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Levels of VCAM-1 and ICAM-1 in serum of active and inactive Systemic Lupus Erythematosus patients as biochemical markers for risk of cardiovascular disease

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Abstract

Background: Cardiovascular complications represent one of the consequences of the chronic autoimmune disease such as Systemic Lupus Erythematosus (SLE), which has significant rates of morbidity and mortality. Dyslipidemia can be brought on by steroid medications, which is frequently given to SLE patients and are considered to be one of the major risk factors for cardiovascular diseases.

Objectives: This study attempted to investigate a potential association between circulating vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) as risk factors for atherosclerosis and their relationship to cardiovascular risk.

Patients and methods: A total of 100 patients and 50 apparently healthy controls were included in the study. All patients were from the Department of Rheumatology, Baghdad Hospital / Medical City during the period from 1 December 2021 to 1 March 2022 who were all treated with antimalarial drugs as immunosuppressants such as chloroquine (CQ) or hydroxychloroquine HCQ). They were divided according to the SLE disease activity index 2000 (SLEDAI-2K) into the active group (SLEDAI ≥ 10) and the inactive group (SLEDAI).

Results: Serum VCAM and ICAM were significantly high in all study groups of SLE patients. The VCAM mean ± SD were (271.9±63.90), (247.9±82.92) and (97.7±24.69) in the active, inactive controls respectively. The ICAM mean ± SD were (3.1±0.91), (2.7±0.79) and (1.8±0.22) in the active, inactive and controls respectively. The values have increased gradually with increasing disease activity. The area under curve (AUC) of ICAM and VCAM were (0.802), (0.776) in active SLE patients and (0.858), (0.674) in inactive SLE patients. However, the AUC of VCAM and ICAM in active group were the highest.

Conclusion: In SLE patients, VCAM-1 and ICAM-1 serum levels may operate as disease detection and severity differentiation indicators, and they may be linked to the number of coronary lesions in people at risk of developing CVD.

Keywords: SLE, Atherosclerosis, VCAM, ICAM.

Introduction:

Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune disease with a large variation in severity and duration [1, 2]. It is characterized by a proclivity for flares and a complex and diverse immunological dysregulation. SLE affects more females than males and generally begins in early or mid-adulthood [3]. Multi-organ/system involvement in SLE includes hematologic, renal, mucocutaneous, cardiac, and all the musculoskeletal [1].

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Environmental, endocrine, genetic and immunological factors contribute to the loss of immunological tolerance to self-antigens, which causes the emergence of pathogenic autoantibodies that harm tissues through a variety of mechanisms [4].

The pathophysiology of SLE is complicated, and our understanding of it is always changing. Autoimmunity is triggered when a person has genetic sensitivity and his tolerance is compromised due to exposure to environmental stimuli. The immune system is exposed to self-antigens as a result of infectious agents and other environmental triggers, which activates and sustains T and B cells in an ongoing, self-directed immunological response. Cytokine release, complement activation, and the development of autoantibodies all lead to organ damage [4]. More than 90% of SLE patients have physiological symptoms,

which are typically the initial manifestation. The signs and symptoms include anorexia, fever, fatigue, weight loss and malaise. While a lupus flare may be the cause of fever in more than 40% of SLE patients, infectious diseases must always be cleared out beforehand due to these patients' immunocompromised status. SLE is also an extremely unusual form of fever with no known etiology [4]. Immunomodulation drugs are essential for treating SLE symptoms and controlling inflammation quickly, which works to avoid long-term organ and tissue injury. In Western countries, several cohort studies showed that HCQ reduce SLE flares and mortality [5]. Cardiovascular disease (CVD) is the main cause of mortality globally. CVD is a prominent consequence of systemic lupus erythematosus (SLE) and is currently a main cause of mortality in persons with the disease [6, 7]. Furthermore, SLE illness-related factors may be considered when estimating heart disease and stroke risks. The majority of SLE patients were found to have dyslipidemia, which can play a key role in the development of CVD in SLE [8,9,10,11]. It had been found that one distinguishing feature of this autoimmune inflammatory disease is SLE endothelial dysfunction. In order for inflammatory cells to penetrate tissues, endothelial dysfunction causes an overabundance of cell adhesion molecules and the release of chemokines and cytokines [12,13,14,15]. The presence of the soluble cell adhesion molecules like intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1) had been reported by studies to indicate the inflammatory reaction in the endothelium. These molecules play a crucial role in the development of atherosclerotic plaques by establishing a coordinated and overlapping mechanism for transporting leukocytes into the artery wall. [16]. Normal endothelial cells (sICAM-1 and sVCAM-1) only weakly exhibit, but when there is local or systemic inflammation, they are upregulated, frequently in conjunction with increased Interleukin-1b (IL-1b) and tumor necrosis factor (TNF), then they promote leukocyte adherence and dissemination to the endothelial surface after which they are transmitted through endothelial cells [17]. VCAM-1 levels have indeed been discovered to be greater in the sera and urine of SLE patients. This has also been linked to the disease activity [18]. In SLE patients, increased VCAM-1 plasma levels have been linked to cardiovascular risk, coronary artery calcium score, and atherosclerotic plaque formation [19]. ICAM-1 studies in SLE have shown contradictory results in both blood and urine [20]. When employing a continuous scale, the Receiver Operating Characteristic (ROC) curve has been widely used in medical studies to evaluate the precision of a diagnostic biomarker in illness screening in addition to diagnosis. The binary test rule derived at each potential threshold point is shown by the ROC curve, which also shows sensitivity vs. specificity as a function of threshold point [21].

Patients and methods

This case control study included SLE patients divided into: 1. the active group (n = 60 patients, 56 females and 4 males) and 2. The inactive group (n=40 patients, 36 females and 4 males) in addition to healthy controls (n= 50 cases, 43 females and 7 males) where randomly selected (from the community their age matched the patients). All the patients that met ≥ 4 of the American College of Rheumatology Criteria (updated in 1982) for the categorization of SLE were included in the study. [22]. They were clients of the Department of Rheumatology, Baghdad Hospital, Medical City and their data were collected during the period from 1 December 2021 to 1 March 2022. They were all treated with antimalarial drugs as immunosuppressants such as CQ or HCQ. They were diagnosed by a specialist rheumatologist through clinical examinations and laboratory tests. The SLE Disease Activity Index 2000 (SLEDAI-2K) was employed to assess the clinical disease activity [23]. Sixty SLE patients had (SLEDAI ≥ 10) and were classified as the active group, while 40 SLE patients had (SLEDAI < 10) and were classified as the inactive group that is characterized by a continuing lack of disease activity with or without a steady dosage of immunomodulating medications for at least four months. Both patients and healthy controls were free from CVD within the past six months.

Exclusion criteria: Hematological, endocrine, acute infectious diseases and tumors.

VCAM-1 and ICAM-1

The (sVCAM-1 and sICAM-1) were measured by enzyme-linked immunosorbent assay (ELISA) kits from the Picokine™. The PicokineTM Human VCAM1 Pre-Coated ELISA kit is a solid phase immunoassay specifically designed to measurement of Human VCAM1 and ICAM1 with a 96-well strip plate that is pre-coated with the antibody specific for VCAM1 and ICAM1. It is based on the Sandwich-ELISA principle.

Biochemistry Analyser

Total Serum Cholesterol, HDL, triglyceride (TG) (cobas c111, ROSH, Germany) were measured and the LDL level was determined using the Friedewald formula [24].

Systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K)

Disease activity was evaluated using the SLE disease activity index (SLEDAI). The index was applied to all patients by a rheumatologist who is familiar with the system.

Measurement of body mass index (BMI): According to the WHO categorization, baseline BMI calculated

as the bodyweight (Kg) divided by the square height (m^2), was used to classify the cases and controls into six groups, table 1 [25, 26].

Table 1: Classification of BMI groups

BMI groups	(Kg/m^2)
Underweight	<18.5
Normal weight	18.5 to 24,9
Over weight	25 to 29.9
Obese G_1	30 to 34.9
Obese G_2	35 to 39.9
Obesity G_3	≥40

Statistical Analysis

All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 26 and XLSTAT add on Microsoft excel 2010 software. The one-way Analyses of variance ANOVA test followed by LSD post hock used for comparison between different groups mean. All tests were two-sided, and the results are presented as means ± standard deviation (SD) for continuous variables, while categorical variables were expressed as percentages with 95% confidence intervals. The sensitivity, specificity, cut off and area under the curve were explored with Receiver Operating Characteristic (ROC) curve analysis. The P-value below 0.05 was considered statistically significant.

Results

1. Serum VCAM-1 and ICAM-1 levels and ROC analysis

The age of the active group was between (14-58) years, while the inactive group was between (13-59) years and the control group between (14-52) years. (Table 2) shows that the VCAM mean ± SD was (271.9±63.90), (247.9±82.92) and (97.7±24.69) in the active, inactive and control groups respectively. The ICAM mean ± SD were (3.1±0.91), (2.7±0.79) and (1.8±0.22) in the active, inactive and control groups respectively. The values increased gradually with increasing disease activity.

Table 2: Serum VCAM-1 and ICAM-1 levels in SLE patients and the controls

Parameters	Controls	Active SLE	Inactive SLE	P- value
VCAM	97.7±24.69	271.9±63.90		< 0.0001
	97.7±24.69		247.9±82.29	< 0.0001
		271.9±63.90	247.9±82.29	<0.05
ICAM	1.8±0.22	3.1±0.91		< 0.0001
	1.8±0.22		2.7±0.79	< 0.0001
		3.1±0.91	2.7±0.79	<0.006

To evaluate the accuracy of ICAM and VCAM in detecting the SLE patients at risk of CVD in each patient group, ROC test was done, as presented at table 3.

Table 3: ROC test of ICAM and VCAM in active and inactive SLE cases

Variables		Area	Cut off value	Asympt-otic Sig.[b]	Sens-itivity	Specifi-city
Active SLE	ICAM	0.802	2.36	.000	78.3%	71.1%
	VCAM	0.776	208	.000	78.3%	66.3%
Inactive SLE	ICAM	0.558	2.40	.282	52.5%	59.2%
	VCAM	0.674	228	.001	60%	58.3%

The active SLE patient group has cut off value of ICAM and VCAM (2.36) and (208), AUC (0.802), (0.776), with sensitivity (78.3%), (78.3%), specificity (71.1%), (66.3%) and P- value (<0.0001), (<0.0001), figure 1. The inactive SLE patient group has cut off value of ICAM and VCAM (2.4), (288), AUC (0.558), (0.674), with sensitivity (52.5%), (60%), specificity (59.2%), (59.3%) and P- value (0.282), (0.001), figure 2.

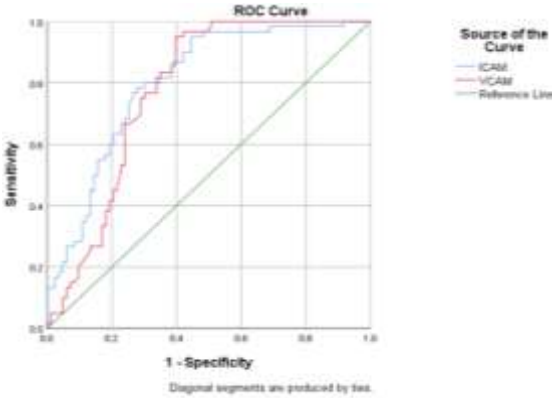

Figure 1: detecting active SLE patients

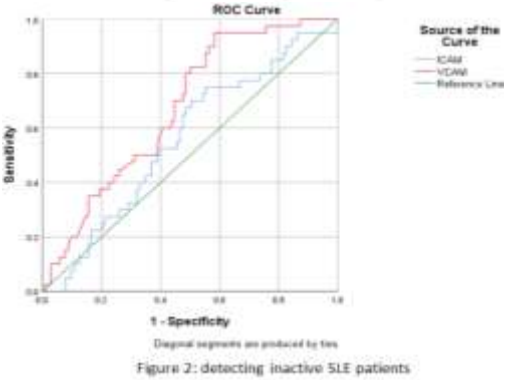

Figure 2: detecting inactive SLE patients

2. Lipid profile in the SLE and atherogenic index

As shown in table 4 the serum lipid profile variables were significantly lower in SLE patients compared to apparently healthy controls. The TC/HDL ratio was significantly higher in patients with active and inactive SLE disease compared to healthy controls.

Table 4: The mean ± SD values of lipid profile variable in the three study groups

TEST	Controls	Active SLE	Inactive SLE	P value	Reference
Total cholesterol	207.8±36.44	158.9±46.20		< 0.0001	<200 Mg/dl
	207.8±36.44		155±42	< 0.0001	
		158.9±46.20	155±42	0.649	
Triglycerides	162.5±21.70	109.9±40.49		< 0.0001	<150 Mg/dl
	162.5±21.70		108±37.70	< 0.0001	
		109.9±40.49	108±37.70	0.817	
High density lipoprotein cholesterol	50.4±13	32.3±14.68		< 0.0001	40 – 60 Mg/dl
	50.4±13		34±15	< 0.0001	
		32.3±14.68	34±15	0.644	
Very low-density lipoprotein cholesterol	32.5±36.28	21.3±8.90		< 0.0001	<30 Mg/dl
	32.5±36.28		20.2±8.42	< 0.0001	
		21.3±8.90	20.2±8.42	0.654	
Low density lipoprotein cholesterol	128.0±36.00	102.1±42.40		< 0.0001	<129 Mg/dl
	128.0±36.00		94.9±39.14	< 0.0001	
		102.1±42.40	94.9±39.14	0.470	
TC/HDL	4.1±0.80	5.6±1.78		<0.001	<5 Mg/dl
	4.1±0.80		4.9±1.39	<0.038	
		5.6±1.78	4.9±1.39	<0.05	

Discussion:

In the current investigation, the results show that the serum levels of soluble cell adhesion molecules VCAM-1 and ICAM-1in SLE patients are increased and raised parallel to the disease activity and they are higher compared to apparently healthy control subjects. They are significantly greater in active SLE patients than the inactive once, and also higher than apparently healthy control subjects. The findings regarding the susceptibility to CVD in SLE patients revealed that the SLE patients had higher levels of serum VCAM-1 and ICAM-1. As a result. they may have a higher probability of developing atherosclerosis than the healthy control. These results agree with a study on 127 female SLE patients and 124 healthy women, where ICAM-1 was significantly higher in patients compared to healthy controls. These findings were helpful in exploring the etiology of increased CVD risk in SLE patients because cell adhesion molecules (CAM) may be a mediator between atherosclerosis and inflammation. The study indicated that the upregulation of endothelial CAM expression in SLE patients causes increased levels of ICAM-1. In fact, ICAM-1 promotes leukocyte adhesion and trans-endothelial migration, a crucial first stage in inflammatory vascular disease, by acting as a binding site for fibrinogen. [26] Another study on 74 patients who were getting their first coronary angiography for diagnostic purposes and were grouped into 1) No lesions, 2) mild lesions, 3) intermediate lesions, and 4) serious lesions. Blood biochemical markers and serum levels of E-selectin, intercellular adhesion, molecule-1 vascular cell adhesion molecule-1, and matrix metalloproteinase were studied. Serum VCAM-1 may be related to the severity of coronary lesions in those who are at risk of developing acute coronary syndrome. Additionally, their finding raises the potential that VCAM-1 is associated with cardiovascular disease prognosis and atherosclerosis severity (CVD). [16] To confirm that elevated serum VCAM-1 and ICAM-1 may be associated with the atherosclerosis, another study on 855 patients who had stable carotid atherosclerosis of more than (6.2) year duration, reported that ICAM-1 levels greater than 335 ng/mL raised that risk by (3.4) fold, while VCAM-1 value greater than 837 ng/mL raised that risk by 2.5-fold. Their finding showed that in individuals with stable carotid atherosclerosis, these compounds were strong and independent indicators of death. [27] In our study the levels of Serum TC, TG, HDL, LDL and VLDL in the active and inactive groups were less than the control but they were still with the normal range because the effect of HCQ leads to decreased levels of the lipid profile. However, the traditional risk factors (lipid profile) fail to fully explain the increased risk of CVD in these SLE patients; the TC/HDL ratio was higher in both patient's group compare to control and this ratio can be adopted as risk factor to indicate the possibility of the patient's exposure to CVD and atherosclerosis. According to several studies, dyslipidemia in SLE patients is a major factor in the development of atherosclerosis. It appears that atherosclerosis commonly manifests itself when SLE is in progress. [29] According to a Brazilian cohort study of 185 SLE patients, 60% had hypercholesterolaemia and hypertriglyceridemia, 48% had hypercholesterolaemia, and 30% had hypertriglyceridemia. Dyslipidaemia was discovered in patients with SLE at rates of 65.3% to 84.6% in Asia, with total cholesterol levels rising about 43%, levels of LDL dropping by 26.4%, TG

rising about 44.2%, while HDL levels falling by 26% [30]. By establishing the dysregulated blood lipid profile and its relationship with the disease activity in 71 female individuals with SLE disease who were included in a study similar to ours, with the potential to have therapeutic applications. The lipid profile alterations were found to be substantially correlated with the activity of the SLE illness, with SLEDAI showing positive correlations with TG and VLDL-C and negative correlations with HDL-C, LDL-C, ApoA, and ApoB. The metabolism of lipid dysregulation may be used to diagnose and assess the severity of SLE. Because SLE disease activity is directly linked to the source of dyslipidemia, evidence suggests that young SLE patients who have dyslipidemia may also be at an increased risk of cardiovascular disease [29]. Steroids, which are used to treat SLE, have a history of altering lipid profiles, including raising total cholesterol, TG, and LDL levels while lowering HDL levels [31]. A cross-sectional study of 41 female SLE patients using a correlative analytic methodology, with the mean age of the cases being 30.0 ± 9.29 years, HDL, LDL, TG, and total cholesterol were all correlated with steroid dosage at p = 0.016, p = 0.007, p = 0.196, and p = 0.05, respectively. [32] Eight studies altogether, comprising four case-control studies, two cohort studies, and two randomized controlled trials (RCTs), on a total of 717 patients, 336 in the group of CQ or HCQ treatment, and 381 SLE patients who did not receive antimalarial (AM) medication. When compared to the control group, TC, VLDL-C,and TG all showed a statistically significant decline (P =0.00001, P =0.0004, P =0.01, P =0.04), while HDL-C did not (P =0.12). The findings have some clinical value since they demonstrated that HCQ can lower the TC, TG, LDL-C, and VLDL-C in SLE patients. The blood lipids, which are the main risk factor for atherosclerosis and coronary heart disease, can be reduced by CQ or HCQ (CAD) [33].

Conclusion

The VCAM-1 and ICAM-1 are significantly greater in active SLE patients than the inactive ones, and the apparently healthy control subjects. Therefore; they can act as detecting markers for the disease and as differentiating markers for its activity in patients. sVCAM-1 and sICAM-1 levels may be correlated with the severity of coronary lesions in patients with a risk of developing CVD. The sVCAM-1 levels were found to be more sensitive than sICAM-1 levels, thus, they can be more useful in detecting arteriosclerosis in SLE patients. The use of CQ or HCQ may be associated with lowering serum lipid profile independently of the other variables. The TC/HDL ratio, however, remained high. Therefore, the serum lipid profile levels cannot be adopted alone in the detection of CAD in SLE patients. The levels of VCAM-1 and ICAM-1in serum together with TC/HDL ratio is necessary to promote early detection of CAD in SLE patients.

Author's Contributions:

Hajar Walid Khammas: sample collection and practical part.
Dr.Ghid Hassan Hadi: The theoretical part and discussion of the results.
Dr.Muhammad Hadi: Diagnosis of the disease and identification of signs and symptoms.

Authors Contributions

We hereby confirm that all the Figures and Tables in the manuscript are mine/ ours. Besides, the Figures and images, which are not mine /ours, have been given permission for re-publication attached with the manuscript.-Authors sign on ethical consideration's approval-Ethical Clearance: The project was approved by the local ethical committee in College of Medicine/ University of Baghdad according to the code number (1439.6.11.2021).

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مستويات VCAM-1 و ICAM-1 في مصل مرضى الذئبة الحمامية الجهازية النشطة وغير النشطة كواسمات كيميائية حيوية لخطر الإصابة بأمراض القلب والأوعية الدموية

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الخلاصة

الخلفية العلمية: تمثل المضاعفات القلبية الوعائية إحدى نتائج أمراض المناعة الذاتية المزمنة مثل الذئبة الحمامية الجهازية (الذئبة الحمراء)، والتي لها معدلات كبيرة من الوفيات والمراضة. يمكن حدوث عسر شحميات الدم عن طريق الأدوية الستيرويدية، والتي تُعطى بشكل متكرر لمرضى الذئبة الحمراء وتعتبر أحد عوامل الخطر الرئيسية لأمراض القلب والأوعية الدموية.

الأهداف: حاولت هذه الدراسة التحقق من وجود ارتباط محتمل بين VCAM-1 و ICAM-1 في المرضى العراقيين الذين تم تشخيص إصابتهم بالذئبة الحمامية الجهازية كعوامل خطر لتصلب الشرايين وعلاقتها بمخاطر القلب والأوعية الدموية.

المنهجية: تم تضمين 100 مريض و 50 شخص يبدون بصحة جيدة في هذه الدراسة. جميع المرضى في قسم أمراض الروماتيزم، مستشفى بغداد / المدينة الطبية في الفترة من 1 كانون الأول 2021 إلى 1 آذار 2022 وعولجوا جميعاً بأدوية مضادة للملاريا كمثبطات مناعية مثل الكلوروكين أو الهيدروكسي كلوروكين. تم تقسيمهم وفقًا لمؤشر نشاط مرض (SLEDAI≥10) كمجموعة نشطة و (SLEDAI<10) كمجموعة غير نشطة.

النتائج: كان مستوى VCAM و ICAM في المصل مرتفعا بشكل ملحوظ في جميع مجموعات الدراسة لمرضى الذئبة الحمراء. كان متوسط ± الإنحراف المعياري ل VCAM (63.90 ± 271.9)، (82.92 ± 247.9) و (97.7 ± 24.69) في عناصر تحكم نشطة وغير نشطة وعناصر تحكم على التوالي. وكان متوسط ± الإنحراف المعياري ل ICAM (0.91±3.1)، (0.79 ± 2.7) و (1.8 ± 0.22) في عناصر التحكم النشطة وغير النشطة والضوابط على التوالي. زادت القيم تدريجياً مع زيادة نشاط المرض. كانت المنطقة تحت المنحنى (AUC) لـ ICAM و VCAM (0.802) ، (0.776) في مرضى SLE النشطين و (0.858) ، (0.674) في مرضى SLE غير النشطين. ومع ذلك ، كانت AUC لـ VCAM و ICAM في المجموعة النشطة هي الأعلى.

الإستنتاج: في مرضى SLE، قد تعمل مستويات مصل VCAM-1 و ICAM-1 كمؤشرات للكشف عن المرض وتمايز الخطورة، وقد تكون مرتبطة بعدد الآفات التاجية لدى الأشخاص المعرضين لخطر الإصابة بأمراض القلب والأوعية الدموية.

مفتاح الكلمات: مرض الذئبة الاحمراري, تصلب الشرايين, جزيئات الالتصاق.