Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.92300
Ulus Romatol Derg 2025;17(2):77-84

Flow mediated dilation in association with hyperuricemia as predictors of subclinical atherosclerosis in patients with systemic lupus erythematosus

Sistemik lupus eritematozuslu hastalarda subklinik aterosklerozun tahmin edicileri olarak hiperürisemi ile birlikte akımla aracılık edilen dilatasyon

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Abstract

Objective: Reduced flow mediated dilation (FMD) in systemic lupus erythematosus (SLE) patients indicates impaired endothelial function while elevated uric acid contributes to increased oxidative stress. These factors can synergistically promote the development of atherosclerosis. This study aimed to estimate subclinical atherosclerosis through measuring carotid intima media thickness (CIMT) and brachial artery FMD in SLE patients, correlating these measurements with uric acid levels.

Methods: This study included 60 SLE patients who were divided into two groups based on their FMD results. All patients underwent a comprehensive medical evaluation. CIMT was measured using carotid Doppler ultrasound, and brachial artery FMD was assessed with ultrasound. Serum uric acid levels were also measured. We investigated various factors that may influence FMD in patients with SLE by comparing the characteristics of the two groups.

Results: Patients with abnormal FMD exhibited higher disease activity based on modified SLE disease activity index 2000 (p=0.002) and significantly elevated uric acid levels compared to those with normal FMD (p=0.012). Mean CIMT was significantly higher in patients with abnormal FMD (0.64±0.17 mm) compared to those with normal FMD (0.51±0.11 mm). Regression analysis revealed that increased CIMT, representive of subclinical atherosclerosis, was primarily associated with higher disease activity index, abnormal FMD, and hyperuricemia.

Conclusion: Our findings highlight that FMD and uric acid can serve as potential markers of subclinical atherosclerosis in SLE patients. The association with increased CIMT emphasizes the importance of addressing these factors to reduce cardiovascular risk.

Keywords: Systemic lupus erythematosus, subclinical atherosclerosis, endothelial dysfunction, flow-mediated dilation, carotid intima-media thickness, hyperuricemia

Özet

Amaç: Bu çalışma, sistemik lupus eritematozus (SLE) hastalarında karotis intima media kalınlığı (CİMK) ve brakiyal arter akımla aracılık edilen dilatasyonu (FMD) kullanarak subklinik aterosklerozu değerlendirmeyi ve bu ölçümleri ürik asit düzeyleri ile ilişkilendirmeyi amaçlamıştır.

Yöntem: Bu çalışma, FMD sonuçlarına göre iki gruba ayrılan 60 SLE hastasını dahil etmiştir. Tüm hastalar kapsamlı bir tıbbi değerlendirmeden geçirilmiştir. CİMK, karotis Doppler ultrasonografi ile ölçülmüş ve brakiyal arter FMD'si ultrasonografi ile değerlendirilmiştir. Serum ürik asit düzeyleri de ölçülmüştür. İki grubun özelliklerini karşılaştırarak SLE'li hastalarda FMD'yi etkileyebilecek çeşitli faktörler araştırılmıştır.

Bulgular: Anormal FMD'li hastalar, modifiye edilmiş SLE hastalığı aktivite indeksi 2000'e göre daha yüksek hastalık aktivitesi (p=0,002) ve normal FMD'ye sahip olanlara göre anlamlı derecede yüksek ürik asit düzeyleri göstermiştir (p=0,012). Ortalama CİMK, normal FMD'ye sahip olanlara göre anormal FMD'li hastalarda anlamlı derecede daha yüksektir (0,51±0,11 mm vs. 0,64±0,17 mm, p=0.001). Regresyon analizi, subklinik aterosklerozu temsil eden artmış CİMK'nin öncelikle daha yüksek hastalık aktivite indeksi, anormal FMD ve hiperürisemi ile ilişkili olduğunu ortaya koymuştur.

Sonuç: Bulgularımız, SLE hastalarında subklinik ateroskleroz belirteçleri olarak FMD ve ürik asidin potansiyelini vurgulamaktadır. Artmış CİMK ile olan ilişki, kardiyovasküler riski azaltmak için bu faktörlerin ele alınmasının önemini vurgulamaktadır.

Anahtar Kelimeler: Sistemik lupus eritematozus, subklinik ateroskleroz, endotel disfonksiyonu, akımla aracılık edilen dilatasyon, karotis intima-media kalınlığı, hiperürisemi

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Received / Geliş Tarihi: 20.01.2025 **Accepted / Kabul Tarihi:** 20.05.2025 **Publication Date / Yayın Tarihi:** 31.07.2025

Cite this article as / Atıf: Ibrahem EM, Alaal RFA, Hassan LA, Hassanein S. Flow mediated dilation in association with hyperuricemia as predictors of subclinical atherosclerosis in patients with systemic lupus erythematosus. J Turk Soc Rheumatol. 2025;17(2):77-84

Introduction

Systemic lupus erythematosus (SLE) is closely tied to accelerated atherosclerosis and increased cardiovascular risk. Traditional risk factors alone cannot fully explain this association, suggesting a complex interplay of factors.[1] Subclinical atherosclerosis is a significant predictor of cardiovascular risk and an early finding in patients with SLE.[2] Atherosclerosis is now known to have immunologic aspects. Inflammation plays a pivotal role in atherosclerosis development.[3]

SLE impacts repair mechanisms and the integrity of endothelial cells via deposition of circulating immune complexes and binding of antibodies directly to endothelial cells.[4] Endothelial dysfunction (ED) is thought to be the first step in the pathogenesis of atherosclerosis.[5]

A number of non-invasive imaging surrogate measures have been employed to assess functional and morphological alterations in the arterial wall and ED. Carotid intima media thickness (CIMT) is a dependable and non-invasive indicator of subclinical atherosclerosis that effectively predicts future cardiovascular events.[6] Additionally, brachial artery reactivity testing is a non-invasive technique employed to assess endothelial function through the responsiveness to reactive hyperemia or flow mediated dilation (FMD). FMD quantifies the vasodilatory capacity of the brachial artery in response to an increase in blood flow, primarily mediated by nitric oxide release. A diminished FMD response signifies impaired endothelium-dependent vasodilation, indicative of ED.[7]

Uric acid (UA) is an established independent risk factor for cardiovascular disease (CVD).[8] The elevated prevalence of hyperuricemia in SLE patients is likely multifactorial, stemming from various endogenous and exogenous factors, including inflammation, hypertension, and renal involvement, which are common manifestations of the disease.[9]

This study aims to highlight the role of FMD as a non-invasive marker of ED in SLE patients and to investigate factors affecting it. Additionally, we will explore the association between serum UA levels and the risk of CVD in this population. By elucidating these relationships, we seek to identify potential targets for early intervention and improved CVD management in SLE patients.

Materials and Methods

Study Setting and Design

This is a cross sectional study carried out at the Rheumatology & Clinical Immunology Unit in the Department of Internal Medicine at Assiut University Hospitals. Sixty SLE patients from Outpatient Clinics or admitted to the Rheumatology & Clinical Immunology Unit were enrolled. It was carried out between June 2022 and June 2023. Registered in clinicalTrials.gov (NCT05342285).

Selection Criteria

Patients aged ≥18 years meeting the 2019 the American College of Rheumatology/the European League Against Rheumatism classification criteria for SLE.[10] Exclusion criteria included: History of cardiac disease [primarily ischemic heart disease or coronary heart disease defined as a documented previous myocardial infarction or coronary artery revascularization (including percutaneous coronary interventions or coronary artery bypass grafting, additionally, patients with history of typical angina or already on anti-ischemic drugs were excluded], end-stage renal disease, and/or other autoimmune diseases.

Ethics Approval and Consent to Participate

The study received ethical clearance from the Faculty of Medicine's Institutional Review Board, Assiut University (approval number: 17101668, date: 07.03.2022). The study adhered to the ethical principles outlined in the Declaration of Helsinki. Prior to enrollment, all subjects provided written informed consent.

Data Collection

- Comprehensive medical history including demographics, course of the disease, comorbidities, and medications.
- Clinical evaluation and disease activity assessment using modified version of the SLE disease activity index (SLEDAI-2K).[11] Activity levels were categorized as follows: no activity (SLEDAI-2K=0), mild (SLEDAI-2K=1-5), moderate (SLEDAI-2K=6-10), high (SLEDAI-2K=11-19), and very high (≥20).

Laboratory Tests

Complete Blood Count with Reticulocytes: Performed using a Sysmex XN 1000 System (Siemens, Germany).

Liver Function Tests: Including alanine transaminase, Aspartate transaminase, total protein, and serum albumin which were measured using an Advia 1800 System (Siemens, Germany).

Kidney Function Tests: Included blood urea, serum creatinine, albumin-to-creatinine ratio, 24-hour urinary proteins, and glomerular filtration rate performed using an Advia 1800 System (Siemens, Germany).

C-reactive protein (CRP): Measured using an Advia 1800 System (Siemens, Germany).

Erythrocyte Sedimentation Rate: Assessed via the Westergren method.

Complement Levels (C3 and C4): Assessed using an indirect immunofluorescence method with a Kallestad kit.

Random Blood Sugar and Glycosylated Hemoglobin: Measured using a Sysmex CA 1500 System (Siemens, Germany).

Serum Uric Acid: Measured using a Pars Azmoon kit.

Urine Analysis: Included evaluation of active urinary sediments.

Lipid Profile: Cholesterol level, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides were measured in mg/dL using an enzymatic colorimetric assay by STANBIO (USA).

Antiphospholipid antibodies: Lupus anticoagulants (LA), detected by *in vitro* clotting tests, anticardiolipin antibodies immunoglobulin G (IgG), IgM and β_2-glycoprotein I IgG, IgM detected by solid-phase enzyme-linked immunosorbent assays.

Cardiovascular Assessments

Electrocardiogram (ECG): A baseline 12-lead ECG was performed on all participants (150 Hz low pass filter, 25 mm/s paper speed, 10 mm/mv voltage).

Echocardiography: Two-dimensional echocardiography was carried out with a 2.5 MHz transducer using an ACUSON scanner (Siemens, Germany). Left ventricular volumes and ejection fraction were calculated.

Carotid Duplex Examination: CIMT was estimated via high-resolution B-mode ultrasonography utilizing a 10 MHz transducer. Measurements were obtained from both the near and far walls of the right and left common carotid arteries, the carotid bifurcations, and the proximal internal carotid arteries. CIMT corresponds to the distance between the lumen-intima interface and the media-adventitia interface. A mean CIMT value of less than 0.80 mm was considered within the normal range.[12]

Brachial Artery Diameter and FMD: FMD measures the increase in brachial artery diameter after a brief period of blood flow restriction. This dilation reflects the artery's ability to respond to increased blood flow. Reduced dilation indicates vascular dysfunction.

FMD was assessed using a 10 MHz linear array ultrasound transducer (UNEXEF18G, Unex Co., Ltd., Nagoya, Japan). The right brachial artery was examined after an 8-hour fast and 12 hours of refraining from caffeine or exercise. Patients rested for 10-15 minutes before the procedure. Baseline measurements of artery diameter and blood flow velocity were obtained. Subsequently, an occlusion cuff was inflated around the upper arm for approximately 5 minutes, temporarily halting blood flow to the forearm. This period of ischemia induces vasodilation in the vessels below the cuff, leading to a decrease in vascular resistance. Upon cuff deflation, the reduced resistance facilitates a significant increase in blood flow to the forearm. FMD is the difference between the baseline arterial diameter and the maximum diameter achieved following cuff release. FMD was calculated as the percentage increase in arterial diameter following reactive hyperemia using the equation FMD = (peak flow diameter/baseline diameter) × 100. A normal FMD value ranges from 8-15%.[13]

Statistical Analysis

All data were analyzed using SPSS version 26 (IBM SPSS Inc, Chicago, IL, USA). Categorical variables were presented using frequencies and percentages. The normality of numerical variables were assessed using the Shapiro-Wilk test. Data were presented as mean and standard deviation or as median and range based on data distribution. The independent Sample t-test or Mann-Whitney U test was employed to compare mean or median difference between normal and abnormal FMD. The chi-square/Fisher's exact tests were used to compare proportions between normal and abnormal FMD. Pearson/Spearman correlations were used to identify correlation between percentage of FMD, carotid intimal media thickness, UA and other variables. Predictors of abnormal CIMT were determined by logistic regression analysis. Statistical significance was defined as a p-value <0.05.

Results

The study included 60 participants with SLE, divided into two groups based on FMD:

- Normal FMD Group: Thirty women with SLE and normal FMD (8-15%). The mean percentage of FMD in this group was 11.20±2.20 with a range between 9-16.
- Abnormal FMD Group: Thirty women with SLE and reduced FMD (<8%). The mean percentage of FMD in this group was 5.20±1.37 with a range between 4-7.

Demographic and Clinical Characteristics of the Participants in Each Group (Table 1)

No statistically significant differences were observed between the study groups, in mean age, body mass index, or comorbidities. Both groups of patients had similar frequencies of diabetes mellitus and other recorded

comorbidities. However, patients with abnormal FMD had higher SLEDAI-2K scores indicating greater disease activity [median (range) 9.0 (0.0-32.0) in patients with normal FMD vs. 17.50 (0.0-46.0) in patients with abnormal FMD p<0.001].

All patients received hydroxychloroquine (HCQ) at a dose of 400 mg daily. Prednisolone was administered orally to 53 patients (88.3%). Among these, 26 (86.7%) had normal FMD, and 27 (90.0%) had abnormal FMD. There was no significant difference in the mean dose of corticosteroids between the two groups. Other demographic and clinical data are detailed in Table 1.

Laboratory Data Among the Studied Groups (Table 2)

Among our patient population, no cases met the clinical criteria for antiphospholipid syndrome. However, based on the presence of antiphospholipid antibodies using common clinical thresholds (LA 44 sec, anti-cardiolipin IgG >12, anticardiolipin IgM >12 MPL U/mL, β_2-glycoprotein I IgM >20, β_2-glycoprotein I IgG >20 U/mL), the estimated rate of seropositive patients having at least one positive antibody is 3.6%. There was no significant difference in the mean levels of antiphospholipid antibodies between the two groups. Detailed data are presented in Table 2.

Table 1. Baseline demographic and clinical characteristics of the study population

	Total (n=60)	Normal FMD (n=30)	Abnormal FMD (n=30)	p-value
Age (years)	28.20±8.47 (18-55)	26.57±8.29 (18-55)	29.83±8.46 (18-44)	0.137
Disease duration (years)	6.37±3.15 (1-15)	6.13 (2.89)	6.60 (3.43)	0.571
Body mass index (kg/m²)	25.52±3.53 (19-32)	25.63±3.52 (20-31)	25.40±3.60 (19-32)	0.801
Blood pressure (mm/hg)				
Systolic	135.67±28.76 (90-190)	133.67±27.94 (10-190)	137.67±29.90 (90-180)	0.595
Diastolic	78.58±14.05 (50-100)	77.17±14.89 (50-100)	80.00±13.26 (60-100)	0.440
Mean BP	96.40±17.25 (66.0-126.0)	93.22±15.04 (66-116)	99.57±18.92 (70-126)	0.156
Manifestations				
Articular manifestations	31 (51.7%)	18 (60.0%)	13 (43.3%)	0.196
Mucocutaneous manifestations	25 (41.7%)	12 (40.0%)	13 (43.3%)	0.793
Serositis	11 (18.3%)	4 (13.3%)	7 (23.3%)	0.506
Pulmonary manifestations	9 (15.0%)	6 (20.0%)	3 (10.0%)	0.472
Hematological affection	11 (18.3%)	6 (20.0%)	5 (16.7%)	0.739
Lupus nephritis	21 (35.0%)	8 (26.7%)	13 (43.3%)	0.176
Neuropsychiatric manifestations	8 (13.3%)	3 (10.0%)	5 (16.7%)	0.706
Presence of comorbidities				
Diabetes mellitus	13 (21.7%)	6 (20.0%)	7 (23.3%)	0.754
Hypertension	10 (16.7%)	6 (20.0%)	4 (13.3%)	0.488
Chronic kidney disease	6 (10.0%)	3 (10.0%)	3 (10.0%)	1.000
SLEDAI_ 2K categories				
Remission	8 (13.3%)	6 (20.0%)	2 (6.7%)	
Mild disease activity	7 (11.7%)	6 (20.0%)	1 (3.3%)	
Moderate disease activity	14 (23.3%)	9 (30.0%)	5 (16.7%)	**0.013**
High disease activity	14 (23.3%)	3 (10.0%)	11 (36.7%)	
Very high disease activity	17 (28.3%)	6 (20.0%)	11 (36.7%)	
SLEDAI-2K value (median (range)	11.50 (0.0-46.0)	9.0 (0.0-32.0)	17.50 (0.0-46.0)	**0.002**
Drugs:				
Corticosteroid (n%)	53 (88.3%)	26 (86.7%)	27 (90.0%)	
Dose (mg)	22.54±13.49 (5-60)	21.05±12.65 (5-60)	23.98±14.34 (5-60)	0.436
Corticosteroid duration (in years)	6 (1-10)	5.73 (2.57)	5.92 (2.61)	0.785
Azathioprine	8 (13.3%)	3 (10.0%)	5 (16.7%)	
Cyclophosphamide	7 (11.7%)	4 (13.3%)	3 (10.0%)	
Mycophenolate mofetil	9 (15.0%)	5 (16.7%)	4 (13.3%)	
Cyclosporine	4 (6.7%)	3 (10.0%)	1 (3.3%)	

FMD: Flow mediated dilation, SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000. Data were expressed as frequency and %, mean ± standard deviation or median and range as appropriate.

Chi-square/Fisher's exact test compares proportion between normal and abnormal FMD.

Independent Sample U test/Mann-Whitney U test compares mean/median difference between normal and abnormal FMD

The serum UA levels were significantly different between patients with normal FMD (4.0±1.7 mg/dL, range 1.7-9.0) and those with abnormal FMD (5.25±1.7 mg/dL, range 1.7-10.0) (p=0.012). A detailed comparison of laboratory investigations between the two groups is presented in Table 2.

Echocardiographic Findings and Intima Media Thickness in the Studied Groups

No significant differences were observed between the two groups regarding echocardiography and ECG findings. Mean pulmonary artery systolic pressure was 32.77±10.47 mmHg in patients with normal FMD and 33.73±8.68 mmHg in patients with abnormal FMD (p=0.699). Ejection fraction was 61.03±3.77% in patients with normal FMD and 61.00±4.23% in patients with abnormal FMD (p=0.974). Meanwhile, patients with abnormal FMD exhibited significantly higher CIMT (0.64±0.17 mm) compared to those with normal FMD (0.51±0.11 mm) (p=0.001).

Correlation of FMD, CIMT and Uric Acid with Other Variables (Table 3)

A significant negative correlation was observed between FMD and the SLEDAI-2K score (r=-0.402, p=0.001), indicating that higher disease activity was associated with lower FMD values. A strong negative correlation was found between FMD and CIMT (r=-0.709, p<0.001), suggesting an inverse relationship between endothelial function and arterial stiffness. A significant negative correlation was observed between FMD and serum UA levels (r=-0.343, p=0.007).

Serum UA levels showed a positive correlation with the presence of hypertension (r=0.260, p=0.045) and chronic

Table 2. Difference between patients with normal and abnormal FMD regarding laboratory investigations

	Normal FMD (n=30)	Abnormal FMD (n=30)	p-value
Complete blood count			
White blood cells (10^3/uL)	6.377±2.16 (2.8-12.0)	6.733±2.07 (2.4-11.4)	0.518
Hemoglobin (g/dL)	10.07±1.75 (5.80-13.00)	10.44±1.64 (6.40- 14.00)	0.397
Platelets (10^3/uL)	279.50±87.26 (90-453)	253.07±76.39 (30-437)	0.217
Random blood glucose (mmol/L):	4.43±0.93 (2.9-7.3)	4.80±1.14 (2.6-7.3)	0.171
Inflammatory markers			
Erythrocyte sedimentation rate 1st hr (mm/hr)	70.00 (12-112)	87.50 (10-112)	0.107
C-reactive protein (mg/dL)	4.35 (0.4-41.0)	6.00 (0.8-52.0)	0.058
Kidney function tests			
Urea (mmol/L)	4.65 (2.70-54.00)	4.05 (2.40-6.50)	0.091
Creatinine (umol/L)	70.0 (42-435)	72.50 (38-421)	0.762
Albumin/creatinine ratio (mg/g)	300 (25-1890)	140 (50-2300)	0.900
Uric acid (mg/dL)	4.0 (1.7-9.0)	5.25 (1.7-10.0)	**0.012**
Liver function tests			
Total protein (g/L)	71.77±6.40 (58.0-84.0)	74.46±5.54 (59.0-82.1)	0.087
Albumin (g/L)	38.40±4.54 (26.0-44.3)	40.20±3.38 (32.0-45.1)	0.088
Alanine transaminase (u/L)	22.71±9.42 (6.0-41.0)	19.29±7.49 (7.5-36.0)	0.125
Aspartate transaminase (u/L)	24.17±10.07 (7.8-54.0)	21.42±8.66 (8.6-36.4)	0.262
Lipid profile			
Cholesterol (mg/dL)	196.23±50.85 (100-287)	187.50±41.27 (109-270)	0.468
Low density lipoproteins (mg/dL)	115.67±36.76 (49-220)	113.63±29.79 (56-175)	0.815
High density lipoproteins (mg/dL)	41.53±8.01 (26-53)	41.53±12.61 (27-94)	0.999
Triglycerides (mg/dL)	180.00 (58-530)	131.50 (57-373)	0.071
Antiphospholipid antibodies			
Lupus anticoagulant (sec.)	30.17±9.89 (17-60)	30.23±9.68 (17-58)	0.979
Anticardiolipin IgG (MPL U/mL)	8 (IQR:3) (3-40)	7 (IQR:5) (2-44)	0.330
Anticardiolipin IgM (MPL U/mL)	6.87±2.46 (3-11)	7.23±2.74 (2-11)	0.587
β_2-glycoprotein I IgG (U/mL)	11.97±3.70 (6-19)	12.10±4.05 (6-19)	0.894
β_2-glycoprotein I IgM (U/mL)	11.73±3.59 (5-19)	11.63±3.44 (5-18)	0.913

Data were expressed as mean ± standard deviation or median (IQR) and range as appropriate.
Independent Sample U test/Mann-Whitney U test compares mean/median difference between normal and abnormal FMD.
FMD: Flow mediated dilation, Ig: Immunoglobulin, IQR: Interquartile range

kidney disease (r=0.368, p=0.004). A strong positive correlation was also observed between serum UA and lupus nephritis (r=0.430, p=0.001). Correlations between FMD, CIMT, and serum UA with other variables are detailed in Table 3.

Regression Analysis for Predictors of Abnormal CIMT in Patients with SLE (Table 4)

Significant variables associated with occurrence of abnormal CIMT in bivariate analysis were entered in multivariate logistic regression model adjusted with age and the significant predictors associated with occurrence of increased CIMT, a marker of subclinical atherosclerosis, in multivariate logistic regression were: abnormal FMD [odds ratio (OR)= 3.98, confidence interval (CI)=2.23-8.02, p-value <0.001], increase in serum UA level (OR=1.76, CI=1.11-3.01, p-value=0.01), and increase SLEDAI-2K score (OR=1.56, CI=1.33-2.98, p-value=0.01).

Discussion

FMD represents a non-invasive technique to assess endothelial function. Reduced FMD often indicates ED, which can lead to vascular inflammation and atherosclerotic plaque formation. ED, an early indicator of atherosclerosis, is linked to a heightened risk of future cardiovascular events, even in individuals with normal coronary angiograms. Unlike established atherosclerosis, ED is often reversible.[14] While imaging techniques can identify signs of atherosclerosis, such as thickened carotid intima, these changes often manifest late in the disease process.

Table 3. Correlations between percentage of FMD, CIMT, uric acid and other variables

	FMD (percentage %)		CIMT (mm)		Uric acid (mg/dL)	
	r	p-value	r	p-value	r	p-value
FMD (percentage %)			**-0.709**	**<0.001**	**-0.343**	**0.007**
CIMT (mm)	**-0.709**	**<0.001**			**0.431**	**0.022**
Uric acid (mg/dL)	**-0.343**	**0.007**	-0.070	0.593		
Age (years)	-0.091	0.490	-0.077	0.558	0.046	0.728
Body mass index	0.061	0.642	-0.138	0.291	0.050	0.706
Disease duration (years)	0.044	0.739	-0.085	0.520	0.131	0.318
Investigations						
Erythrocyte sedimentation rate 1st hr. (mm/hr)	-0.236	0.069	0.103	0.434	0.417	0.054
C-reactive protein	-0.327	0.056	0.089	0.498	0.161	0.220
Low density lipoproteins (mg/dL)	0.014	0.914	0.056	0.670	-0.108	0.410
High density lipoproteins (mg/dL)	0.105	0.426	-0.182	0.164	-0.100	0.445
Triglycerides (mg/dL)	0.230	0.077	-0.046	0.729	**-0.312**	**0.015**
Cholesterol (mg/dL)	0.154	0.241	-0.154	0.241	-0.098	0.456
SLEDAI-2K score	**-0.402**	**0.001**	0.236	0.069	0.069	0.602
Comorbidities						
Diabetes mellitus	-0.061	0.643	0.013	0.922	0.245	0.059
Hypertension	0.080	0.541	-0.021	0.875	**0.260**	**0.045**
Chronic kidney disease	-0.063	0.633	0.184	0.160	**0.368**	**0.004**
Lupus nephritis	-0.188	0.151	0.037	0.782	**0.430**	**0.001**
Corticosteroid dose	-0.179	0.198	0.169	0.226	0.333	0.151

CIMT: Carotid intimal media thickness, FMD: Flow mediated dilation, SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000.
r (correlation coefficient), Pearson/Spearman correlation as appropriate

Table 4. Multivariate logistic regression analysis for factors associated with occurrence of increased carotid intimal media thickness

	AOR	95% confidence interval	p-value
Age	0.71	0.32-1.65	0.22
Body mass index	1.14	0.50-2.22	0.09
Steroid therapy	0.89	0.11-1.09	0.55
SLEDAI-2K	1.56	1.33-2.98	**0.01**
Abnormal FMD	3.98	2.23-8.02	**<0.001**
Hyperuricemia	1.76	1.11-3.01	**0.01**

Logistic regression analysis
AOR: Adjusted odds ratio, FMD: Flow mediated dilation, SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000

SLE patients frequently exhibit elevated UA levels through different mechanisms. Elevated levels of serum UA have been linked to increased oxidative stress and inflammation. These factors can contribute to ED and accelerate atherosclerosis progression.[15]

Here, in the current study we aimed to assess applicability of brachial FMD and serum UA as non-invasive tools for early prediction of subclinical atherosclerosis, detected by measuring CIMT, in female patients with SLE.

Our findings demonstrate that patients with abnormal FMD had significantly higher disease activity as assessed by SLEDAI-2K, emphasizing the clinical value of FMD as a non-invasive biomarker. This observation aligns with the study by Diószegi et al.,[16] which reported reduced FMD in SLE patients with higher disease activity. Higher SLEDAI-2K scores exhibit a greater risk of organ damage and adverse outcomes in SLE patients. Thus, effective management of SLE disease activity can help minimize the risk of cardiovascular complications.

We could not find a strong link between CRP levels and ED, despite previous studies reporting such a correlation in other autoimmune diseases, such as rheumatoid arthritis. This may be partly explained by the limited reliability of CRP as a marker of disease activity in SLE. Unlike in other inflammatory conditions, many patients with active SLE do not exhibit a significant elevation in CRP levels.

Significantly higher serum UA levels were observed in SLE patients with HTN, CKD, and lupus nephritis. These conditions can contribute to elevated UA levels, which in turn may exacerbate systemic inflammation, worsen hypertension, and impair renal function creating a vicious cycle. Another key finding in our study was the strong association between both abnormal FMD and elevated serum UA with subclinical atherosclerosis in female SLE patients. Our findings revealed that patients with abnormal FMD had significantly higher UA compared to those with normal FMD. These results align with those of previous research.[17,18]

One of the primary findings of this study was that mean CIMT was significantly elevated in patients with abnormal FMD compared to those with normal FMD. Consistent with these findings, previous research has reported elevated CIMT in patients with SLE compared to controls.[14,19] Additionally, a previous study observed decreased FMD in SLE patients with arterial stiffness as measured by IMT.[20]

Our analysis identified SLEDAI-2K, abnormal FMD, and hyperuricemia as predictors of increased CIMT, an early marker of CVD in SLE patients.

Medications used in the management of SLE can also impact the cardiovascular system. Corticosteroids, while effective in controlling lupus activity, are associated with various metabolic side effects. Prednisone has been linked to changes in blood pressure, glucose intolerance, increased body mass index, elevated total cholesterol and levels of LDL-C accompanied by reduced HDL-C levels collectively contribute to a heightened risk of CVD.[21] However, this association was not observed in our study, as the proportion of patients using corticosteroids was similar between the two groups, with no significant difference in the mean corticosteroid dosage. Nonetheless, long-term corticosteroid therapy necessitates regular monitoring and careful dose management.

Studies have demonstrated that HCQ contributes to reductions in blood glucose levels, serum cholesterol, carotid plaque formation, and overall vascular damage in patients with lupus. By minimizing disease flare-ups and helping to maintain remission, this antimalarial agent exerts both immunomodulatory and atheroprotective effects.[22] HCQ is now considered a cornerstone of long-term SLE management and is recommended for all patients, except in cases of contraindications or significant side effects.[23] In line with these guidelines, all patients in our study were prescribed HCQ.

Non-pharmacological interventions, including a healthy diet, regular physical activity, and smoking cessation, play a significant role in cardiovascular protection for patients with SLE. Consequently, optimal disease management alongside lifestyle modifications is essential for lowering cardiovascular risk in this population.

Study Limitations

Key limitations of this study include the relatively small sample size and its single-center design. Furthermore, the lack of long-term follow-up data for all participants. Yet, the study was considered the first study that enrolled the role of FMD and UA in early atherosclerosis in patients with SLE.

Conclusion

Based on the evidence presented, it is evident that SLE patients are at an elevated risk of CVD. The increased CIMT and decreased FMD observed in our study are strong indicators of early atherosclerotic changes. Additionally, the positive association between disease activity, UA levels, and subclinical atherosclerosis further emphasizes the need for vigilant monitoring and management of CVD in SLE patients. FMD and serum UA could potentially serve as valuable tools for early identification of patients at risk for subclinical atherosclerosis and guide targeted interventions. Incorporating FMD and UA into risk stratification models could help clinicians identify patients who require more aggressive management strategies. Early identification of ED

in SLE patients offers a valuable window for implementing primary preventive strategies to delay CVD progression.

Therefore, future research should focus on validating these findings in larger, longitudinal studies and evaluating the effectiveness of interventions targeting FMD and UA.

Ethics

Ethics Committee Approval: The study received ethical clearance from the Faculty of Medicine's Institutional Review Board, Assiut University (approval number: 17101668, date: 07.03.2022). The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Informed Consent: Prior to enrollment, all subjects provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.M.I., R.F.A.A., L.A.H., S.H., Concept: R.F.A.A., Design: E.M.I., R.F.A.A., Data Collection and Processing: L.A.H., S.H., Analysis or Interpretation: L.A.H., Literature Search: S.H., Writing: E.M.I.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

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