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Arterial Stiffness in Systemic Lupus Erythematosus and Its Correlation with Disease Severity: A Case Control Study

T. Jayapal[1], K. V. Vysakha[1], C. Rajasekharan[1*] and Akhilkrishna[1]

[1]Department of Internal Medicine, Government Medical College Hospital, Thiruvananthapuram, Kerala, India.

Authors' contributions

This work was carried out in collaboration between all authors. Authors TJ, KVV, CR and Akhilkrishna were responsible for conception of the idea and conducting the study. All the authors were responsible for writing, re-writing, editing and formatting of the manuscript, tables, figures and referencing. Authors TJ and CR were responsible for revising the manuscript. All authors read and approved the manuscript.

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ABSTRACT

Introduction: Arterial stiffness is an emerging field of interest in atherosclerosis. Patients with systemic lupus erythematosus (SLE) are predisposed to have premature atherosclerosis.
Aims: To compare the arterial stiffness among patients with SLE and non-SLE controls. The study also compared arterial stiffness among SLE patients in relation to disease activity (SLEDAI) and end organ damage (SLICC index).
Study Design: Case control study.
Place and Duration of Study: Patients attending rheumatology clinic and those admitted to medical wards of the Internal Medicine and Nephrology departments of Government Medical College Hospital, Thiruvananthapuram.
Methodology: 53 SLE patients and 53 non-SLE controls were studied. Data was obtained in a

**Corresponding author: E-mail: drcrajasekharan@yahoo.com;*

structured format. Arterial stiffness indices were obtained by measuring the brachial ankle pulse wave velocity (baPWV). The SLEDAI Score and SLICC Damage index were measured in the SLE group. Age-matched controls were obtained from the general population.

Results: SLE patients had higher brachial ankle pulse wave velocity (baPWV) than the control non-SLE population (1194.9 ± 169.6 cm/s vs 1008.5 ± 62.5 cm/s; p<0.001), Mean arterial stiffness index (ASI) among SLE patients was significantly higher than that of control (26.2 ± 3.9 mm Hg vs. 23.7 ± 3.7 mm Hg, p=.001), mean augmentation index(AI) among SLE patients was significantly higher when compared with the control non-SLE population (13.9± 6.7% vs 6.2 ± 1.7%, p<0.001). Patients with SLE-related end organ damage (SLICC index ≥1) had baPWV elevated over those with SLICC index=0 (1234.5 ± 181.5 cm/s.1 vs 1124.1 ± 121.1 cm/s, p=.021). No significant difference was observed between the mean ASI among the patients with SLICC index ≥1 and those with SLICC=0. (26.9 ± 4.1 mm Hg vs 24.8 ± 3.3 mm Hg, p=.070), and mean AI among SLICC index ≥1 was significantly higher than that of SLICC index ≥1 (15.6 ± 6.7% vs 11.1 ± 5.8%, p= .017). Patients with high disease activity (SLEDAI ≥6) had baPWV of 1278.9 ± 131.0 cm/s (95%CI 1229 cm/s.1-1328.7 cm/s) vs (1093.4 ± 156.5 cm/s; 95% CI 1027.3 cm/s -1159.4 cm/s p<0.001) when compared with those having low activity (SLEDAI<6).

Conclusion: Patients with SLE had increased arterial stiffness. End organ damage and high disease activity among SLE patients correlated to increased arterial stiffness, and is contributory to an increased risk of atherosclerosis.

Keywords: Systemic lupus erythematosus; arterial stiffness; brachial ankle pulse wave velocity; atherosclerosis.

ABBREVIATIONS

AIX : Augmentation index
ASI : Arterial stiffness index
BMI : Body mass Index
baPWV : Brachial ankle pulse wave
cf-PWV : Carotid femoral pulse wave velocity
ESC : European Society of Cardiology
ESH : Velocity European Society of Hypertension
NIBP : Non-invasive blood pressure
SLICC : The Systemic Lupus International Collaborating Index
SLEDAI: SLE disease activity index

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organs and cells undergo damage mediated by tissue-binding auto antibodies and immune complexes. Prevalence and incidence rates of SLE vary widely in the literature. Reported prevalence frequencies range from 20 to 240 per 100,000 persons, and reported incidence rates range from 1 to 10 per 100,000 person-years [1]. SLE demonstrates a striking female predominance with a peak incidence during reproductive years [2].

The bimodal mortality pattern of SLE was described by Urowitz et al. [3]. They observed that deaths early in the disease (<5 years) were due to active SLE or associated conditions such as sepsis, whereas late SLE deaths (>5 years) were attributed to atherosclerotic complications.

Framingham risk factors alone cannot explain the high prevalence of atherosclerosis in SLE. The complex interactions between traditional risk factors and factors associated either with the disease per se or its treatment contributes to the accelerated atherosclerotic process in SLE [4-6]. Chronic vascular inflammation, the hallmark of SLE, may contribute to the development of vascular stiffness [3,6,7]. Arterial stiffness, measured in large epidemiological studies including the Framingham Heart Study [8], is a risk factor for the complications of cardiovascular disease that is independent of classical metabolic and genetic risk factors. The current literature points to the fact that assessment of PWV is a non-invasive, simple, rapid tool for assessing large artery stiffness. Moreover, it carries the advantage of being the most non-invasive, reproducible to determine the PWV [9, 10]. Assessment of PWV may therefore play an important role in cardiovascular disease prevention and the evaluation of treatment efficacy [11]. PWV determination has significant usefulness for use in the routine clinical practice as currently recommended by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). PWV is considered the gold standard method for assessing arterial stiffness. It is a tool to evaluate the arterial system damage, vascular adaptation, and therapeutic efficacy [12].

Pulse wave velocity (PWV) is the velocity at which the arterial pulse propagates through the circulatory system and is dependent on and varies with the elastic recoil of the vessel wall. The velocity of propagation is higher when the vessel wall is less elastic [13,14]. The measurement is made on the basis of the time taken to travel by the pressure wave over a specific distance and is calculated as the distance between the two positions of the pulse transducer divided by the time delay measured between pressure upstroke at each site. The most convenient sites are recordings between carotid and femoral artery sites to provide a measure of aortic stiffness. High-fidelity applanation tonometers can be used for direct measurement of pressure waves [15]. Another modality are mechanotransducers or ultrasonographic systems, which detect arterial wall motion secondary to pulse pressure [16-20]. Pulse wave velocity (PWV) is now recognized as a standard method for the measurement of AS. Determination of PWV is the most reliable and reproducible method among the various indices of AS [21-23]. The strongest predictor of cardiovascular mortality was PWV in a cohort of elderly patients [24].

Recently, non-invasive methods to measure arterial stiffness have become available and are relatively easy to perform [25]. Arterial stiffness is assessed in patients by measurements of pulse wave velocity (PWV), and it has been proposed that routine measurements of PWV might provide an earlier and therefore better predictor of cardiovascular disease and preventive treatments.

This study aims to investigate the relation between arterial stiffness among SLE patients and non-SLE controls. It also attempts to find out the relation between disease activity and end organ damage among SLE patients with arterial stiffness.

2. MATERIALS AND METHODS

A case control study was conducted among 53 SLE patients attending rheumatology clinic and those admitted to medical wards of the Internal Medicine and Nephrology departments of Government Medical College Hospital, Thiruvananthapuram. SLE was diagnosed on the basis of the 1997 Update to the 1982 American College of Rheumatology Revised Criteria for Classification [26]. Fifty-three age and sex matched subjects who were not diagnosed cases of SLE and had no symptoms suggestive of SLE, diabetes, hypertension, or coronary artery disease were taken as controls.

Arterial stiffness was assessed in patients by measurements of pulse wave velocity (PWV). Pulse wave velocity was measured with the help of a non-invasive PeriScope^{TM}-cardio vascular analyzer by Genesis medical system validated by study conducted at Nissan Institute in 2005 [8]. PeriScope uses automatic simultaneous limb NIBP (non-invasive blood pressure) measurement and ECG waveform to calculate important parameters such as arterial stiffness index, pulse wave velocities, ankle brachial index, and augmentation index. Additionally, it incorporates oscillometric envelopes and interpretive monograms. These are established as independent markers to analyze the arterial stiffness and atherosclerosis. Electrodes of electrocardiogram were placed on both infraclavicular areas and medial side of ankles, and BP cuffs were wrapped on both the upper arm brachial artery and above the tibial artery of ankles. The cuffs were connected to a plethysmographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures blood pressure volume waveforms from the brachial and tibial arteries. All the pressure recordings were done for about 10 seconds and data was stored in a computer for analysis. SLE disease activity was assessed using the SLE disease activity index (SLEDAI). The Systemic Lupus International Collaborating Index (SLICC), also called the American College of Rheumatology Index, was used to record end organ damage in SLE. Quantitative variables were expressed as mean and standard deviation and categorical variables were expressed as proportion. Between group comparison of quantitative variables were analyzed by independent sample t test and that of categorical variables by Chi-square test or Fisher's exact test and Yates correction was applied if necessary.SLE groups and controls were compared using unpaired t test in various indices of pulse wave velocity. Correlation of arterial stiffness with SLICC/SLEDAI was assessed using Pearson correlation coefficient. A p value < .05 was considered as statistical significant.

3. RESULTS AND DISCUSSION

We studied 53 SLE patients and 53 age and sex matched controls over a period of 1 year. The mean age of study population was 32.5 years, and the majority were females (n=48; 90.6%).

Average baPWV among SLE patients was 1194.9±169.6 cm/s and that of non-SLE patient was 1108.5±62.5 cm/s. The observed difference was statistically significant p<0.05). We found that SLE patients, compared with the control non-SLE population, had higher mean arterial stiffness index (ASI) (26.2 ± 3.9 mm Hg vs 23.7 ± 3.7 mm Hg , p=.001), carotid femoral pulse wave velocity (721.7 ± 127.2 cm/s vs 609.4 ±55.48 cm/s; p<0.001), and augmentation index (%) (13.9± 6.7 vs 6.2 ±1.7, p<0.001) (Table 1). The box plot diagram (Fig. 1) describes the variations in arterial stiffness indices between SLE and non-SLE patients.

Among various parameters studied, use of cyclophosphamide, relapses of SLE and presence of anti-phospholipid antibody were found to be significantly associated with SLICC damage index (p<0.05) (Table 2).

Mean baPWV, cfPWV and AIX among SLE patients with SLICC damage index of ≥1 were significantly higher than that of SLE patients with SLICC damage index of 0 (p<0.05) but the observed difference in ASI between SLICC damage index of ≥1 and 0 was not statistically significant (p>0.05) (Table 3).

Number of relapses and azathioprine use was found to be significantly associated with SLEDAI score (p<0.05) (Table 4). The scatter plot diagram (Fig. 2) describes the weak positive correlation between SLICC score and ASI (r=0.214, p=0.124).

Table 1. Comparison of age, sex, BMI, baPWV, cfPWV, ASI, AIX between SLE patients and controls

	Category	N	Mean	sd	t	p
Age in years	SLE	53	32.5	10.8	0.000	1.000
	Controls	53	32.5	10.8		
BMI (Kg/m^2)	SLE	53	25.3	4.2	1.118	0.268
	Controls	53	24.4	3.7		
baPWV (cm/s)	SLE	53	1194.9	169.6	7.511	<0.001
	Controls	53	1008.5	62.5		
ASI (mm Hg)	SLE	53	26.2	3.9	3.290	0.001
	Controls	53	23.7	3.7		
CfPWV	SLE	53	721.7	127.2	5.891	<0.001
	Controls	53	609.4	55.5		
AIX	SLE	53	14.0	6.7	8.137	<0.001
	Controls	53	6.2	1.7		

Table 2. Comparison of various clinical parameters among SLE patients with SLICC damage index between 0 and ≥1

	SLICC				χ^2	df	p
	0 (N=19)		≥1 (N=34)				
	N	%	N	%			
Diabetes	3	15.8	8	23.5	0.098	1	0.754†
Smoking	1	5.3	1	2.9	0.000	1	1.000†
Steroid	18	94.7	34	100.0	-	-	0.358††
Hydroxychloroquine	11	57.9	19	55.9	0.020	1	0.887
Azathioprine	3	15.8	7	20.6	0.004	1	0.950†
Cyclophosphamide	1	5.3	12	35.3	4.427	1	0.035†
Mycophenolate mofetil	2	10.5	3	8.8	0.000	1	1.000†
Regular treatment	14	73.7	20	58.8	1.170	1	0.279
Relapse	1	5.3	11	32.4	3.677	1	0.055†
Statin	0	0.0	2	5.9	-	-	0.531††
Cholesterol	6	31.6	13	38.2	.235	1	0.628
Anti-phospholipid antibodies	3	15.8	0	0.0	-	-	0.041††

† - Yates correction; †† - Fisher's Exact test

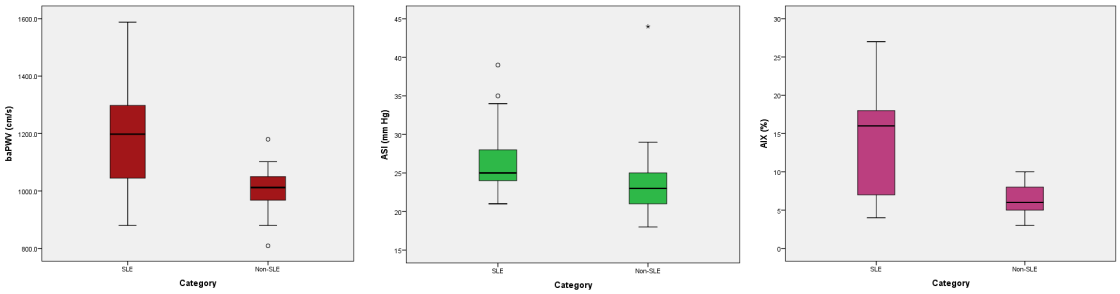

Fig. 1. Box plot diagram describing baPWV, ASI and AIX of SLE and non-SLE group

Table 3. Comparison of age, sex, BMI, baPWV, cfPWV, ASI, AIX among SLE patients with SLICC damage index 0 and ≥1

	SLICC	N	Mean	sd	t	p
BAPWV	0	19	1124.1	121.1	2.372	0.021
	≥1	34	1234.5	181.1		
ASI	0	19	24.8	3.3	1.852	0.070
	≥1	34	26.9	4.1		
C F PWV	0	19	674.8	96.3	2.067	0.044
	≥1	34	747.9	135.9		
AIX	0	19	11.1	5.8	2.472	0.017
	≥1	34	15.6	6.7		

Table 4. Comparison of various clinical parameters among SLE patients with SLEDAI score of <6 and ≥6 or more

	SLEDAI				χ^2	p
	≤6 (N=24)		>6(N=29)			
	N	%	N	%		
Diabetes	5	20.8	6	20.7	0.000	1.000†
Smoking	1	50.0	1	3.4	0.000	1.000†
Corticosteroids	23	44.2	29	100.0		0.453††
Hydroxychloroquine	12	40.0	18	62.1	0.779	0.378
Azathioprine	8	80.0	2	6.9	4.393	0.036†
Cyclophosphamide	6	46.2	7	24.1	0.005	0.942
Mycophenalate mofetil	3	60.0	2	6.9	.0.050	0.824†
Regular treatment	17	50.0	17	58.6	0.852	0.356
Relapse	2	16.7	10	34.5	5.127	0.024
APLA	2	66.7	1	3.4	0.029	0.866†

† - Yates correction; †† - Fisher's exact test

Patients with active disease (SLEDAI >6) had mean baPWV, cfPWV, ASI and AIX higher than those with SLEDAI < 6 and the observed difference was statistically significant ($p<0.05$) **(**Table 5). Scatter plot diagram (Fig. 3) describing the significant positive correlation between SLEDAI score and ASI ($r=0.302$, $p=0.028$).

ROC curves were plotted (Fig. 4) to decide the optimal cut-points for BAPWV to determine SLEDAI score >6. A BAPWV score of 1115 was associated with a sensitivity of 89.7%, a specificity of 75%, and an area under an ROC curve of 0.829 (95% CI 0.696-0.962) to predict SLEDAI score >6 (Fig. 4).

3.1 Discussion

In our study, 53 SLE patients and 53 non-SLE patients were studied over the period of 1year. The ratio of females to males was 9.6, which was consistent with others studies [27]. Arterial stiffness indices including brachial ankle pulse wave velocity (baPWV), carotid femoral pulse wave velocity (cfPWV), arterial stiffness index (ASI) and augmentation index (AIX) have been of

recent interest as indirect measurements of subclinical atherosclerosis.

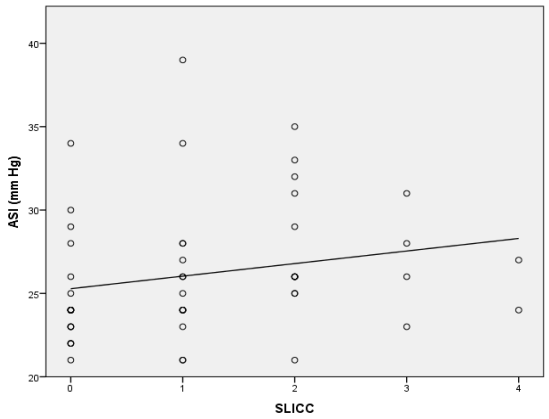

Fig. 2. The scatter plot shows a linear correlation between SLICC score and ASI

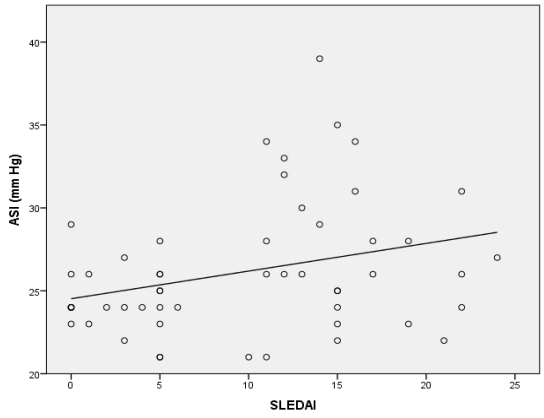

Fig. 3. The scatter plot shows linear correlation between SLEDAI score and ASI

In this study, there was no significant difference in mean age and mean BMI between the SLE patients and the controls. The brachial pulse wave velocity, the arterial stiffness index, the carotid femoral pulse wave velocity and the augmentation index of the SLE patients were significantly higher than that of non-SLE patients ($p < 0.05$) [28]. Cypiene et al. [29] studied 30 young SLE patients without significant organ damage and 66 healthy controls matching on renal function and lipid profile, focusing on pulse wave velocity and augmentation index. SLE patients were higher than controls in both respects. This was similar to the result obtained in our study. This elevation in arterial stiffness indices among the SLE patients relative to the control non-SLE population was statistically significant.

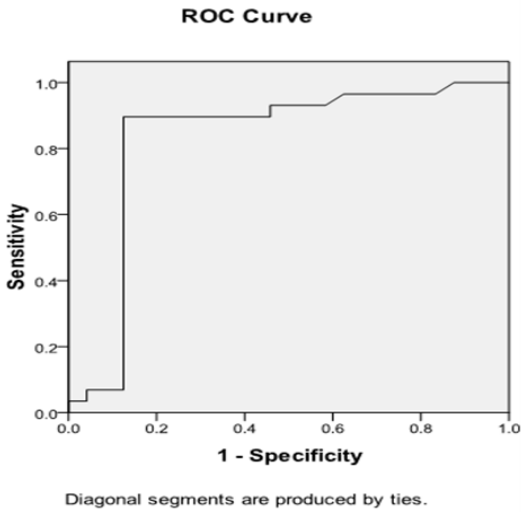

Fig. 4. ROC curve for finding the optimum cut-off value of baPWV to predict SLEDAI score ≥6

SLEDAI score and SLICC ACR damage index were used to assess the disease activity and end organ damage at the time of study [30]. The mean SLEDAI score of the study population was 9.8, and SLICC damage index was 1.1. We studied various disease-related and patient-related factors influencing the SLICC damage index and found that cyclophosphamide use, number of relapses and presence of anti-phospholipid antibody were associated with higher SLICC damage index at a statistically significant level. The SLEDAI score had a significant association with use of azathioprine and number of relapses. This was consistent with results obtained by Nossent [31] and Laccarino et al. [32] who showed that increased organ damage and disease activity was related to frequent relapses. They failed to show association between increased organ damage and disease activity, on the one hand, and APLA, azathioprine and cyclophosphamide use on the other, whereas ankle brachial pressure index (ABI), body mass index (BMI), C-reactive protein (CRP), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, lipoprotein a, and homocysteine were comparable between the two groups. Valero et al. [33] studied SLE specific factors and PWV. Significant association was found between PWV and SLICC/ACR score ($p = 0.006$). Multivariate analysis in this study showed that increased PWV was independently associated with metabolic syndrome SLICC/ACR score, which was consistent with the results obtained in our study [7,33,34].

Table 5. Comparison of baPWV among SLE patients with SLEDAI score <6 and ≥6

	SLEDAI	N	Mean	sd	95% CI	t	p
BAPWV	≤6	24	1093.4	156.5	1027.3-1159.4	4.699	<0.001
	>6	29	1278.9	131.0	1229.1-1328.7		
Cf PWV	≤6	24	615.7	68.3	586.8-644.5	8.487	<0.001
	>6	29	809.4	92.9	774.1-844.8		
ASI	≤6	24	24.5	2.0	23.6-25.3	3.072	0.003
	>6	29	27.6	4.6	25.8-29.3		
AIX	≤6	24	8.0	4.0	6.4-9.7	9.861	<0.001
	>6	29	18.9	4.0	17.4-20.4		

There was a significant association between SLEDAI score and arterial stiffness indices. Thirty-two females and 32 female normal controls were studied by Shang et al. [35]. Patients with active disease (SLEDAI ≥ 3) had significantly higher carotid AI (34.4 ± 9.7% vs. 17.8 ± 17.3%, $p<0.05$) than stable ones (SLEDAI <3). Patients with organ damage (SLICC ≥ 1) had significantly higher heart-ankle PWV (9.69 ± 1.13 m/s vs. 8.61 ± 1.02 m/s, $p< 0.05$) than those with SLICC = 0. This was similar to the result obtained in our study. Yehia et al. [36] studied 16 children and found that pulse wave velocity was elevated in those with disease activity and contributed to premature atherosclerosis.

The ROC curve was used to determine the optimal cut-off value for baPWV to distinguish between SLE patients with high and low disease activity. Therefore, a baPWV of 1115 cm/s was taken as cut-off to distinguish between SLE patients with high and low disease activity. Area under ROC curve was 0.829, which indicated that baPWV has fair accuracy to distinguish between the two groups.

Arterial stiffness indices, which indirectly measure vascular stiffness, are found to be significantly elevated in SLE patients compared to the control population. Those with higher disease activity had indices elevated over those of well-controlled cases. Thus, SLE is a pro-inflammatory state with accelerated atherosclerosis: arterial stiffness indices can be used to predict cardiovascular mortality, and various lifestyle and pharmacologic treatments can be advised early in the disease to reduce it.

4. CONCLUSION

Patients with SLE had increased arterial stiffness. End organ damage and high disease activity among SLE patients correlated to increased arterial stiffness, and is contributory to an increased risk of atherosclerosis.

5. LIMITATIONS OF STUDY

Study population represented a small cohort of patients attending Medical College Hospital, Trivandrum, Kerala, India, for both SLE and non-SLE controls. The study was done on a small sample of 53 SLE and 53 non-SLE patients, and the study findings could be more realizable with a larger sample size.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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