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Original Article

Study of endothelial dysfunction and its correlation with disease activity in systemic lupus erythematosus patients without conventional cardiovascular risk factors

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ABSTRACT

Background: Endothelial dysfunction is an important cause of cardiovascular morbidity and mortality in patients of systemic lupus erythematosus (SLE), causing atherosclerosis and its related complications, even in the absence of conventional cardiovascular risk factors.

Objective: The present study was aimed at finding the prevalence of endothelial dysfunction in SLE and its relation with disease activity.

Methods: Fifty SLE patients without traditional cardiovascular risk factors, and equal number of age and sex matched controls were chosen. Endothelial function was assessed by flow mediated vasodilatation (FMV) on brachial artery, using B-mode ultrasonography.

Results: Mean age of SLE patients was 26.06 ± 6.231 years. Thirty-seven (74%) of the patients were having severe disease activity, defined as systemic lupus erythematosus disease activity index (SLEDAI) > 8. We found significantly lower levels of basal brachial artery diameter in SLE patients (0.3499 ± 0.075 cm) compared to controls (0.3826 ± 0.0002 cm), as also impaired FMV (2.57 ± 2.32% and 8.7082 ± 1.5776%, respectively). Flow mediated vasodilatation significantly correlated with SLEDAI ($r = -0.52$) and complement (C3) levels ($r = 0.33$).

Conclusion: Endothelial dysfunction in SLE correlates with disease activity.

Keywords: *Endothelial dysfunction, SLEDAI, complement level, flow mediated vasodilatation*

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease which can affect virtually every organ system. The pathogenesis is not yet fully understood, but the disease is thought to result from the aberration of host immune system regulation triggered by alteration in hormonal milieu and some unknown environmental factors in genetically susceptible individuals.[1] The organs and cells undergo autoantibody, immune complex and complement mediated damage. Among the various organ systems affected, skin, kidneys, lungs and cardiovascular system involvement is most notable. In spite of the introduction of newer therapeutic regimes, the morbidity and mortality continues to remain significant.

A variety of cardiovascular manifestations can be seen in SLE with substantially increased morbidity and mortality.[2,3] Morbidity includes accelerated premature atherosclerosis and valvular heart disease.[4] In several large clinical series, the cumulative prevalence of coronary artery disease (CAD) related events was 6–10%, and the annual incidence rate of CAD in SLE populations was about 1.3–1.5%.[4] Among the clinical challenges of SLE, one of the most compelling is the high incidence of atherosclerosis in young women. Classical risk factors are similar to those in the general population

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but the increased risk of atherosclerosis is not exclusively related to traditional Framingham risk factors alone, with a recent report highlighting SLE itself as an independent risk.[5] Whereas several studies have highlighted the presence of subclinical atherosclerosis in SLE, the pathogenesis is not fully understood.[6] It has been proposed that autoimmune vascular injury in SLE may predispose to atherosclerotic plaque formation.[7] Endothelial dysfunction is considered as the first step in the atherogenic process and a harbinger of premature atherosclerosis. Different ways of measuring this endothelial dysfunction are: plasma Von Willebrand factor (vWF) antigen, fibronectin and plasminogen activator activity.[8] A non-invasive method for assessment of endothelial dysfunction is flow mediated vasodilatation (FMV) on brachial artery using vascular ultrasonography.[9] This is a non-invasive and reproducible study and can show early changes in endothelial dysfunction, making it a useful screening method. Early detection of this endothelial dysfunction can be a useful method in preventing subsequent cardiovascular morbidity and mortality in SLE patients.

Systemic lupus erythematosus disease activity index (SLEDAI) is considered a reliable predictor of disease severity with good inter-observer agreement. It includes the various disease parameters, namely seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leucopenia.[10] Many studies have shown strong correlation between SLEDAI and endothelial dysfunction in these patients.[11] Thus patients with severe disease are more prone to develop vascular complications. Another marker of SLE disease activity is complement level in blood (C3 and C4). With high activity, the complement level drops, presumably as a result of immune complex formation and activation of complement in various sites, accelerating the tissue damage.

Our study aimed at evaluating endothelial function in patients of SLE without traditional risk factors for CAD by FMV, a non-invasive and cost effective method, and finding any relation between endothelial dysfunction and disease activity.

PATIENTS AND METHODS

This comparative, cross-sectional study was conducted for 1 year. Sixty-five patients, attending the outpatient department or getting admitted in the Departments of Medicine and Rheumatology, Calcutta Medical College, who satisfied the revised American College of Rheumatology Criteria (ACR-1982) for SLE were enrolled and screened.[12,13] Exclusion criteria were: (a) age > 45 years and < 15 years; (b) patients presenting before menarche, after menopause, and pregnant or contemplating pregnancy; (c) obesity (body mass index ≥ 30 kg/m^2); (d) dyslipidemia; (e) hypertensive or pre-hypertensive (systolic blood pressure ≥ 120 mmHg or diastolic blood pressure ≥ 80 mmHg); (f) diabetic or impaired glucose tolerance (fasting plasma glucose ≥ 100 mg/dL or, plasma glucose ≥ 140 mg/dL 2 hours after 75 g glucose intake); (g) azotemia (serum creatinine level ≥ 3 mg/dL); (f) SLE patients taking high dose of steroid (prednisolone > 20 mg/day or equivalent); (h) electrocardiogram or echocardiography suggestive of any heart disease; (i) infection during the previous 4 weeks; (j) patients using tobacco within last 30 days; and (k) patients on vasoactive medications like nitrates, taken within the last 30 days. After screening, 50 SLE patients were chosen, and compared with equal number of healthy age and sex matched controls.

After obtaining written informed consent, both the groups were subjected to thorough clinical examination and routine investigations. For the SLE patients, additional tests included anti-double-stranded DNA, rheumatoid factor, C-reactive protein (CRP) and complement (C3) level. Thereafter, B-mode ultrasonography of the brachial artery was done in both the groups with HP Agilant machine (Netherlands). The diameter of the brachial artery was measured just above the anticubital crease using a 10 MHz transducer probe by Doppler, on the interface between the media and adventitia of the anterior and posterior wall. The measurements were performed in supine position on the right arm after 10–20 minutes resting in a quiet room. Hyperaemia was induced by inflation of a sphygmomanometer cuff (12.5 cm wide) at 230–250 mmHg for 4 minutes on the most proximal portion of the upper arm. The arterial diameter measurement was repeated 45–60 seconds after sudden deflation of the cuff. The average of the three measurements done on 3 consecutive days, of basal (before occlusion by cuff) and post-hyperaemia (after occlusion by cuff) diameter was used for the analysis. Flow mediated vasodilatation represents the relative increase in brachial artery diameter during hyperaemia, and defined as (post-hyperaemia diameter—basal diameter)/basal diameter. Expressed as a percentage, it is used as a measure of endothelial function.[14] To be considered interpretable, a study needed to have distinct visualisation of the proximal and distal intimae-media arterial layers perpendicular to the ultrasound beam with < 5% diameter variation across the field of measurement. All the measurements were done by a single operator expert in radiology. To assess reproducibility of the technique,

we looked at the reliability of reading scans in eight normal healthy controls 1 week apart on three separate occasions by the same observer. The disease activity was assessed by SLEDAI calculated online.[15]

Data were presented as mean ± standard deviation (SD) for continuously distributed variables, and in absolute numbers and percentages for the discrete variables. Student's *t* test was performed to compare parametric variables between cases and controls. Pearson correlation co-efficient was used to examine the relation between brachial FMV and several study variables. A *P*-value < 0.05 was considered as statistically significant. Microsoft office Excel 97–2003 version and GraphPad QuickCalcs software (Graphpad Software Inc, La Jolla, CA, USA) were used for statistical analysis. The study got clearance from the institutional ethical committee.

RESULTS

We had a total of 50 SLE patients and 50 age and sex matched controls. We excluded 15 patients as 12 of these patients had SLE nephropathy with hypertension (four of them having azotemia); two were on > 20 mg prednisolone, and one had impaired glucose tolerance.

Out of those 50 patients, 47 (94%) were females. Twenty (40%) patients were from rural areas, 26 (52%) had oral ulcers on presentation, 32 (64%) had polyarthritis, and malar rash were present in 28 (56%) patients (Table 1). Twenty-nine (58%) patients had urinary protein excretion > 1 g/24 hours. Anaemia was present in 25 (50%) patients. Among SLE patients, 48 (96%) were antinuclear antibodies (ANA) positive and 40 (80%) were anti-ds DNA positive. Mean complement C3 level was 102.64 ± 40.36 mg/dL (normal: 90–180 mg/dL) with 25 (50%) of the patients having values below 90 mg/dL. Cardiovascular risk factors like blood pressure, fasting and post-prandial plasma glucose and fasting lipid profiles were also normal and ECG showed no significant changes in any of the patients. Calculation of SLEDAI of the SLE patients (Figure 1) shows that 37 (74%) of the patients were in severe disease activity group (SLEDAI > 8).

At the time of study, 40 (80%) SLE patients were on one or more disease modifying antirheumatic drugs (DMARDs)

Table 1 Demographic profile and clinical and laboratory parameters of the systemic lupus erythematosus patients, compared with controls

Parameter	*Value in SLE patients (n = 50)*	*Value in controls (n = 50)*	*P value*
Demography			
Age (yr)	26.06 ± 6.23	27.84 ± 7.43	NS
Sex ratio (M:F)	3:47	4:46	NS
Disease duration (yr)	6.25 ± 3.49	NA	NA
Rural population	20 (40%)	25 (50%)	NS
Clinical parameters			
BMI (kg/m^2)	20.75 ± 4.16	20.51 ± 1.03	NS
Polyarthritis	32 (64%)	NA	NA
Malar rash	28 (56%)	NA	NA
Oliguria	13 (26%)	NA	NA
Oral ulcer	26 (52%)	NA	NA
Family history of SLE	5 (10%)	NA	NA
Laboratory parameters			
Raised ESR	50 (100%)	8 (16%)	< 0.0001
ANA positivity	48 (96%)	NA	NA
Anti-ds DNA positivity	40 (80%)	NA	NA
Low C3 levels (N 90–180 mg/dL)	25 (50%)	NA	NA
Fasting plasma glucose (mg/dL)	81.33 ± 5.71	82.57 ± 6.32	NS
Post-prandial plasma glucose (mg/dL)	116.5 ± 9.51	115.22 ± 8.35	NS
Total cholesterol (mg/dL)	158.67 ± 39.47	156.86 ± 30.27	NS
Triglycerides (mg/dL)	105 ± 8	110.5 ± 23.99	NS

Note. Values expressed as percentage of total number of patients in each group; BMI = body mass index; SLE = systemic lupus erythematosus; ESR = erythrocyte sedimentation rate; ANA = antinuclear antibodies; DNA = deoxyribonucleic acid; NS = not significant; NA = not applicable.

like hydroxychloroquine (400 mg/day) or methotrexate (15–25 mg weekly). Twenty-three (46%) patients had earlier received cyclophosphamide for renal disease. Renal biopsy performed in 33 patients showed that 13 had stage III, 12 had stage IV and seven had stage II nephritis and one had stage V nephritis. Sixteen (32%) patients were on oral steroids at the time of study (mean dose: prednisolone 7.5 ± 2.17 mg or equivalent). Steroids were continued at the time of measuring FMV. Mean disease duration of the patients was 6.25 ± 3.49 years. A measure of the vascular parameters of the SLE patients showed that the SLE patients had significantly lower baseline brachial artery diameter (mean 0.35 ± 0.075 cm) and also, lower flow mediated vasodilatation (2.57 ± 2.32%), compared to controls (Table 2). Table 3 shows the bivariate correlation of FMV with some other parameters in the SLE patients. It was seen that SLEDAI, which reflects disease activity, had a significant negative correlation with FMV (Pearson's correlation co-efficient $r = -0.52$; $P < 0.05$), represented in Table 3 and Figure 2. Also, the baseline brachial artery diameter showed some correlation with subsequent FMV ($r = 0.28$; $P < 0.05$), thereby suggesting that endothelial dysfunction is associated with significant baseline vasoconstriction (Table 3). The serum C3 (complement level) also correlated significantly with the FMV ($r = 0.33$; $P < 0.05$), whereas the disease duration did not (Table 3 and Figure 3).

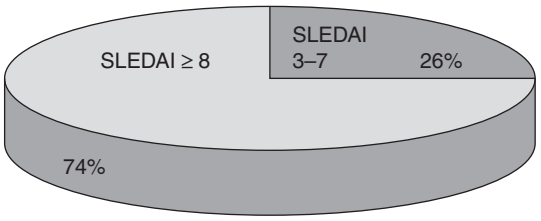

Figure 1 Pie diagram showing percentage of patients with severe disease (SLEDAI ≥ 8) at presentation; $n = 50$. SLEDAI = systemic lupus erythematosus disease activity index.

DISCUSSION

Systemic lupus erythematosus is a systemic disease with pronounced cardiovascular consequences, not only due to vasculitis, but also due to accelerated atherosclerosis. Patients with SLE have high incidence of atherosclerosis along with its consequence, CAD. As per the study by Manzi et al., women with SLE aged 35–45 years were 50 times more likely to develop myocardial infarction than

Table 2 Comparison of the vascular parameters of the systemic lupus erythematosus patients and controls

Parameter	*SLE patient (mean ± SD) in cm (n = 50)*	*Control subject (mean ± SD) in cm (n = 50)*	*P value (two tailed, Student's t test)*
Brachial artery diameter (basal)	0.35 ± 0.08	0.38 ± 0.00	< 0.001
Brachial artery diameter (post-hyperemic)	0.36 ± 0.01	0.42 ± 0.01	< 0.001
Flow mediated vasodilatation (%)	2.57 ± 2.32	8.71 ± 1.58	< 0.001

SLE = systemic lupus erythematosus; SD = standard deviation.

Table 3 Bivariate correlation of flow mediated vasodilatation with selected variables in patients of systemic lupus erythematosus ($n = 50$)

Variables	*Pearson's correlation co-efficient (r)*	*P value*	*Comments*
LDL	0.12	NS	–
VLDL	–0.10	NS	–
TG	–0.06	NS	–
Total cholesterol	0.21	NS	–
CRP	–0.003	NS	–
SLEDAI	–0.52	< 0.0001	Moderate degree of negative correlation
Disease duration	–0.11	NS	–
Brachial artery diameter (basal) (BAD-BO)	0.28	< 0.0001	Low positive correlation
Complement C3	0.33	< 0.0001	Low positive correlation

LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; TG = trigonelline; CRP = C-reactive protein; SLEDAI = systemic lupus erythematosus disease activity index; NS = not significant.

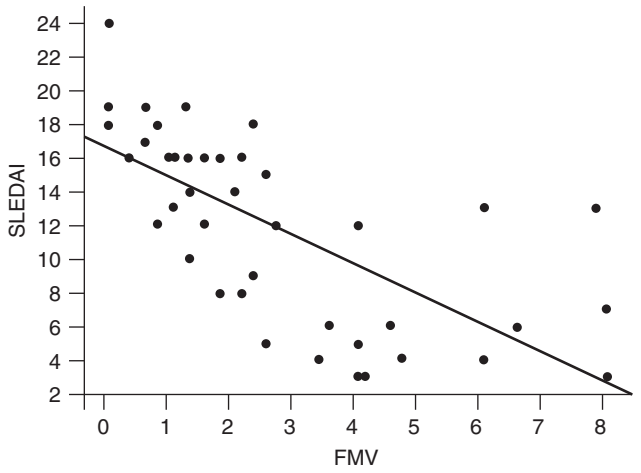

Figure 2 Scatter diagram showing the correlation between SLEDAI and FMV ($r=0.52$; $P<0.0001$). SLEDAI = systemic lupus erythematosus disease activity index; FMV = flow mediated vasodilatation.

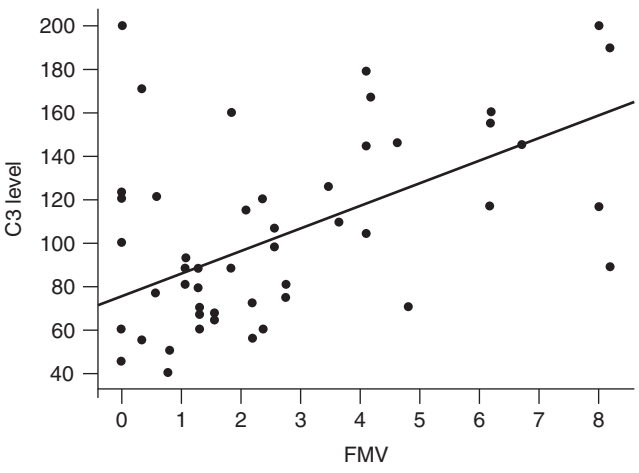

Figure 3 Scatter diagram showing the correlation between FMV (%) with C3 levels (mg/dL) ($r=0.33$; $P=0.000013$). FMV = flow mediated vasodilatation.

the others.[5] Bruce et al. found increased levels of very low-density lipoprotein (VLDL) cholesterol and total triglycerides in SLE patients compared to age and sex matched controls.[16] Cardiovascular risk is even higher in lupus patients also having secondary antiphospholipid syndrome (APS) because of the additive effects of SLE- and APS-related risk factors.[17] Some in vitro studies suggest that antibodies to oxidised low-density lipoprotein (LDL) can be considered as markers of the pathogenic determinants of atherosclerosis, such as enhanced lipid oxidation, proinflammatory stage and impaired vasodilatation.[18] The first reversible step in the atherogenesis process is endothelial dysfunction.[9] Endothelial dysfunction causes loss of normal function of endothelial cells like control of vascular tone and blood pressure, regulation of neutrophil traffic from blood to tissue, platelet adhesion and aggregation, maintenance of balance between blood procoagulation and anticoagulation, control of growth and development and differentiation of vessel wall cell.[5] Many theories have been postulated for pathogenesis of this dysfunction. The most popular hypothesis is that, chronic inflammation is the key factor contributing to endothelial dysfunction and subsequent atherogenesis in SLE; yet other mechanisms mediating endothelial dysfunction, e.g. insulin resistance, hyperhomocysteinemia, or ADMA, a recently described inhibitor of nitric oxide synthase, could be more important in SLE.[19] One recent theory suggests possible role of high level of interferon I that causes death of endothelial progenitor cells.[20] Another theory for endothelial damage in SLE is the anti-endothelial cell antibodies (AECAs), which are a heterogeneous group of antibodies against a variety of antigenic determinants on endothelial cells (EC). Anti-endothelial cell antibodies are known to play an immunopathogenic role in triggering EC activation, leading to vascular damage.[21] All these can give rise to different vascular events. An easy and non-invasive way of quantitatively measuring endothelial function is by FMV.[14] Reactive hyperaemia produces a shear stress stimulus that induces the normal endothelium to release nitric oxide (NO), which acts as vasodilator. Reduced endothelial function is associated with decreased release of NO and less vasodilatation, resulting in less FMV. However, methods like pulse amplitude tonometry may be superior to FMV in predicting endothelial dysfunction.[22]

The first study done by Lima et al. showed that, SLE patients presented with lower FMV than age and sex matched controls, even in subjects without traditional cardiovascular risk factors.[23] In our study, FMV in SLE patients were significantly lower than the control subjects ($2.57 \pm 2.32\%$ *vs.* $8.7082 \pm 1.58\%$, $P<0.05$). Indian patients have also shown the same pattern of endothelial dysfunction in SLE. A study by Bhatt et al. considered ultrasonographic measurement of carotid intimae-media thickness (CIMT) and presence of plaque as markers of subclinical atherosclerosis in SLE.[24] Another study from north India in 2009 by Ghosh et al. showed that FMV was significantly lower in SLE patients and it correlated with CIMT. However, they showed that with glycerol trinitrate the dilatation returned to normal. This study also showed that endothelial dysfunction in SLE increases with age.[25] Studies on vascular dysfunction in SLE from Eastern India are lacking, but studies from other parts of India have shown that this is highly prevalent in

Table 4 Comparison of the flow mediated vasodilatation percentages in systemic lupus erythematosus patients found in different studies

Study (yr)	*Age of patients with SLE (yr)*	*FMV (%)*
Aizer et al. (2009)[22]	48.8 ± 8.8	12.5 ± 5.1
Wright et al. (2006)[29]	45 ± 8	2.4% median
Turner et al. (2005)[30]	Median age (inter-quartile range): 42.5 (32.0–47.5)	2.1% median
Ghosh et al. (2009)[25]	31 ± 9	9.97 ± 5.51
Present study (2010)	26.06 ± 6.231	2.57 ± 2.32

SLE = systemic lupus erythematosus; FMV = flow mediated vasodilatation.

Indian patients as well.[26,27] Table 4 shows the FMV in SLE patients found in different studies.

The significant lower baseline brachial artery diameter found in SLE patients can also be explained from endothelial dysfunction, for which apoptosis and increased interleukins have been implicated.[27] Use of angiotensin converting enzyme (ACE) inhibitors can increase FMV, probably by generating more bradykinin. Thus, ACE inhibitors are helpful not only for renal disease but also for vascular dysfunctions.[28]

Masoud EI-Magadmi et al. studied endothelial function in SLE, assessed by FMV of brachial artery in response to reactive hyperemia.[7] They concluded that patients with SLE have endothelial dysfunction that remained significant even after adjustment for other classic risk factors. In our study we selected patients with no cardiovascular risk factors. Still the SLE patients were found to have significant FMV abnormalities. In this study we have found a moderate degree of inverse correlation between SLEDAI score and FMV, i.e. with increasing severity of disease activity, the degree of impairment of FMV is also increased in SLE patients. A study from UK also had a similar outcome.[29] A study by Caraba et al. showed positive correlation between FMV and complement ($r = 0.71$), which was also found in our study ($r = 0.33$).[11] This shows that systemic inflammatory activity strongly correlates with vascular pathologies.

CONCLUSION

Young to middle aged patients with SLE having high SLEDAI score and high ESR, free from cardiovascular risk factors and overt cardiovascular disease, have an altered endothelial reactivity, which correlates inversely with the SLEDAI score. This impaired endothelial reactivity indicates a higher susceptibility to the development of atherosclerotic disease. Flow mediated vasodilatation using vascular ultrasonography on brachial artery represents a non-invasive, repeatable, useful and cheap method for the assessment of endothelial dysfunction. The major limitation of our study is the cross-sectional nature of the study, and relatively small number of patients. A large multicentric, prospective study would be ideal to know the exact effect of this endothelial dysfunction on future cardiovascular events.

DISCLOSURE

According to the authors, there is no conflict of interest.

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