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## ORIGINAL ARTICLE

# Atherosclerosis biomarkers in female systemic lupus erythematosus patients with and without cardiovascular diseases

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## KEYWORDS

Cardiovascular disease;  
 Systemic lupus erythematosus;  
 Homocysteine;  
 Leptin

**Abstract** *Background:* Cardiovascular diseases (CVD) and atherosclerosis are over presented in patients with systemic lupus erythematosus (SLE).

*Aim of the work:* The aim of this study is to determine the frequency of some atherosclerosis biomarkers in SLE patients with and without CVD compared with controls.

*Patients and methods:* 28 female SLE patients with a mean age of  $30.1 \pm 7.2$  years and a history of CVD (SLE cases) were compared with 25 age matched SLE female patients but without a history of CVD (SLE controls) and 25 age matched population based control women (population controls). Intima, media thickness (IMT) was measured by B-mode ultrasound as a potential measure of atherosclerosis. Nontraditional biomarkers of atherosclerosis such as leptin, oxidized LDL (oxLDL) and homocysteine were also investigated.

*Results:* SLE cases had significantly increased IMT compared with SLE controls and population controls ( $p < 0.001$ ), whereas IMT of SLE controls did not differ from population controls. Compared to SLE controls, SLE cases had raised circulating levels of leptin ( $p < 0.001$ ), homocysteine, dyslipidemia with raised triglycerides ( $p < 0.001$ ), decreased HDL-cholesterol concentration, ( $p < 0.001$ ), lupus anticoagulants ( $p = 0.01$ ), and higher cumulative prednisone dose ( $p = 0.4$ ). Disease duration was comparable between the two SLE groups and the blood pressure and body mass index (BMI) were similar among the 3 groups.

*Conclusion:* A set of distinct CVD risk factors (biomarkers of atherosclerosis) separate SLE cases from SLE controls and normal population controls. If confirmed in a prospective study, they could be used to identify SLE patients at high risk of CVD in order to optimize treatment.

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## 1. Introduction

Patients with systemic lupus erythematosus (SLE) have a significantly increased risk of cardiovascular morbidity and mortality, particularly related to premature atherosclerosis (AS). Oxidized LDL (oxLDL) plays an important role in atherogenesis and may contribute to the immune activation and inflammation present in the atherosclerotic lesions, because it has chemotactic, immune-stimulatory, and toxic properties and is taken up by macrophages and other cells in the atherosclerotic plaque, which develop into foam cells [1–6].

Although traditional cardiac risk factors, such as older age, high blood pressure (BP), high cholesterol and triglycerides, smoking, obesity, diabetes mellitus, appear to play a critical role in the determinism of AS, these factors alone cannot adequately explain the increased incidence of cardiovascular disease commonly reported in patients with SLE [1,3]. In Egyptian SLE patients, metabolic syndrome was considered a remarkable risk factor for the development of subclinical atherosclerosis and increased carotid intima-media thickness (IMT) [7–9]. Accordingly, early accelerated AS in SLE is the result of complex cross talk between the usual traditional cardiac risk factors and non-traditional SLE biomarkers of inflammation [1,3,4].

The non-traditional AS biomarkers included both leptin and homocysteine, where leptin acts on the immune system as a proinflammatory cytokine. In animal models, its deficiency is associated with an increased susceptibility to infection and reducing the inflammation [10]. It promotes the proliferation and activation of T lymphocytes and induces production of Th1 cytokines [11–13]. Studies have reported increased leptin levels in SLE patients [14,15]. On the other hand studies stated that homocysteine levels are predictors for the development of coronary artery disease (CAD) and the occurrence of stroke in the general population. In addition, homocysteine levels have been identified as a predictor of atherosclerosis in patients with SLE, in whom high levels may be predictive levels of coronary calcification [16], platelet progression [17] and increased IMT [7,18].

The aim of this study was to determine the frequency of some of the atherosclerosis biomarkers in SLE patients with and without CVD to develop an early screening tool for the identification of high risk SLE patients.

## 2. Patients and methods

### 2.1. Study population

We have enrolled 53 SLE patients fulfilling the 1982 revised criteria of the American Rheumatism Association for the classification of SLE [19], with a mean age of  $30.5 \pm 9.6$  years and mean disease duration of  $3.6 \pm 4.3$  years, in addition to 25 age matched healthy populations with a mean age of  $30.4 \pm 7.1$  years. The studied group was classified into two further groups, group (I) which included 28 patients with a history of CVD (SLE cases) and group (II) which included 25 age matched SLE patients without history of CVD (SLE controls). All subjects were informed about the aim of the study and gave their consent. The study was approved by the local ethics

committee. The control subjects were unrelated to patients but were ethnically and socioeconomically similar. Physical examinations for them were normal, with blood pressure  $< 135/85$  mmHg, no urine abnormalities, and no history of autoimmune or rheumatic disease or any other diseases with a known genetic or hereditary predisposition.

All SLE patients were subjected to full history taking, general examination, cardio pulmonary, abdominal, neurological and locomotor systems examination. During routine laboratory investigations (complete blood count, liver and kidney functions by Jaffe kinetic method, and urine analysis), High sensitivity C-reactive protein (hsCRP) was measured using (latex-immunoturbidimetric method:  $< 1$  mg/L low risk,  $1-3$  mg/L medium risk, and  $> 3$  mg/L high risk). Immunological assays (ANA and anti-DNA) were done by indirect immunofluorescence and serum C3 and C4 levels by nephelometry (Beckman, USA). Twenty-four hour urine samples were collected to estimate total urinary protein levels by the colorimetric method. Blood and urine samples were always collected on the same day. Detection of the anticardiolipin (ACL) antibodies was done using the enzyme linked immunosorbent assay (ELISA), while detection of lupus anticoagulant was done using the dilute Russel viper venom time (dRVVT) clotting assay.

Systemic hypertension was recorded when systolic  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg, measured in multiple occasions or when antihypertensive medication was taken. Dyslipidemia was defined as any of the following or in combination: raised low density lipoprotein (LDL) cholesterol  $> 130$  mg/dl, total cholesterol  $> 200$  mg/dl, triglycerides  $> 150$  mg/dl, or low level of high density lipoprotein (HDL) cholesterol  $< 40$  mg/dl. Diabetes mellitus was defined either by fasting blood sugar  $> 120$  mg/dl or taking insulin or hypoglycemic drugs. The global disease activity was assessed by SLE disease activity index (SLEDAI) [20].

All patients were taking steroids (dose range 15–50 mg/day), 45 patients on hydroxychloroquine (dose range 200–400 mg/day), 25 patients on azathioprine (dose range 100–150 mg/day) and 18 patients were receiving monthly cyclophosphamide pulse therapy depending on extent of renal lesion (dose range 700–1000 mg).

### 2.2. Measurement of serum biomarkers

Clotted samples were stored at  $-20^\circ\text{C}$  until the time of analysis.

- Oxidized LDL was assayed using kit purchased from immunodiagnostic AG (catalog No. K7810). That was a sandwich ELISA for direct measurement of oxLDL in human serum. Standards, controls and samples containing human oxLDL were added to wells of microplate that were coated with high affinity antibodies. A dose response curve of absorbance unit (optical density at 450 nm) versus concentration was generated; using the values obtained from standard. oxLDL present in the patient samples was determined directly from this curve. Patients taking statins in the past 3 months were excluded.
- Leptin was analyzed by leptin kit, (DRG instruments GmbH, division of DRG International, Inc, Vers. 9.0, Ref: EIA-2395, Germany) through ELISA.

- Homocysteine was analyzed by homocysteine kit, (DRG instruments GmbH, division of DRG International, Inc, Vers. 5.1, Ref: EIA-2925, Germany) through ELIZA.

Carotid intima media thickness (cIMT) was measured using a B-mode ultrasound using automated Qlab software (Philips Medical System) as a measurement of the presence of atherosclerotic plaques. All ultrasound were performed by 4 registered vascular radiologists, who were trained to perform the studies according to a preset protocol [21]. The same radiologist interpreted all studies, and was blinded with regard to the patients' demographic characteristics, SLE status and any previous ultrasound results. cIMT was assessed at three levels on each side: common carotid artery (10 mm before the bulb), bulb (5–10 mm cranially to the start of the bulb) and internal carotid artery (10 mm after the flow divider); mean cIMT (m-cIMT) was defined as the mean of the three cIMT measurements on each side, while the maximum cIMT, the highest cIMT value found among the six segments studied [22]. According to current sonographic criteria, we refer to "normal" cIMT when complex intima-media is  $<0.9$  mm; the cIMT  $>0.9$  mm was considered indicative of thickened intima, while  $>1.3$  mm indicative of atherosclerotic plaque [4,22]. Any history of CVD was detected by either a history of myocardial infarction (MI) or a compensated CAD with angiogram or stress test, history of cerebrovascular events (CVE) included transient ischemic attacks (confirmed by a physician) or stroke (confirmed by imaging).

### 2.3. Statistical method

The data were coded and entered using the statistical package SPSS version 15. The data were summarized using descriptive statistics: mean, standard deviation, median, minimal and maximum values for quantitative variables and number and percentage for qualitative values. Statistical differences between groups were tested using Chi Square test for qualitative variables, Student's *T* test between 2 groups for quantitative normally distributed variables while Nonparametric Mann–Whitney test and Kruskal–Wallis test were used for quantitative variables which are not normally distributed. Correlations were done to test for linear relations between variables. *p*-Values less than 0.05 were considered statistically significant.

## 3. Results

### 3.1. Characteristics of the study groups

Fifty-three females with SLE; 28 with CVD (group 1) and 25 without (group 2) and 25 healthy female volunteers were included in this study. The main demographic and clinical features of the studied SLE patients are shown in Table 1.

### 3.2. Traditional risk factors

Disease duration, blood pressure, body mass index (BMI) and diabetes did not differ between the two groups. On the other hand there was a significant difference involving the hsCRP and the ESR between the two SLE groups ( $p < 0.001$  respectively), in addition a significant difference was found between

**Table 1** Demographic, laboratory data, clinical manifestations and intima media thickness in SLE patients.

Parameter	SLE patients mean $\pm$ SD or <i>n</i> (%)	
Demographic	Age (years)	30.5 $\pm$ 9.6
	Disease duration (years)	3.6 $\pm$ 4.3
	BMI	26.5 $\pm$ 4.5
	Steroid dose	24.4 $\pm$ 15.6
Laboratory data	ESR (mm/1st hour)	71.6 $\pm$ 39.2
	hsCRP (mg/L)	4.51 $\pm$ 8.13
	Hemoglobin (g/dl)	12.4 $\pm$ 1.9
	WBCs ( $10^3/\text{mm}^3$ )	7.2 $\pm$ 3.8
	Platelets ( $10^3/\text{mm}^3$ )	223 $\pm$ 78.8
	Serum creatinine (mg/dl)	1.8 $\pm$ 0.3
	Serum albumin (gm/dl)	3.3 $\pm$ 0.8
	Urine protein (gm/24 h)	1.2 $\pm$ 0.9
	Cholesterol (mg/dl)	202.5 $\pm$ 47
	Triglycerides (mg/dl)	170.6 $\pm$ 120.6
	HDL (mg/dl)	60.1 $\pm$ 28.0
	LDL (mg/dl)	140.9 $\pm$ 37.7
	Leptin (ng/ml)	32.3 $\pm$ 24.2
	Homocysteine (mmols/L)	16.85 $\pm$ 2.7
FBS (mg/dl)	94.2 $\pm$ 14.8	
Clinical manifestations	ACL antibodies	28 (52.8)
	Lupus anticoagulant	21 (39.6)
	$\beta$ 2GP IgG	8 (15.1)
	Seropositive ANA	53 (100)
	Anti-ds DNA	49 (92)
	Fever	20 (37)
	Malar rash	40 (75)
	Photosensitivity	45 (85)
	Alopecia	10 (18)
	Oral ulcers	30 (56)
	Vasculopathy	20 (37)
CIMT	Hypertension	29 (54)
	Arthritis	30 (56)
	Nephritis	33 (62)
	Serositis	39 (73)
	Secondary APS	27 (50.9)
	Raynauds phenomena	16 (30)
	SLEDAI	20.1 $\pm$ 6.4
	Right	5.8 $\pm$ 1.1
Left	5.7 $\pm$ 1.1	
Carotid plaque	2 (3.8)	

BMI: body mass index, ESR: erythrocyte sedimentation rate, hsCRP: high sensitivity C-reactive protein, WBCs: white blood cells, FBS: fasting blood sugar, ACL: anti cardiolipin,  $\beta$ 2GP IgG: beta-2 glycoprotein, ANA: anti-nuclear antibodies, Anti-ds DNA: anti-double stranded, APS: antiphospholipid syndrome, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. CIMT: carotid intima media thickness.

SLE cases who had increased levels of both lupus anticoagulants ( $p = 0.01$ ), ACL antibodies ( $p = 0.006$ ), higher cumulative prednisone dose ( $p = 0.4$ ) and SLEDAI score (0.001) compared with SLE controls (without CVD).

### 3.3. Biomarkers of atherosclerosis

Carotid ultrasound has showed a thickened intima in about 30% of SLE patients, while carotid plaques have been demonstrated in 3.8% of the SLE patients. SLE cases had increased

**Table 2** Comparison between the two SLE groups (with and without CVD) regarding demographic, laboratory and clinical characteristics as well as the carotid IMT.

Parameters mean $\pm$ SD or <i>n</i> (%)		SLE patients ( <i>n</i> = 53)		
		Group (1) ( <i>n</i> = 28)	Group (2) ( <i>n</i> = 25)	<i>p</i> value
Demo graphic	Disease duration (years)	4.4 $\pm$ 4.6	3.1 $\pm$ 3.9	0.2
	Age (years)	30.9 $\pm$ 11.9	30.3 $\pm$ 7.9	0.8
	BMI	27.9 $\pm$ 4.0	24.9 $\pm$ 4.6	0.015
	Steroid dose (mg/d)	24.4 $\pm$ 15.6	28.3 $\pm$ 13.1	0.3
Laboratory data	ESR (mm/h)	42.7 $\pm$ 24.5	35.3 $\pm$ 22.5	< 0.001
	hsCRP (mg/L)	12.8 $\pm$ 4.2	11.8 $\pm$ 3.4	< 0.001
	Hemoglobin (g/dL)	10.8 $\pm$ 2.3	10.1 $\pm$ 1.5	0.2
	WBCs ( $10^3/\text{mm}^3$ )	8.1 $\pm$ 4	6.5 $\pm$ 3.5	0.1
	Platelets ( $10^3/\text{mm}^3$ )	250.9 $\pm$ 71.7	204.4 $\pm$ 78.8	0.02
	Creatinine (mg/dL)	1.3 $\pm$ 0.5	1.2 $\pm$ 0.6	< 0.001
	Cholesterol	270 $\pm$ 20.4	200 $\pm$ 18.5	< 0.001
	TGs (mg/dL)	200.3 $\pm$ 20.5	170.3 $\pm$ 18.5	< 0.001
	HDL (mg/dL)	47.5 $\pm$ 15.4	74.2 $\pm$ 32.2	0.001
	LDL (mg/dL)	158.6 $\pm$ 29.5	121.1 $\pm$ 36.5	< 0.001
	Leptin (ng/mL)	70.3 $\pm$ 10.1	55.0 $\pm$ 7.8	< 0.001
	Homocysteine ( $\mu\text{M/L}$ )	20.3 $\pm$ 4.2	13.4 $\pm$ 1.2	< 0.001
	ANA	27 (96.4)	24 (96)	1.0
	Anti ds-DNA	16 (57.1)	12 (48)	1.0
	ACL	20 (71.4)	8 (32)	0.006
	Lupus anticoagulants	16 (57)	5 (20)	0.01
	$\beta$ 2GP 1	6 (21)	25 (8)	0.05
Low complement	18 (64)	10 (40%)	0.1	
Clinical manifestations	Hypertension	17 (60)	12 (48)	0.4
	Diabetes	4 (14)	2 (8)	0.7
	Psychosis	6 (21)	3 (12)	0.3
	Serositis	18 (64)	17 (68)	0.2
	Arthritis	10 (35)	9 (36)	0.6
	Myositis	6 (21)	4 (16)	0.2
	Vasculitis	2 (7)	3 (12)	0.4
	Nephritis	11 (39)	17 (68)	0.06
	APS	20 (71)	7 (28)	0.002
SLEDAI	21.7 $\pm$ 6.5	8.3 $\pm$ 6.2	0.001	
CIMT (mm)	8.3 $\pm$ 0.7	4.5 $\pm$ 0.6	< 0.001	

BMI: body mass index, ESR: erythrocyte sedimentation rate, hsCRP: high sensitivity C-reactive protein, WBCs: white blood cells, TG: triglycerides, HDL: high density lipoprotein, LDL: low density lipoprotein, ANA: anti-nuclear antibodies, Anti-ds DNA: anti-double stranded, ACL: anti cardiolipin,  $\beta$ 2GP IgG: beta-2 glycoprotein, APS: antiphospholipid syndrome, SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. CIMT: carotid intima media thickness.

IMT compared with SLE controls ( $p < 0.001$ ) and population controls ( $p < 0.001$ ), whereas IMT of SLE controls did not differ from population controls. SLE cases had raised circulating levels of leptin ( $p < 0.001$ ), homocysteine, dyslipidemia with raised triglycerides ( $p < 0.001$ ), decreased HDL-cholesterol concentration ( $p < 0.001$ ) compared with SLE controls, in addition to a higher oxLDL level in SLE patients than control population ( $p < 0.001$ ) (Table 2).

#### 4. Discussion

In this study, we investigated the biomarkers of atherosclerosis in 53 SLE patients with and without CVD. The common carotid IMT of SLE cases was greater than those of SLE controls and population controls, a finding that validates our selection of patients and also indicates that subclinical atherosclerosis plays an important role in arterial disease in SLE. The IMT

of SLE controls was not different from population controls. The SLE cases tended to have more plaques than SLE controls, and both SLE cases and SLE controls had significantly more plaques than population controls. In addition, in the SLE cases SLEDAI score had a significant difference to SLE controls which is in conjunction with other studies that stated that high damage score has been considered as an independent predictor of carotid plaque [23,24].

Oxidized LDL has pro-inflammatory and atherogenic properties [25]. It is possible that oxidized LDL may contribute to arterial disease in SLE patients. In the present study, plasma oxidized LDL was significantly enhanced in SLE cases than in SLE controls and healthy controls whereas the latter two groups were comparable. Our data were in line with several studies which showed that Oxidized LDL predicts an increased risk for MI, and its level is increased in young survivors of MI [26–28].

The antiphospholipid antibody syndrome is characterized by both arterial and venous thrombosis and is common in SLE [29]. In this study, ACL,  $\beta_2$  glycoprotein antibodies and lupus anticoagulants showed significant association with CVD in SLE. It is possible therefore that the increased risk of CVD in SLE is to some extent caused by thrombosis.

Homocysteine is increasingly recognized as a risk factor in SLE. Homocysteine is thought to exert atherogenic effect through oxidative damage and, induced oxidative stress causing endothelial dysfunction and lipid peroxidation [16–18]. In our study homocysteine levels were higher in SLE patients with CVD, while other studies have demonstrated no relation between homocysteine and CVD in SLE patients [30,31].

Leptin is a proinflammatory cytokine that appears to contribute to systemic inflammation in autoimmune rheumatic diseases, including SLE [14,15]. McMahon et al. [3] had stated that leptin levels were independently associated with carotid plaque and positively correlated with oxidized phospholipids in SLE patients. In the present study, leptin levels were significantly higher in SLE cases when compared with the SLE control group, a finding that was also observed in other studies [15,32,33].

Steroid treatments are often believed to be atherogenic due to its effect on plasma lipoproteins and because inflammation is implicated in atherogenesis. Our study showed that in spite of the high cumulative prednisone dose, the SLE control group did not have an increased common carotid intima media thickness while SLE cases had an increased IMT.

In our current study hsCRP was significantly elevated in SLE cases which coincides with other studies that showed hsCRP as an independent predictor of thickened intima in SLE patients [34,35].

Our study identifies a variety of risk factors for CVD in SLE patients, not only traditional factors such as dyslipidemia and diabetes but also a range of factors of acute and chronic inflammation, including indices of enhanced LDL-oxidation, leptin plasma levels and homocysteine. Larger prospective studies are suggested to clarify and evaluate, whether these factors can predict future CVD. If so, they can be used to identify a high risk group that would be eligible for intense intervention, with anti-oxidants and anti-inflammatory agents.

#### Conflict of interest

None.

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