An Investigation of Some Immunological and Hematological Variables in Women with Systemic Lupus Erythematosus

Hawraa S. Al-Mozani, Sajidah F. Hasan

Department of Biology, College of Sciences, University of Kerbala, Holy Karbala City, Iraq

Abstract

Background: The autoimmune disease systemic lupus erythematosus (SLE) can cause multisystemic tissue damage because of the interaction between the autoantibodies and self-antigens. The complement system has a role in the development of the disease activity after its activation by the immune complexes. In addition to the impairment in the function of T and B cells. **Objectives:** The current study aimed to determine some hematological and immunological factors that could be indicated to disease activity. **Materials and Methods:** In this cross-sectional study, venous blood from 54 SLE patients, who were referred to Medical City, Baghdad Teaching Hospital, and 46 healthy subjects were withdrawn from January 2022 to July 2022. The levels of blood parameters such as erythrocyte sedimentation rate (ESR), white blood cells (WBC), and Hb were measured for the patients and controls. The levels of anti-dsDNA antibodies, C3, C4, IL-6, and IL-17a, were determined for patients and controls by enzyme-linked immunosorbent assay technique. Clinical diagnosis was made for all SLE patients according to the standards approved by the American College of Rheumatology, and the disease activity was determined by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). Information such as age, history of diagnosis of the disease, and family history were collected by using a questionnaire provided for this study. **Results:** The age range shows a high rate of SLE disease in the age group 25–34, 24 (44.44%). The inactive group of patients was the largest among all patient's groups (28 [51.85%]). ESR rate and WBCs count were significantly higher in patients. Anti-dsDNA antibodies were significantly high, with an average of 4.84 U/mL in patients compared to healthy controls. C3 and C4 showed an obvious reduction in the sera of patients (111.57, 0.278, respectively) compared to healthy people (126.08, 0.0489, respectively). Anti-dsDNA antibodies appeared with high significant levels in the active group of patients compared to other groups. For cytokines results, IL-6 was significantly high in patients (70.62 ng/l), and the levels of IL-6 and IL-17a were differentiated significantly with disease activity. **Conclusions:** CD3, C4, and dsDNA could be the most efficient indicators for disease diagnosis. However, dsDNA, IL-6, and IL-17a are the best to indicate disease activity.

Keywords: C3, C4, disease activity, ESR, IL-17a, IL-6, Iraqi women, SLE

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by dysfunction of B and T cells that leads to multisystem tissue damage because of the effects of inappropriate immune response. In addition to the interaction of autoantibodies with self-antigens forms immune complexes that deposit in various tissues.[1] Activation of the complement system by the immune complexes and then its involvement in SLE's pathogenesis is well defined due to the contribution of these immune complexes in inflammation and tissue damage.[2]

The complement system, as a part of the innate immune system, consists of over 30 proteins. C3 component is the highest concentration in human plasma compared to other complement's proteins, and it is followed by C4, which represents the second abundant concentration. C3 and C4 are soluble polypeptides that could enhance inflammation and tissue injuries by different mechanisms, such as attracting phagocytosis, promoting vasodilation, and histamine's liberation from mast cells.[3] There are two reasons to use the complement as an indicator of SLE

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Address for correspondence: Dr. Sajidah F. Hasan, College of Sciences, University of Kerbala, 56001 Holy Karbala City, Iraq.
E-mail: sajida.f@uokerbala.edu.iq

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infection; one of them is the deficiencies in complement components, especially C3 and C4 that participate in the disease pathogenesis, and the second is complement dysregulation that is happened during the disease course.[4-6]

The formation of autoantibodies against the cellular antigens, such as nuclear and cytoplasmic antigens, could be associated with complement activation and represented by fluctuations in the serum levels of C3 and C4.[7] During SLE development, the complement activation rises, and it could be consumed; therefore, the generation of the activation-derived products increases relatively. On the other hand, some references refer to the decreased levels of complement's components, especially C3 and C4, do not considered markers for SLE flare because some individuals genetically have low levels of C3 or C4.[8-10]

On the other hand, investigating the cytokines profile for any autoimmune disease is an important process to evaluate the role or function of these cytokines in disease pathogenesis or disease cure. Interleukin-6 (IL-6) and interleukin-17a (IL-17a) are considered the most recognized cytokines in autoimmune diseases. IL-6 is a proinflammatory cytokine having multi duties, and it can be released from different cells, such as macrophages, dendritic cells, and endothelial cells. IL-6 can induce autoimmunity and pathological inflammation because of its role in developing naïve B cells into plasma cells and differentiation of T cells into cytotoxic T cells.[11]

IL-17a is also a proinflammatory cytokine, which has an important immunological role against microbial pathogens. $CD4^+$, $CD8^+$, and gamma-delta T cells (γδ-T) are the main sources of IL-7a.[12] Several studies indicate that IL-17a can be associated with the pathogenicity of many autoimmune diseases.[13]

The diagnosis of SLE and determining its activity require closely related laboratory indicators that synchronize with the disease symptoms and pathological screening. The current study tried to find a connection between the levels of C3, C4, IL-6, IL-17a, and anti-dsDNA antibodies and disease activity, which could be useful in detecting the status of the disease and determining the suitable treatment.

Materials and Methods

This cross-sectional study included a collection of 100 blood samples from patients and healthy individuals; the age of participants ranged 15–51 years. The samples were collected from the Medical City, Baghdad Teaching Hospital, in Baghdad Governorate for the period between January 2022 to July 2022.

The clinical diagnosis was made for all pathological cases according to the standards approved by the American College of Rheumatology in terms of the availability of at least four disease indicators out of eleven indicators, such as zygomatic rash, discoid rash, serious infections, photosensitivity, oral ulcers, and anti-nuclear antibodies and antibodies against duplex DNA.[14] The information about the patients and controls was recorded according to a questionnaire prepared for this study, and it was included health and social details such as the name, age, residence, educational attainment, history of illness, and the period of illness and treatment history. The questionnaire also was filled out for the group of apparently healthy people (control samples) who did not suffer from any chronic condition or any autoimmune diseases and did not have any genetic or systemic diseases. The patients suffering from genetic or respiratory disease, patients with renal impairment, liver diseases, tumors, and pregnant women were excluded from this study. Therefore, depending on the recorded data in the questionnaire and clinical examination, only patients with SLE and with no pathological complications and negative results for any other diseases were included in the study. Disease activity was determined by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), which are set of 24 global indicators to assess disease activity in patients with SLE and includes specific items for evaluating disease manifestations. The disease activity was classified into the lowest level, no flare, mild flare, moderate or high flare, and these approved standards are set by the American College of Rheumatology.[15]

About 10 mL of venous blood was collected from the control and the patients' groups using single-use medical syringes after sterilizing the withdrawal area with 70% ethanol alcohol. Blood samples were distributed to two test tubes as follows: 3 mL in an anticoagulant tube to measure the sedimentation rate of red blood cells and to have the complete blood picture using the automatic device. The rest of the blood (7 mL) was placed in a gel tube and spun by centrifuge (3000 rpm for 10 min) to separate the serum. The extracted serum was distributed in 0.5 mL Eppendorf microtubes and then frozen at a temperature -20°C for the purpose of measuring the concentrations of the immunological parameters included in the study.

The erythrocyte sedimentation rate was measured for the collected blood samples by using the Westergren method according to the standard method for measuring the erythrocyte sedimentation rate, where 0.2 mL of 3.8% sodium citrate solution was mixed with 1.8 mL of blood in a Westergren tube until it reached the mark zero in the tube, and then the tubes placed upside down in a special tube holder. The sedimentation rate of red blood cells is read after 60 min in mL/min. The number of white blood cells, red blood cells, platelets, and hemoglobin level (white blood cells (WBC), red blood cells (RBC), platelet count, hemoglobin) were measured after placing the blood in anticoagulant tubes containing ethylenediaminetetraacetic acid, then inserted into the automated complete blood count analyzer to read the results.

The level of complement proteins C3 and C4 were measured for the sera of patients and controls by using

Table 1: Distribution of the patients and controls according to age groups

Groups	No.	15–24 no. (%)	25–34 no. (%)	35–44 no. (%)	≥45	Chi-square-χ2 (*P*-value)
Patients	54	6 (11.11%)	24 (44.44%)	16 (29.63%)	8 (14.81%)	15.48 0.0074 **
Controls	46	14 (30.43%)	15 (32.61%)	12 (26.09%)	5 (10.87%)	11.525 0.0091 **
Chi-square-(χ2) *P*-value	–	5.92	3.071	1.89	1.55	–
		0.0327 *	0.098 NS	0.327 NS	0.308 NS	

*($P < 0.05$), ** ($P < 0.01$), NS = nonsignificant

Table 2: Distribution of patients according to history of diagnosis of the disease

Group	No.	<1 yr. no. (%)	1–3 yr. no. (%)	>3 yr. no. (%)
Patients	54	13 (24.07%)	20 (37.04%)	21 (38.89%)
Chi-square-(χ^2)	–		2.137	
P-value			0.343 NS	

NS: nonsignificant

the kits manufactured by Shanghai YL Biont, Shanghai, China, and anti-dsDNA antibodies were measured by the kit manufactured by Demeditec, Kiel, Germany. The levels of IL-6 and IL-17a were also measured for the sera of patients and controls by using the kits manufactured by Shanghai YL Biont. The principles of the assay are based on the technical principles of sandwich enzyme-linked immunosorbent assay (ELISA).

Statistical analysis was carried out by IBM SPSS Statistics software (Armonk, New York, United States). One-way ANOVA was used to find the significant differences between more than two independent factors, while the *T*-test was used to find the significant comparison between two independent factors. The chi-square test was used for significant comparison qualitative data, where $P < 0.05$ is considered significant, $P < 0.01$ highly significant, and NS is not significant.

Ethical approval

The protocol of the research followed the Helsinki Declaration and was confirmed by the College of Science, University of Kerbala (Approval Code: No. 6.73 on January 9, 2022).

Results

The study included 54 females with lupus erythematosus and 46 healthy subjects. The ages of the participants were between 15 and 51 years. All participants (the patients and the healthy volunteers) were divided into four age groups [Table 1]. It was found that the highest rate of infection occurs in the age group 25–34 (44.44%), followed by the age group 35–44 (29.63%). The two age groups, 15–24, with an infection rate of 11.11%, and ≥45, with an infection rate of 14.81%, were the lowest rate of infection; the *P*-value was 0.0074**.

Table 2 shows the number of years that patients have been in duration. Most of the patients fell with the year groups 1–3 and >3. However, the statistical analysis did not show any significant differences among all groups.

Table 3: Distribution of patients according to family history

Groups	No.	Yes	No
		No. (%)	No. (%)
Patients	54	13 (24.07%)	41 (75.93%)
Chi-square-(χ^2)	–	14.518	
P-value		0.0001**	

** $P < 0.01$

The results also showed significant differences when the two groups, the positive family history with the SLE and the negative group, were compared to determine if there is any connection between the family history and the disease appearance. The highest rate was in the negative family history group [Table 3].

The patients were divided according to disease activity into three categories which are mild, active, and inactive. Mild activity patients were represented 31.48%, active were 16.67%, and inactive were 51.85%. High significant differences appeared among the categories [Table 4].

Table 5 tries to analyze the differences between patients and controls in relation to blood parameters. The erythrocyte sedimentation rate (ESR) and white blood cells count were significantly higher in patients compared to controls. At the same time, the hemoglobin (Hb) level was significantly lower in the patients group.

Although most of the measured blood parameters significantly vary between the groups of patients and controls, these blood parameters did not show significant differences when it analyzed after being distributed according to disease activity [Table 6].

Table 7 illustrates the complement fraction C3, C4, and dsDNA levels in patient and control groups. C3 average was 111.57 mg/dl in the patients' group, compared to the controls' group, which amounted to 126.08 mg/dl, and

Table 4: Distribution of patients according to disease activity

Group	No.	Mild	Active	Inactive
		No. (%)	No. (%)	No. (%)
Patients	54	17 (31.48%)	9 (16.67%)	28 (51.85%)
Chi-square-(χ^2)	--		10.218	
P-value			0.006 **	

** $P < 0.01$

Table 5: Comparison between patients and control groups in blood parameters

Group	Mean ± SE				
	ESR	Hb	RBC	WBC	PLT
Patients	40.05 ± 3.41	11.28 ± 0.23	4.62 ± 0.08	9.03 ± 0.45	279.61 ± 11.90
Control	15.06 ± 0.91	12.23 ± 0.16	4.63 ± 0.09	7.82 ± 0.31	251.39 ± 8.5
T-test	7.508	0.583	0.250 NS	1.135	29.981 NS
P-value	0.0001**	0.0017**	0.686	0.0365*	0.0648

PLT = platelet count, RBC = red blood cells, WBC = white blood cells

* $P < 0.05$, ** $P < 0.01$, NS: nonsignificant

Table 6: Relationship of disease activity and blood parameters in patient's groups

Disease activity	Mean ± SE				
	ESR	Hb	RBC	WBC	PLT
Mild	34.76 ± 4.84	11.48 ± 0.39	4.73 ± 0.13	9.11 ± 0.72	257.71 ± 13.91
Active	44.56 ± 8.39	10.95 ± 0.61	4.79 ± 0.26	9.29 ± 1.26	274.89 ± 15.21
Inactive	41.82 ± 5.26	11.27 ± 0.32	4.51 ± 0.10	8.89 ± 0.66	294.43 ± 20.61
LSD value	18.736 NS	1.276 NS	0.445 NS	2.527 NS	65.06 NS
P-value	0.559	0.762	0.331	0.947	0.394

PLT = platelet count, RBC = red blood cells, WBC = white blood cells

NS: nonsignificant

Table 7: Comparison between patients and control groups in C3, C4, and dsDNA

Group	Mean ± SE		
	C3 (mg/mL)	C4 (mg/mL)	dsDNA (U/mL)
Patients	111.57 ± 4.01	0.0278 ± 0.001	4.84 ± 0.79
Control	126.08 ± 4.49	0.0489 ± 0.003	2.75 ± 0.25
T-test	12.174	0.0053	1.996
P-value	0.0201*	0.0001**	0.0403*

* $P < 0.05$, ** $P < 0.01$

significant differences were observed under *P* value 0.01. The fourth complement fraction (C4) average was in the patients 0.0278 mg/dl and the healthy group 0.0489 mg/dl, and there were significant differences between the two groups. The average of dsDNA was highly significant between the two groups.

The levels of C3, C4, and dsDNA for the patient's sera were statistically analyzed according to the disease activity categories (mild, active, inactive). Significant differences were found for C4 and dsDNA components, while in C3, there were no significant differences. The lowest level for C4 was in the inactive group, and the highest level for dsDNA was in the active group [Table 8].

In Table 9, IL-6 was significantly higher in patients with an average of 70.62 ng/L compared to controls (27.22 ng/L). At the same time, IL-17a was in its comparable rates for the two groups of patients and controls (22.13, 23.98, respectively).

From Table 10, it can be noted that IL-6 and IL-17a clearly participate in disease activity through the significant increase of their concentrations in the active group compared to mild and inactive groups.

Discussion

Diagnosis and monitoring SLE are considered a challenge because of the alternating state of the disease

Table 8: Comparison of the levels of C3, C4, and dsDNA among sera of patient groups which are distributed according to disease activity

Disease activity	Mean ± SE		
	C3 (mg/mL)	C4 (mg/mL)	dsDNA (U/mL)
Mild	114.98 ± 10.33	0.0274 ± 0.002 b	4.045 ± 0.79 b
Active	116.34 ± 7.87	0.0349 ± 0.003 a	9.802 ± 3.88 a
Inactive	107.97 ± 3.92	0.0258 ± 0.001 b	3.725 ± 0.59 b
LSD value	22.116 NS	0.0056	4.058
P-value	0.651	0.010**	0.0161*

This means having the different letters in the same column differed significantly

* $P < 0.05$, ** $P < 0.01$, NS: nonsignificant

Table 9: Comparison between patients and control groups in IL-6 and IL-17a

Group	Mean ± SE	
	IL-6 (ng/L)	IL-17 a (ng/L)
Patients	70.62 ± 12.96	22.13 ± 3.39
Control	27.22 ± 3.23	23.98 ± 5.71
T-test	42.956	8.424 NS
P-value	0.0433*	0.662

* $P < 0.05$, NS: nonsignificant

Table 10: Relationship of disease activity and with IL-6 and IL-17a in patient's groups

Disease activity	Mean ± SE	
	IL-6 (ng/L)	IL-17 a (ng/L)
Mild	59.22 ± 5.28 [b]	20.74 ± 2.92 [b]
Active	252.89 ± 36.62 [a]	40.31 ± 19.26 [a]
Inactive	18.95 ± 1.28 [c]	17.12 ± 0.58 [b]
LSD value	33.798	17.820
P-value	0.0001**	0.0479*

This means having the different letters in the same column differed significantly. *$P < 0.05$, ** $P < 0.01$

between the active and the attenuation. Therefore, there is a persistent need to identify the biomarkers that could be precisely determined the state of disease activity.

Our study involved 100 participants, who were divided into two main groups, the SLE patients (54) and the healthy subjects (46). These two groups were distributed into four age stages (15–24, 25–34, 35–44, ≥45) to analyze the role of age on the percentage of infection. The statistical analysis showed that age groups 25–34 and 35–44 were significantly the highest in the percentage of infection; they were 44.44% and 29.63%, respectively, compared to the 15–24 and ≥45 groups. The patients were also distributed according to how many years they have been infected, and in this aspect, the patients who were 1–3 and >3 years had been registered with the highest rate of infection (37.04% and 38.89%). The highest percentage of infection was in the patients' ages 25–34 and 35–44 because SLE is more prevalent among women of childbearing age due to the association of symptoms of the disease with hormones and an increase in its secretion at a certain age in women. Sex hormones such as progesterone and prolactin have a direct and indirect effect in changing the immune tolerance of B cells and lead to an increase in their secretion of autoantibodies, which are the advantage basic to increasing the incidence and severity in SLE.[16,17] This range of ages was also documented in several research articles.[18-20] The family history did not connect to disease appearance, where 75.93% of patients have no family history related to SLE.

Blood parameters in SLE patients, such as ESR, Hb, and WBCs, were varying in their count or concentrations compared to apparently healthy controls. ESR and WBCs were significantly higher, and Hb was lower in patients. Poor erythropoietin response and the formation of antibodies against erythropoietin can be the reason for causing anemia in SLE patients. However, these parameters did not show significant differences when it was analyzed according to disease activity. This means that variation in the values of these parameters includes all the patients regardless of disease activity. Our results agree with several other studies.[21,22]

The patient's group was divided depending on the disease activity into three categories, which are mild, active, and inactive. There were significant differences among these three groups, and the highest percentage was for the inactive group (51.85%). The levels of C3 and C4 were significantly low in patients compared to the controls group. In the next step when the levels of C3, C4, and dsDNA were statistically analyzed according to the groups of disease activity to determine which component of these three significantly connects to disease activity and can be considered as a marker for disease diagnosis and disease severity, C4 and dsDNA levels were significantly differentiated among the groups of disease activity, where the highest levels of dsDNA were in the active group. The complement system has an essential role in SLE, where its activation by the immune

complexes leads to hypersensitivity type III. Therefore, the presence of complement in the inflamed and damaged tissue is considered a diagnostic tool because consuming the complement in the target tissue results in drooping C3 and C4 in the sera of patients.[9] The test anti-double-stranded DNA (dsDNA) antibodies are widely used in the diagnosis of SLE, in addition to its important role in disease's classification and management. This importance of dsDNA in the diagnosis of SLE was reinforced by the new criteria which were suggested by the European League Against Rheumatism (EULAR) to give it the highest score (6 points) in the diagnosis of SLE.[23] The decline in the levels of C3 and C4 and rising the level of dsDNA in SLE patients in our study are going along with many previous studies.[9,24-26]

Regarding cytokines' results, IL-6 was the only significantly high in the patients' group compared to controls. However, both cytokines (IL-6 and IL-17a) were significantly high in the active group. These results agree with several previous studies.[27-31] IL-17a has harmful effects on the tissue by causing tissue injuries; therefore, targeting the IL-17a pathway could inhibit or decrease the serious effects of SLE.[32-34] Using IL-6 or IL-17a alone is less useful in determining the role of Th17-driven disease. So, using both cytokines and investigating other cytokines may clarify the role of IL-17a in driving activation in SLE.[13]

The limitation of the current study was the small number of patients, and it was restricted to females only due to the very low number of male patients as well as to their nonconsent to participate in the study.

Conclusion

In conclusion, the anti-dsDNA antibodies are the best indicator for SLE presence, and the disease diagnosis could also be supported when there is a reduction in the serum levels of C3 and C4. Furthermore, dsDNA, IL-6, and IL-17a could be the most efficient indicators for disease activity.

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Conflicts of interest

There are no conflicts of interest.

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