Original Paper

Disease Activity and Subclinical Atherosclerosis in Systemic Lupus Erythematosus

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ABSTRACT ***Background*:** Atherosclerosis is the most common pathologic process leading to cardiovascular disease and systemic immune and inflammatory diseases, such as systemic lupus erythematosus (SLE), are associated with increased morbidity and mortality, most of it attributable to cardiovascular events. Non invasive measurement of arterial stiffness allows the detection of early vascular injury and help the clinicians improve the long term prognosis of these patients. ***The aim*** of this study was to evaluate the relationship between non invasive vascular assessment and SLE disease activity index. ***Methods***: Our prospective study included 53 patients with SLE, from Rheumatology department, Emergency County Hospital Craiova. All of them have fulfilled the American College of Rheumatology revised criteria for SLE. ***Results***: As expected, most of the patients were women (50, 94%), with a a mean age of 31,92 years (SD 5,55; limits 22-44), similar in women and men. Patients with persistent active disease (SLEDAI>8), had a mean AIx of 35,91% (SD 7,04; 95%CI 32,786 - 39,032), 1,31 times higher than the ones with SLEDAI<8 (27,39%; SD 5,89; 95%CI 25,228 - 29,546), statistically significant (p<0,001), a higher cfPWV-9,523m/s (DS 0,407; 95%CI 9,342-9,703), but not statistically significant (p=0,301) and a mean CIMT of 0,909mm (SD 0,03182; 95%CI 0,895-0,923) versus 0,897mm (SD 0,03699; 95%CI95% 0,884-0,911) in patients with SLEDIA<8, with no significant differences (p=0,242). AIx was the only marker of subclinical atherosclerosis that moderately correlated with SLEDAI (r=0,46; 95%CI 0,2134 - 0,6476; p<0,001). ***Conclusion:*** The results of our study show that SLEDAI significantly correlated with AIx, suggesting that disease flare or aggravation may play a permissive role in vascular injury through vascular inflammation and endothelial dysfunction, which will decrease arterial compliance.

KEY WORDS *systemic lupus erythematosus, SLEDAI, augmentation index, pulse wave velocity, intima-media thickness.*

Introduction

Atherosclerosis is the most common pathologic process leading to cardiovascular disease (CVD), including myocardial infarction (MI) and stroke, the number one killers in general population [1, 2, 3]. Atherosclerosis is increasingly considered an immune system mediated process of the vascular system. The presence of macrophages and activated lymphocytes within atherosclerotic plaques supports the concept of atherosclerosis as an immune system mediated inflammatory disorder [2, 4].

Systemic immune and inflammatory diseases, such as systemic lupus erythematosus (SLE), are associated with increased morbidity and mortality, most of it attributable to cardiovascular events [5, 6]. Inflammation is associated with endothelial dysfunction, atherosclerosis, damage of the arterial wall and causes increased arterial stiffness, recognized as a modifiable, independent predictor of cardiovascular risk [7, 8], as it is now known that a decrease in elasticity is an early sign of vascular changes [9, 10]. Non invasive measurement of arterial stiffness allows the detection of early vascular injury and help the clinicians improve the long term prognosis of these patients.

Study objective: The aim of this study was to evaluate the relationship between non invasive vascular assessment (through AIx, cfPWV and CIMT) and SLE disease activity index.

Methods

We evaluated 53 patients with SLE, one year after the diagnosis, from Rheumatology department, Emergency County Hospital Craiova. Imagistic evaluation was performed in the Cardiology department of Emergency County Hospital Craiova. All of them have fulfilled the American College of Rheumatology revised criteria for SLE [11]. We excluded patients with cardiovascular disease, dyslipidemia and diabetes mellitus. All participants were assessed on a routine basis including history, BMI, blood pressure; we measured total cholesterol, tryglicerides, LDL and HDL-cholesterol and fasting blood glucose.

Disease activity was assessed by disease activity index (SLEDAI) [12]. Patients were

classified into SLEDAI groups: SLEDAI >8 (peristent active disease) and SLEDAI<8.

Arterial stiffness was assessed using applanation tonometry (SphygmoCor device, AtCor Medical, Sydney, Australia) and was quantified through the augmentation index (AIx), defined as the difference between the second and first systolic peaks, expressed as a percentage of the pulse pressure, and carotid to femoral pulse wave velocity (cfPWV); pulse waves were obtained consecutively from the carotid and femoral arteries and we measured the distance between the carotid and femoral artery. cfPWV represents the ratio between the distance (carotid-femoral) and the time difference between the carotid and femoral waveforms. For cfPWV normal values were defined <12m/s and the individual values of AIx varies from around −20% in young athletes to about 40% in elderly hypertensive patients [9].

CIMT was measured using a high resolution B-mode ultrasound (Prosound ALOKA CO., LTD) with a 10-MHz linear transducer. IMT was defined as the distance between the leading edge of the luminal eco to that of the media/adventitia echo. The site of the measurement was the common carotid artery, proximal of the bifurcation. We performed two measurements for the 2 carotid arteries (left and right), and we calculated the mean. ITM<0,9mm was defined as normal [13].

Over the past year, from the moment of diagnosis, all patients have received glucocorticoids with or without immunosuppressive agents, depending on the type and severity of clinical features.

The study performed according to the principles of the Declaration of Helsinki, was approved by the local ethics committee and written informed consents were obtained from all participants.

Statistical analyses: comparisons were made between the groups using x^2 statistic for categorical variables and 1-way analysis of variance for continuous variables. Continuous variables are expressed with the standard deviation as the index of dispersion and the standard error for ajusted means. Independence of association with arterial stiffness was performed by stepwise linear regression analysis.

Results

As expected, most of the patients were women (50, 94%), with a a mean age of 31,92 years (SD 5,55; limits 22-44), similar in women and men. The general characteristics of the patients are showen in table 1.

Assessment of subclinical atherosclerosis showed a mean CIMT of 0,9 mm (SD 0,035; 95%CI 0,892 - 0,912), a mean cfPWV of 9,443m/s (SD 0,4729; 95%CI 9,313 - 9,574) and a mean AIx of 30,93% (SD 7,61; 95% CI 28,825 - 33,24) (table 2).

Table 1 : General characteristics of SLE patients

	N	Mean	95% CI	SD	ESM	Median	Min	Max
BMI	53	22,524	21,878 - 23,171	2,3457	0,3222	22,1	18,5	29
SBP (mmHg)	53	117,547	113,945 - 121,149	13,0687	1,7951	120	95	140
DBP (mmHg)	53	66,321	64,332 - 68,310	7,2158	0,9912	65	55	85
HDLc (mg/dl)	53	59,472	56,722 - 62,221	9,9761	1,3703	60	30	76
LDLc (mg/dl)	53	86,34	82,315 - 90,364	14,601	2,0056	85	67	131
TG (mg/dl)	53	120,283	115,919 - 124,647	15,8337	2,1749	120	93	180
Glucose (mg/dl)	53	85,283	83,108 - 87,458	7,8896	1,0837	85	70	94
Hb (g/dl)	53	11,702	11,353 - 12,051	1,2673	0,1741	11,8	8,5	14,2
Le (/mmc)	53	3510,943	3325,592 - 3696,294	672,4532	92,3686	3200	2700	6100
Tr (/mmc)	53	186434	169687,541 - 203180,384	60755,98	8345,475	180000	85000	320000
TGO (U/L)	53	25,547	23,957 - 27,138	5,7698	0,7925	25	17	37
TGP (U/L)	53	25,774	24,314 - 27,233	5,2938	0,7272	27	15	37

BMI-body mass index; SBP systolic blood pressure; DBP-dyastolic blood pressure

Tabel 2: The mean values of subclinical atherosclerosis parametres

	Mean	95% CI	SD	ESM	Median	Min	Max
CIMT	0,902	0,892 - 0,912	0,03509	0,004819	0,91	0,79	0,96
cfPWV	9,443	9,313 - 9,574	0,4729	0,06496	9,6	8,1	10,2
AIxAo	30,925	28,825 - 33,24	7,6154	1,0461	29	18	49

SLEDAI had a mean value of 10,39623 (SD 7,142343; 95% CI 9,345-11,432), identyfing 22 (41,5%) patients with a persistent active disease (SLEDAI>8).

Correlations between SLEDAI and non invasive vascular assessments

Patients with persistent active disease had a mean AIx of 35,91% (SD 7,04; 95% CI 32,786 - 39,032), 1,31 times higher than the ones with SLEDAI<8 (27,39%; SD 5,89; 95% CI 25,228 - 29,546), statistical significant (p<0,001) (table 3) (figure 1). AIx was the only marker of subclinical atherosclerosis that moderately correlated with SLEDAI (r=0,46; IC95% 0,2134 - 0,6476; p<0,001), results confirmed by linear regression (r^2=0,21; F ratio=13,49; p=0,001) (table 4).

Table 3: The mean values of AIx in patients with SLEDAI>8/<8

	N	Mean	95% CI	SD	ESM	Median	Min	Max	P
SLEDAI >8	22	35,909	32,786 - 39,032	7,0435	1,5017	26	22	49	< 0,001
SLEDAI<8	31	27,387	25,228 - 29,546	5,886	1,0572	18	31	43	

Figure 1: Augmentation index in patients with SLEDAI>8/<8

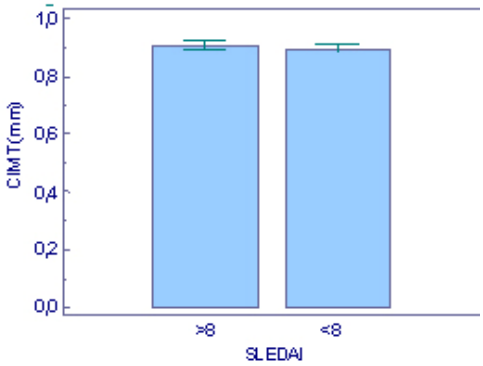

Table 4: ANOVA test for AIx in patients with SLEDAI >8/<8

Source of variation	Sum of squares	D.F.	Mean square
Between groups (influence factor)	934,5251	1	934,5251
Within groups (other fluctuations)	2081,173	51	40,8073
Total	3015,698	52	
F-ratio	22,901		
Significance level	P < 0,001		

Table 5: The mean values of cfPWV in patients with SLEDAI>8/<8

	N	Mean	95% CI	SD	ESM	Median	Min	Max	P
SLEDAI>8	22	9,523	9,342 - 9,703	0,407	0,08677	8,6	8,6	10,2	P=0,301
SLEDAI<8	31	9,387	9,199 - 9,576	0,5136	0,09225	8,1	8,1	10,2	

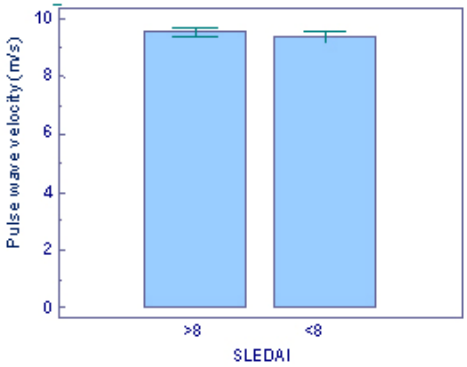

Figure 2: Pulse wave velocity in patients with SLEDAI>8/<8

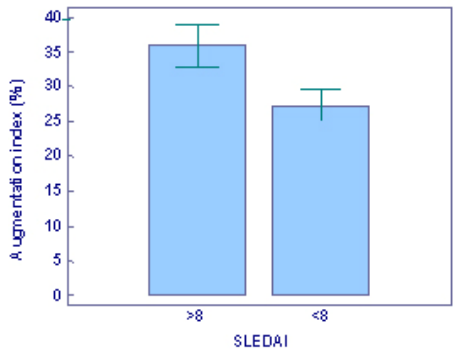

Figure 3: CIMT in patients with SLEDAI>8/<8

Table 6: The mean values of CIMT in patients with SLEDAI>8/<8

	N	Mean	95% CI	SD	ESM	Median	Min	Max	P
SLEDAI>8	22	0,909	0,895 - 0,923	0,03182	0,006783	0,9	0,85	0,96	0,242
SLEDAI<8	31	0,897	0,884 - 0,911	0,03699	0,006643	0,89	0,79	0,95	

Patients with SLEDAI>8 had a higher cfPWV 9,523m/s (SD 0,407; 95%CI 9,342-9,703), but not statistically significant (p=0,301), compared with the ones with SLEDAI<8 (table 5) (figure 2). SLEDAI was not correlated with cfPWV (r=0,06; 95%CI -0,2173 - 0,3217; p=0,6889).

Analysing the value of CIMT in patients with persistent active disease and the ones with SLEDAI<8, we found a value of 0,909mm (SD 0,03182; 95%CI 0,895-0,923) for the first group and 0,897mm (SD 0,03699; 95%CI95% 0,884-0,911) for the second group, with no significant differences (p=0,242) (table 6) (figure 3). There was no correlation between CIMT and SLEDAI (r=0,16; 95%CI-0,1156 - 0,4122; p=0,2535).

Disscution

This study confirmed the presence of subclinical atherosclerosis in patients with SLE and showed the relationship with disease activity.

Non-invasive measurement of PWV and AI may allow the early detection of increased arterial stiffness [14]. Disease flare may facilitate vascular damage through endothelial dysfunction, deposition of antigen antibody complex and vascular inflammation, which will decrease arterial compliance and increase the arterial impulse that transits across the artery. The amplified wave reflection will merge with the initial waveform in late systole, resulting an increase of AIx [15, 16]. Therefore, patients with a high disease activity causing persistent inflammation, will be liable to the development of arterial stiffening, which in turn will be a marker of end organ damage.

Although increase ITM and plaques are considered evidence of atherosclerosis, patients can have subclinical atherosclerosis, with increased arterial stiffness as illustrated by pulse wave velocity assessment. In patients with SLE, atherosclerosis and high prevalence of plaque have been previously reported [17] and in previous studies, including both SLE patients with inactive as well as active disease, IMT correlated with SLEDAI [18, 19]. In our study, increased CIMT was found in patients with active disease, but we failed to find a correlation between CIMT and SLEDAI, similar to the study of Maksimowicz-McKinnon et al [20].

Conclusion

The results of our study show that SLEDAI significantly correlated with AIx, suggesting that disease flare or aggravation may play a permissive role in vascular injury through vascular inflammation and endothelial dysfunction, which will decrease arterial compliance. Therefore patients with a high disease activity will be prone to the development of arterial stiffening, which in turn will be a marker of end-organ damage.

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