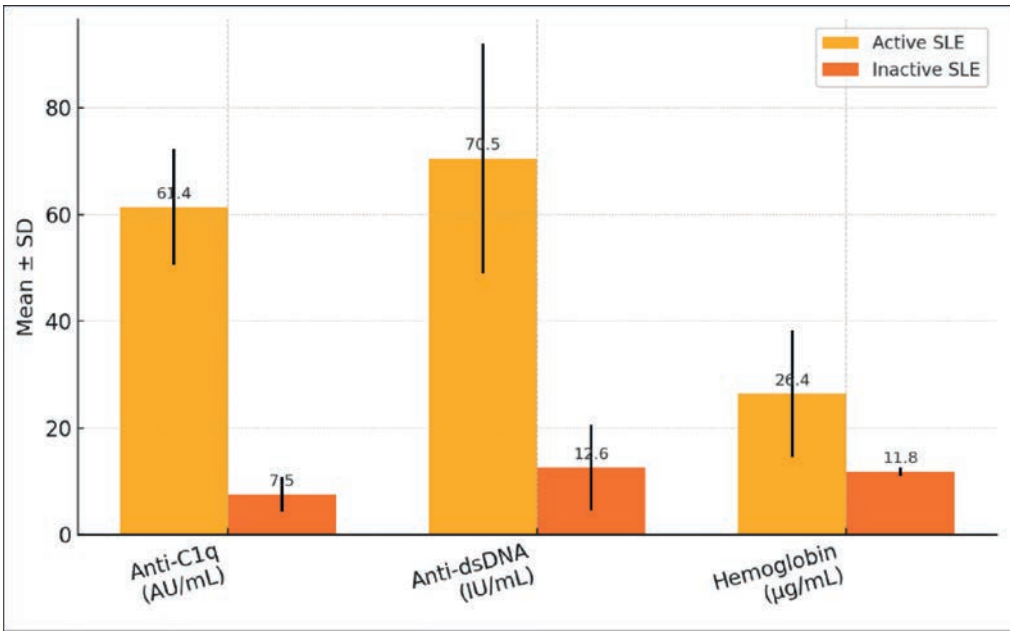

FIGURE 3. *Serum levels of anti-C1q, anti-dsDNA, and hemoglobin in active and inactive SLE patients*

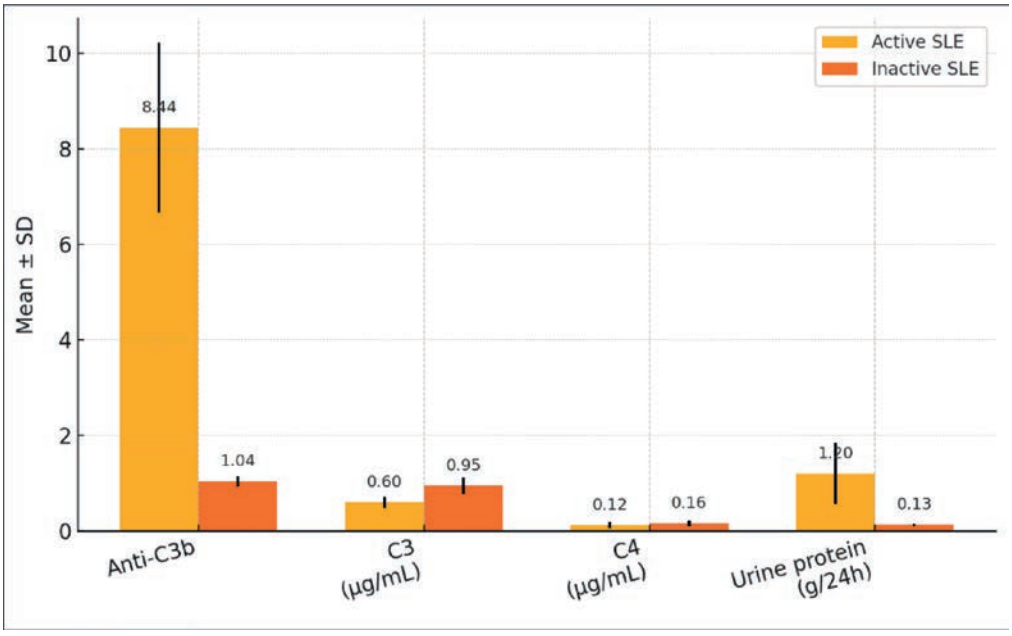

FIGURE 4. *Serum levels of anti-C3b, C3, C4, and urine protein in active and inactive SLE patients*

Correlations of anti-C1q and anti-C3b autoantibodies with anti-dsDNA autoantibodies, C3 and C4 Level, and SLEDAI scores

Serum anti-C1q levels were also strongly positively correlated with the anti-dsDNA (r = 0.824**), moderately positively correlated with SLEDAI (r = 0.562**), and moderately negatively correlated with C3 (r = -0.651**) and C4 (r = -0.564**). Likewise, anti-C3b levels were moderately positively correlated with anti-dsDNA (r = 0.608**) and SLEDAI (r = 0.613**). The anti-C1q and anti-C3b antibodies were also inversely correlated with the components of complement, which implies that higher levels of the autoantibodies are associated with the use of complement and the pathophysiology of the disease. Table 4 shows the correlation between anti-C1q autoantibodies and anti-C3b autoantibodies.

DISCUSSION

SLE is a chronic disease, an autoimmune disease that is characterized by varying manifestations, and, therefore, requires subtle biomarkers to monitor the activity of this disease. One of the most possible ways of assessing SLE is through autoantibody tests [15,16]. In this study, we have quantitated serum anti-dsDNA,

TABLE 4. *Correlation between anti-C1q autoantibodies and anti-C3b autoantibodies with SLEDAI, in addition to anti-dsDNA*

Variable	Anti-C1q	Anti-C3b	Anti-dsDNA	C3	C4	SLEDAI
Anti-dsDNA	0.824**	0.608**	1			
C3	-0.651**	-0.432**	-0.627**	1		
C4	-0.564**	-0.544**	-0.416**	0.627**	1	
SLEDAI	0.562**	0.613**	0.475**	-0.311*	-0.378*	1

anti-C1q and anti-C3b IgG to find out their association with SLE activity.

The anti-dsDNA rates were positive (80% vs. anti-C1q (51.6%) and anti-C3b (30%)) with a significant difference ($p < 0.01$). These results also align with Birmingham et al. (2016) that also indicated that although anti-dsDNA is quite specific to SLE [18], anti-C1q and anti-C3b were considerably high during active disease phases. Our findings validate that the high scores in SLEDAI are indeed related to high levels of antibodies that justify the use of the scale in the determination of disease severity.

Anti-C1q antibodies disrupt physiologic results of apoptotic cell and immune complex clearance in a mechanistic manner. This malfunctioned clearance enhances inflammation and renal deposition which clarifies the close correlation between the scores of anti-C1q and active disease that we observed in this study. In the same way, opsonization can be interfered with by anti-C3b antibodies. Nonetheless, we demonstrated that anti-C3b was a weakly sensitive marker (30% positivity) in comparison with anti-C1q. This sensitivity loss is probably due to the transient character of C3b epitopes that undergo rapid degradation into inactive fragments thus restricting their immunogenicity.

Our data depicted anti-c1q and anti-c3b were also negatively correlated with the elements of complement (C3 and C4) indicating complement use in active disease. Even though minimal levels of anti-C1q are possible in healthy people, high levels are strongly relevant. The use of anti-C1q and anti-C3b in conjunction with the standard anti-dsDNA could have a better disease management in the clinical practice. Anti- C1q can be specifically used to detect patients with an extreme level of immune complex deposition but anti- C3b shows that there is still some level of dysregulation in complement. The use of these biomarkers can help the clinician narrow down on the immunosuppressive therapy and keeping a check on the condition of the disease..

Study limitations and future directions

The study has some limitations to be considered. As it is cross-sectional, it does not provide any time or clinical significance data. More specifically, we cannot assess if antibody levels changed in conjunction with the disease flare over time, which could have revealed further details regarding the immunological response. Furthermore, we did not account for treatment exposure such as the use of hydroxychloroquine or prednisolone, which could affect complement activity and autoantibodies. The size of number of healthy controls (n = 30) was also relatively small, and they were not included in multivariable adjustments, which may reduce the strength of the association. Finally, measured concentrations may not be accurate due to variability in the laboratory, notably anti-C3b.Despite these limitations, the study contributes to the understanding of complement-related autoantibodies in SLE. The findings support the value of anti-C1q, anti-C3b, and anti-dsDNA as markers associated with disease activity and complement consumption. Further longitudinal studies are needed to clarify their temporal behavior and prognostic utility.

CONCLUSION

Patients with SLE, particularly those with active disease, possessed significantly more antibodies to C1q, C3b and dsDNA than controls. Furthermore, these antibodies were associated with disease activity and complement levels, indicating that classical pathway activation is occurring during active disease. Supportive evidence shows that complement-related autoantibodies can detect disease activity in systemic lupus erythematosus. In contrast, longitudinal studies could clarify the dynamic behaviour and clinical significance of these biomarkers, mainly because this cross-sectional study cannot establish any temporal nor clinical significance relationships.

Conflict of interests

The authors declare no conflicts of interest.

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Authors' contribution

All authors contributed significantly to the conception, design, and development of the manuscript

Wameedh Hashim Abbas Alqatrani led the study design and coordinated the research activities.

Zainab Khalid Khaleel and Niaam Nafie Jammil performed the data collection and initial analysis.

Abeer Laily Mohammed contributed to the interpretation of results and drafted the initial version of the manuscript. All authors participated in critical revision of the content, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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