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MYOCARDIAL PERFUSION ABNORMALITIES IN YOUNG AND PREMENOPAUSAL WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS, DETECTED WITH 99MTC MIBI MYOCARDIAL PERFUSION SCINTIGRAPHY – PREVALENCE AND CORRELATION WITH PROATHEROGENIC FACTORS

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ABSTRACT

Introduction: Atherosclerosis in young and premenopausal women with systemic lupus erythematosus (SLE) is frequent, premature and progressive. Although asymptomatic or with atypical clinical presentation, the patients are at high risk of cardiac events. Aim of this study is to estimate the risk profile for atherogenesis and the prevalence of myocardial perfusion abnormalities with 99mTc myocardial perfusion scintigraphy (MPS) in young and premenopausal women.

Material and methods: Sixty female patients, aged 30-72 years (divided into two subgroups - patients under 45 years of age and patients over 45 years), diagnosed with SLE for over of 5 years, in active phase of the disease were analyzed for disease activity scores (SLEDAI), the immunologic status of the disease (ANA and a-DNA antibodies in the serum), procoagulant tendency (antiphospholipid antibodies -APhL and lupus-anticoagulant-LAC), the activity of the inflammatory process (hsCRP), the anti-SLE therapeutic approach and the presence of traditional risk factors for atherosclerosis (BMI, smoking, hypertension, hyperlipidemia, diabetes, and familial history for the CAD). Using one-day Dipyridamol – Rest 99mTc SPECT Gated MPS SPECT the extent, severity and reversibility of myocardial perfusion abnormalities were estimated, along with summed scores at stress, rest and summed difference scores and left ventricle volumes and ejection fraction.

Results: Abnormal MPS SPECT were detected in 27/60 or in 45% of patients, with one vessel affection of 66.7% (18/27pts) of LAD and 14.8% (4/27pts) o RCA and with two vessel disease of LAD/RCA in 2/27 pts (7.4%) and LAD/Cx in 3/27pts (11.1%). Myocardial perfusion abnormalities were equally prevalent in subgroups of patients younger than 45 years (44,4%) and in patients older than 45 years (45.5%) (ns). The subgroups did not differ significantly concerning the extent of perfusion abnormalities (9,8±3.2% of LV myocardial mass vs. 9,8±7.1%,ns), their severity (with predominance of mild perfusion defects, 48,6% vs. 51,3%,ns) and reversibility (reversible in 41.3% and 58.6%, ns). The differences between the summed scores of severity and the extent of ischemia in the two subgroups were statistically nonsignificant. Younger patients had significantly higher end-diastolic, end-systolic and stroke volumes during stress and rest conditions, compared to older patients ($p<0,01$) although there were no differences in systolic function, which was not affected in either of the groups as expressed threw ejection fraction.

Although nonsignificant, younger patients had higher values of hsCRP and higher procoagulant activity (positive aPhL, LAC) while they were with more active disease activity, with higher SLEDAI score compared to older patients ($p=0.028$). Higher SLEDAI score and LV volumes, especially EDV at stress were identified as predictor of abnormal MPS in younger groups and more aggressive multidrug anti SLE treatment as predictor of normal MPS.

Conclusion: The prevalence and characteristics of myocardial perfusion abnormalities in young SLE are equal as the same in older SLE patients, which indicates the presence of premature, accelerated athero-

sclerosis in young cohort of patients with SLE. Younger SLE patients with pure disease control (higher SLEDAI score, less aggressive treatment, high hsCRP values and pronounced procoagulant tendency) should undergo screening for myocardial perfusion abnormalities s using 99mTc MIBI MPS).

Keywords: young/premenopausal SLE patients, premature atherosclerosis, proatherogenetic risk factors, myocardial perfusion, myocardial perfusion scintigraphy

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a multisystem, chronic, inflammatory autoimmune disease that characteristically occurs in young women. The association of SLE with atherosclerosis has been recognized more than four decades ago, when Urowitz indicated myocardial infarction as the most common cause of late mortality in patients with SLE [1]. The prevalence of symptomatic patients with SLE and atherosclerosis in large number of prospective SLE cohort stydies is higher compared to their non-SLE peers. It varies from 6.6% [2], 8.3% [3] and 10.9% (4,), with the median age of the first coronary event (myocardial infarction, angina, sudden death) from 48-51 years after the mean 7-10 years duration of SLE. Thus, atherosclerosis in young and premenopausal women with SLE is very frequent, premature, progressive with atypical clinical presentation or asymptomatic. At the age of 35-44 years, they are in 5 to 6, up to 50 times higher risk of myocardial infarction than a group of women of similar age in the Framingham study. Two thirds of the first cardiac events after SLE diagnosis occur in women under 55 years of age [2, 5, 6].

Today, SLE is considered as a strong, independent risk factor for atherosclerosis. The pathophysiological mechanisms of its onset and unfavorable evolution have not been fully understood. The traditional risk factors for atherosclerosis (cigarette smoking, hypertension, dyslipidemia, obesity, diabetes mellitus, sedentary lifestyle) play significant, but not exclusive role in SLE-related atherogenesis. More likely, they promote accelerated atherosclerosis operating together with SLE- specific factors such as long duration, high disease activity, poorer immunosuppression and control of disease activity, imbalance of protective and proatherogenetic effects of anti-SLE medications, especially of corticosteroids, and others. They act through complex pathogenesis, with participation in immune mediated systemic inflammation and endothelial dysfunction, causing direct or indirect vascular damage and pronounced procoagulant tendency [7].

Recognition of the risk factors and early diagnosis of subclinical, premature atherosclerosis in young women with SLE are diagnostic challenge for which several diagnostic methods and biological markers-surrogates of atherosclerosis are proposed. This paper aimed to examine the prevalence of myocardial perfusion abnormalities in asymptomatic young women with SLE using the method of 99mTc MIBI myocardial perfusion scintigraphy in correlation with their risk profile for atherosclerosis.

MATERIAL AND METHODS

60 female patients (age range 30-72 years), with SLE (according ACR criteria), were enrolled the study. They were divided into two subgroups (a group of patients under 45 years of age - 27/60 and a group of patients over 45 years – 33/60)., with SLE (according ACR criteria), were enrolled the study. The inclusion criteria were: disease duration of more than five years and active phase of SLE, estimated with SLEDAI score system. Each patient was evaluated for the immunologic status of the disease (ANA and a-DNA antibodies in the serum), procoagulant tendency (antiphospholipid antibodies -APhL and lupus-anticoagulant-LAC), the activity of the inflammatory process (hsCRP), the anti-SLE therapeutic approach and the presence of traditional risk factors (BMI, smoking, hypertension, hyperlipidemia, diabetes, and familial history for the CAD).

All patients underwent one-day Dipyridamol – Rest 99mTc SPECT Gated Myocardial perfusion scintigraphy (Institute of Pathophysiology and Nuclear Medicine, University Clinic of Cardiology). After 24 hours withdrawal of cardi-

ologic therapy and refraining of caffeine content products, in fasting condition a dose of 300MBq of 99mTc MIBI was applied in patients at rest, followed by an ECG-synchronized SPECT acquisition of myocardial perfusion scans (rest study). According to one-day protocol a stress study was performed 3 hours later, using pharmacologic stressor Dipyridamol at dose of 0.56 mg/kg BM/4 min. at , After 3 hours, under blood pressure and ECG- monitoring, followed with injection of 600MBq of 99mTc MIBI and myocardial stress scan acquisition using the same acquisition mode. Myocardial perfusion scans were analyzed visually and with a 17-segment semi quantitative estimation of the relative accumulated radioactivity in the segments, expressed as a percentage in relation to the highest radiotracer acceptance, and then presented according to the score system, as a summarized stress score (SSS), summarized rest (SRS) and summarized differential scores (SDS): score 0 - normal perfusion with 75-100% accumulated radioactivity, score 1 - mild ischemia with 60-75%, score 2 - moderate ischemia with 50-65%, score 3 - severe ischemia with 30-50% and score 4- absent perfusion with, less than 30% of accumulated radioactivity). An abnormal perfusion scan was considered a scan with the presence of reversible perfusion defects, which confirmed the presence of stress-induced ischemia and fixed defects as a mark of a more pronounced myocardial hypo perfusion, persisting on both-rest and stress study. All the segments with attenuation phenomena and segments with reverse redistribution were excluded from the analysis. The ECG synchronized study (Gated modality) enabled the assessment of the functional status of the left ventricle, in stress and rest, through the following parameters: an ejection fraction (EF, normally above 65%), an end-diastolic volume (EDV), and an end- systolic volume (ESV) index of transient ischemic dilatation (TID, normal to 1.2).

Statistical analysis

Statistical analysis was performed utilizing SPSS Inc.Chigaco, IL, (version 15). Continuous variables were expressed as mean±SD, while categorical as absolute values and percentages. Chi square test for categorical and t-test for continuous variables, and non-parametric Fisher's exact and the Mann Whitney U test were used, respectively. Odds ratios were calculated and Mantel Haenszel OR estimate was used for determination of significance of OR. Correlations were presented threw correlation coefficients, uni/multivariate linear (for continuous) or logistic regression analyze (backword conditional) was utilized for identification of prediction variables. Significance was determined at the level of 0,05.

The design and the protocol of the study was previously approved by the Ethics Committee for Human Research at the Faculty of Medicine, University "St. Cyril and Methodius" in Skopje, and all the patients were familiar with the study objectives and protocol and gave their written consent.

RESULTS

A group of 60 female patients with SLE was analyzed, with mean age of the group 48.2 ± 11.6 years (30-72 years) and mean duration of the underlying disease of 16.5 ± 8.3 years (Table 1).For comparative purposes, the group is divided into a group of patients under 45 years of age - 27/60 (45% of patients) and a group of patients older than 45 years - 33/60 (55% of patients).The groups differed significantly for the mean age of 37 ± 4.5 years in the younger, compared with /instead of 57.4 ± 6.4 years in the older group, $p < 0.0001$ and the duration of SLE of 10.3 ± 4.4 years in the younger group, compared with / instead of 21 , 6 ± 7.2 years in the elderly group of patients, $p < 0.0001$.

All patients were in the active phase of the disease, according to the SLEDAI score, but it was significantly higher in younger group compared to the group of the elderly patients ($p < 0.047$ / 0.028), indicating their higher disease activity. Of all examined patients, 81.7% of the patients were positive for ANA and a-DNA, with no significant difference between the groups (87.9% in the group of elderly patients with OR 1.559, CI 95% 0,891-2.729, compared to 74.1% in younger patients). Notable, higher procoagulant tendency was found in younger patients – although not significant, but the positive aPhL and LAC were present in the higher percent of the patients in the younger group (63% with OR 1.229/1.451, CI 95% 0.824-2.048/0.907-2.319, vs 48,5%/42.4% in elderly patients). Additionally, they showed higher inflammatory activity according to hsCRP, as a biological marker of inflammation, which was higher in younger patients, again with no statistical significance. Corticosteroid therapy in combination with only one anti-SLE drug (dual therapy) was

Table 1. *Comparative presentation of proatherogenetic risk profile of the study group according to grouping variable - SLE related risk factors and traditional risk factors for atherosclerosis, in general and in younger (<45years) and older (≥45 years) group*

SLE-RELATED RISK FACTORS FOR ATHEROSCLEROSIS								
Variable	**Total of 60 pts (100%)**	**Group I 27 pts (<45y)**	**Group II 33pts (≥45y)**	**Sig**	**Sig Non-par. tests**	**OR**	**CI (95%)**	**Mantel Haenszel OR sig.**
SLEDAI	4.9±1.9	5.5±2.2	4.5±1.6	0.047	0.028			
ANA/a-DNA	49(81.7%)	20 (74.1%)	29(87.9%)	ns	ns	1.559 (GroupII)	.891-2.729	ns
Anti-PhL AB	33(55%)	17(63%)	16(48.5%)	ns	ns	1.299 (Group I)	.824-2.048	ns
Lupus anticoagulasa	31(51.7%)	17(63%)	14(42.4%)	0.092	ns	1.451 (Group I)	.907-2.319	ns
hsCRP	45.5±27.3	49.6±29.1	42.2±29.7	ns	ns			
Therapy protocol Cortico+1 more Cortico+2 more	 36 (61%) 23 (39%)	 12 (46,2%) 14 (53.8%)	 24 72,7%) 9 (27.3%)	 0,035	 0>039	 1.704 (Group I)	 0.974-2.981	 0.004
TRADITIONAL RISK FACTORS FOR ATHEROSCLEROSIS								
Variable	**Total 60 pts (100%)**	**Group I 27 pts (<45y)**	**Group II 33 pts (≥45y)**	**Sig**	**Sig Non-par. tests**	**OR**	**CI (95%)**	**Mantel Haenszel OR sig.**
Smoking	10(15.7%)	6 (22.2%)	4 (12,1%)	ns	ns			
HTA	30 (50%)	8 (29.6%)	22 66.7%)	0.004	0.005	2.375 (GroupII)	1.236-4.563	0.005
PVD	9 (15%)	3 (11,1%)	6 (18,2%)	ns	ns			
Family history	15 (25%)	2 (7.4%)	13 (39.4%)	0.004	0.005	4.167 (GroupII)	1.117-15.542	0.010
Menopause	25 (60%)	0	25 75,8%)	0,000	0,000			
DM	11 (18.3%)	5 (18.3%)	6 (18.2%)	ns	ns			
Obesity (BMI>30)	15 (25%)	6 (22.2%)	9 (27.3%)	ns	ns			
BMI	26.4±5.8	26.3±6.5	26.2±5.6	ns	ns			
HLP	23 (38.3%)	9 (33.3%)	14 42,4%)	ns	ns			
No of risk factors	2.3±1.7	1.4±1.1	2.9±1.7	0.000	0.001			

Legend: Anti PhL AB- antiphospholipid antibody; ANA/aDNA-antinuclear antibody, anti DNA antibody; BMI-body mass index; hsCRP-C reactive protein; DM-diabetes mellitus; HTA-arterial hypertension; HLP-hyperlipoproteinemia; PVD-peripheral vascular disease; SLEDAI-SLE Disease Activity Index
OR-odds ratio; CI-confidence interval

more frequently used in elderly patients, while younger patients were treated more aggressively, with corticosteroid therapy in combination with two or three more anti-SLE drugs(triple therapy) ($p < 0.05$) (Table 1).

All the examined patients were wihtout heart disease symptoms, without history of previous myocardial infarction or coronary intervention and without coronary arteries by-pass graft surgeries. 20/27 patients (74%) of younger patients and 25/33 (76%) of elderly patients had atypical symptoms of myocardial ischemia - chest discomfort, 4/27 (15%) of young patients, vs. 8/33 (24%) of the elderly patients had fatigue and 3/27 (11%) of young patients had dyspnea.

Considering the presence of traditional risk factors for atherosclerosis and the risk profile of younger versus older SLE patients, as expected, older SLE patients had longer disease duration, more severe risk profile with more CAD risk factors - with 2,375 OR for having hypertension, 4,167 OR for family history for CVD, for menopause ($p<0.005$, $p<0.0001$). The findings were confirmed with non-parametric (Mann-Whitney U, Kolmogorov-Smirnov, Independent samples median test, Independent samples Moses test) tests also, because of the relatively small sample size and large variance of most of the continuous variables which resulted with high standard deviation, although we observed no differences between mean and median for the afore mentioned variables. These findings were confirmed with correlation analysis between the age groups and the risk factors for atherosclerosis (Table 4a).

Table 4a. *Correlation of age subgroups with some risk factors for atherscleros*is

Age group I/II		SLE dur.	CRP	HTA	Familyhistory	Menopause	No of RF	Th triple
	Correlation	,369**	,367**	,369**	,367**	,764**	,400	-,393)**
	Signif. (2-tailed)	,004	,004	,004	,004	,000	,002	,002
	Df	60	60	60	60	60	57	60

In the general group, abnormal MPS SPECT or myocardial perfusion abnormalities were detected in 27/60 or in 45% of patients, with one vessel affection of 66.7% (18/27pts) of LAD and 14.8% (4/27pts) o RCA and with two vessel disease of LAD/RCA in 2/27 pts (7.4%) and LAD/Cx in 3/27pts (11.1%) (Table 2).

Table 2. *Comparative MPS SPECT parameters of the study group in general and and in younger (<45years) and older (≥45 years) group*

Variable	Total (100%)	Group I (<45y)	Group II (≥45y)	Sig	Sig Non-parametric
No of pts and percentage	60 (100%)	27 (45%)	33 (55%)	ns	ns
MPS SPECT					
• Normal	33 (55%)	15 (55.6%)	18 (54.5%)	ns	ns
• Abnormal	27 (45%)	12 (44.4%)	15 (45.5%)		
Abnormal MPS SPECT					
Extent of perfusion abnormalities:					
• LAD extent (%)	9.8±5.6	9.8±3.2	9.8±7.1	ns	ns
• RCA extent (%)	1.9±3.8*	0	3.5±4.6*	ns	ns
• Cx extent (%)	0.7±1.9*	0.5±1.7*	0.9±1.9*	ns	ns
*vs LAD (%)	*p<0.0001	*p<0.0001	*p<0.0001		
Severity of perfusion abnormalities					
• Mild	37/52(71.1%)	18/37(48.6%)	19/37(51.3%)		
• Moderate	14/52(26.9%)	6/14(42.8%)	8/14(57.2%)	ns	
• Severe	1/52 (1.9%)	0	1(100%)		
Reversibility of perfusion abnormalities (total of 52):					
• reversible	29/52(55.7%)	12/29(41.3%)	17/29(58.6%)		
• fixed	7/52(13.5%)	3/7(42.9%)	4/7(57.14%)	ns	
• reverse redistribution	14/52(26.9%)	9/14(64.3%)	5/14(35.7%)		
• diffuse inhomogeneity	2/52(3.8%)	0	2/2(100%)		
LAD severity					
• mild	25 (41.7%)	14(51.9%)	11/33(33.3%)		
• moderate	10 (16.7%)	6 (22.2%)	4 (12.1%)	ns	0.081
• severe	1 (1.7%)	0	1 (3%)		
LAD reversibility					
• reversible	18 (30%)	10 (37%)	8 (24.2%)		
• fixed	7 (11.7%)	3 (11.1%)	4 (12.1%)	ns	0.056
• reverse redistribution	11 (18.3%)	7 (25.9%)	4 (12.1%)		
RCA severity					
• **mild**	**8 (13.3%)**	**2 (7.4%)**	**6 (18.2%)**	**ns**	**0.043**
• **moderate**	**3 (5.0%)**	**0**	**3 (9.1%)**		
RCA reversibility					
• reversible	6 (10%)	0	6 (18.2%)		
• reverse redistribution	3 (5%)	2 (7.4%)	1 (3%)	0.050	0.062
• diffuse inhomogeneity	2 (3.3%)	0	2 (6.1%)		
Cx severity					
• mild	4 (6.7%)	2 (7.4%)	2 (6.1%)	ns	ns
• moderate	1 (1.7%)	0	1 (3.0%)		
Cx reversibility					
• reversible	5 (8.3%)	2 (7.4%)	3 (9.1%)	ns	ns
Quantitative analysis of MPS SPECT / Summed Severity and Extent scores					
SSS	3.1±2.2	2.2±0.6	3.7±2.8	0.067	ns
SRS	0.6±1.5	0.2±0.6	0.9±1.9	ns	ns
SDS	2.6±2.1	2.0±1.0	3.1±2.6	ns	ns
RV	26 (43.3%)	12 (44.4%)	14 (42.4%)	ns	ns
TID	1.1±0.2	1.0±0.1	1.1±0.2	ns	ns
LEFT VENTRICLE FUNCTIONAL PARAMETERS					
ESV stress ml	24.6±12.2	29.5±11.8	20.5±11.2	0.004	
EDV stress ml	83.6±26.2	95.0±24.7	74.3±23.9	0.002	
SV stress ml	59.1±16.1	65.6±14.9	53.8±15.2	0.004	
EF stress %	68±6	68±5	69±6	ns	
ESV rest ml	23.1±13.4	28.3±12.7	18.8±12.5	0.006	
EDV rest ml	79.1±28.5	92.1±24.3	68.1±27.3	0.001	
SV rest ml	56.1±19.3	64.0±16.6	49.3±18.9	0.003	
EF rest %	69±8	70±9	69±8	ns	

*Legend: *-extent of perfusion defect expressed as a % of left ventricular mass; MPS SPECT- myocardial perfusion imaging with single photon emission computed tomography; LAD-left anterior descending coronary artery; RCA-right coronary artery; Cx-circumflex artery; SSS-summed stress score; SRS-summed rest score; SDS-summed difference score; RV-right ventricle; TID-transitory ischemic dilatation; EDV-end-diastolic volume; ESV-end-systolic volume; SV-stroke volume; EF-ejection fraction*

Abnormal MPS SPECT was equally prevalent in subgroups of older (45.5%) and unexpected, in younger patients (44.4%). At the same time, the characteristics of perfusion abnormalities in groups of younger and elderly patients are very similar and listed in Table 2. The extent of perfusion abnormalities is most expressed for the vascular territory of LAD, both in the younger and older patients (ns). In terms of their severity, in general group there were the dominance of mild perfusion (71.1%) and much less moderate (26.9%) and severe abnormalities (1.9%). There were not statistically significant difference in the presence of mild, moderate and sever perfusion abnormalities in both subgroups. The same data are registered for the reversibility of the pathological changes. Separately observed, the vascular territories, abnormalities in the LAD territory dominate in younger patients (non-significant difference), and only statistically significant difference is in the elderly group of patients for the RCA territory. The summed scores of severity and the extent of ischemia in the two subgroups were statistically non-significant.

Patients from Group I (younger than 45 years), had significantly higher end-diastolic, and-systolic and stroke volumes during stress and rest conditions, compared to patients in Group II (older than 45y), although there were no differences in systolic function, which was not affected in either of the groups as expressed threw ejection fraction (Table 2) These findings are also confirmed with the correlation analysis (Table 4b) between the age groups and LV functional parameters, (Table 4b, Figure 1).

Table 4b. Correlation of age subgroups and LV functional parameters

Age group I/II	EDVs	ESVs	SVs	EFs	EDVr	ESVr	SVr	EF
Correlation Coefficient	-.428)**	-.400)**	-.387)**	-.048)	-.453)**	-.434)**	-.372)**	-.115)
Sig. (2-tailed)	.001	.002	.002	.715	.000	.001	.004	.386
df N	60	60	60	60	59	59	59	59

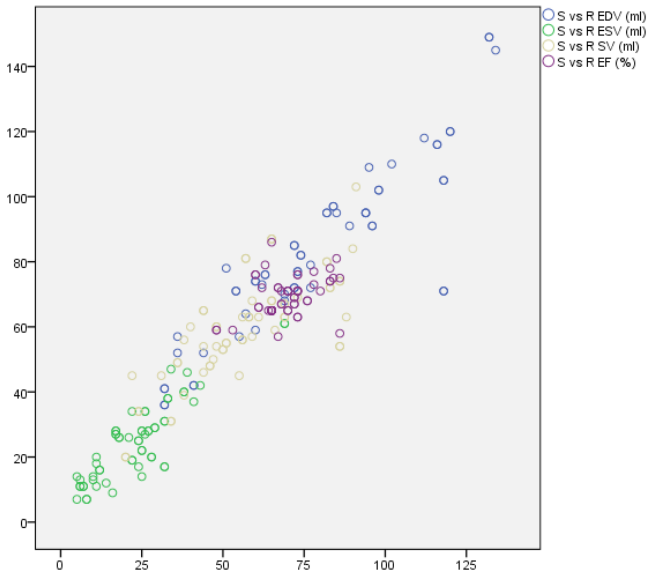

Figure 1. *Scatter plot-Overlay of correlations between LV functional parameters*

The relationship between the therapeutic approach - CS with 1 more (dual-therapy) or CS with 2 more (triple therapy) with anti SLE drugs is shown in Table 3. All our patients received corticosteroid therapy in combination with one, or two and three other DMD (disease modifying drugs). In the elderly group, 72.7% of patients received CS plus monotherapy, while younger subjects were almost equally treated with CS plus mono- and dual/ triple therapy (46.2% and 53.8%). But interesting results were found when we compared intensity of the medical treatment with the MPS results and age group. Younger patients with normal MPS study had 3,088 OR to be on combined CS plus dual/ triple therapy (p=0,047) or they were treated more aggressively. On the other hand, younger patients with pathological MPS were treated more frequently with less aggressive therapeutical approach, receiving CS plus monotherapy, although this data was not significant. (Table 3).

Table 3. Association between SLE therapy, age subgroups and MPS SPECT results

Variable	Total of 60 pts (100%)	Group I (<45y)	Group II (≥45y)	Sig	Sig	Odds Ratio	CI (95%)	Mantel Haenszel OR est.
No	60 (100%)	27 (45%)	33 (55%)	ns				
MPS SPECT • Normal • Abnormal	 33 (55%) 27 (45%)	 15 (55.6%) 12 (44.4%)	 18 (54.5%) 15 (45.5%)	 ns				
CS+1 more CS+2 more	36 (61%) 23 (39%)	12 (44.4%) 15 (55.5%)	24 (72.7%) 9 (27.3%)	0.035	0.039	1.704 (Gr.I/2)	0.974-2.981	 0.004
Normal MPS CS+1 more CS+2 more	33 (100%) 22 (66.7%) 11 (33.3%)	15 (45.5%) 4 (12.1%) 11 (33.3%)	18 (54.5%) 18 (54.5%) 0	 0.004		3.088 (Gr.I/2)	1.297-7.354	0.047
Abnormal MPS CS+1 more CS+2 more	27 (100%) 19 (70.4%) 8 (29.6%)	12 (44.4%) 9 (33.3%) 3 (11.1%)	15 (55.6%) 10 (37%) 5 (18.5%)	 ns		.842 (Gr.I/2)	.424-1.672	

Legend: OR-odds ratio; CI-confidence interval; MPS SPECT- myocardial perfusion scintigraphy with single photon emission computed tomography;CS-corticosteroids;1 or 2 more anti SLE drug

The association of SLE in the adult groups with SLE-related and traditional risk factors for atherosclerosis as well as the therapeutic approach was confirmed and by correlation analysis of these variables in age-related subgroups of patients (Table 4a).

Significant positive correlation with the significance at the level of 0,01 was found for Group II and disease duration, CRP levels, presence of arterial hypertension, family history for CAD, menopause and number of CAD risk factors, but negative correlation for multidrug therapeutical approach (triple therapy) which on the other hand, highly significant correlates with group of younger patients (Group I)

Highly significant negative correlation was observed for LV volume variables with patients age, at the level of 0,01 (Table 4b).

In univariate analyze (Table 5) we identified higher SLEDAI index, and higher LV volumes during stress and rest conditions as variables associated with young SLE patients (Group I). As opposite, more severe risk profile represented older SLE patients (Group II), with OR 4,7 for HTA, OR 8,1 for family history, and 6,0 OR to be on combination of CS+1 more anti SLE drug (dual) therapy. The only MPS SPECT perfusion parameter associated with Group II was RCA vascular territory perfusion severity defect.

Table 5. *Univariate variables associated with age subgroups of SLE patients*

Variable	Sig	Beta	OR	CI (95%)
Disease duration (y)	0.000	.294		
SLEDAI index	0.043	-.281		
HTA	0.005	1.558	4.750	1.584-14.245
Family history for CVD	0.010	2.095	8.125	1.639-40.268
Nr of risk factors	0.001	.679		
RCA severity	0.060	1.408		
CS+1 more (dual)	0.004	1.979	6.031	1.790-20.318
EDV s (ml)	0.005	-.036		
ESV s (ml)	0.008	-.072		
SV s (ml)	0.008	-.056		
EDV r (ml)	0.002	-.035		
ESV r (ml)	0.012	-.067		
SV r (ml)	0.006	-.046		

In the Multivariate Binary Logistic Regression Model (Backward Stepwise (Conditional), a prediction model with chi square 43.288, sig 0.000, with a percent of correct prediction of 83.1% was created out of eleven univariate predictors: SLEDAI index, therapeutic approach (dual or triple therapy) , number of CAD risk factors, HTA, family history, EDV, ESV and SV at stress and rest. Five out of eleven univariate predictors of abnormal MPS SPECT were identified: SLEDAI index higher in Group I (p=0.019), CS plus 1 more anti SLE drug (dual therapy) (p=0.003) and higher EDV at stress (p=0.024) in younger group (Group I), and arterial hypertension (p=0.004) and family history (p=0.054) for Group II (≥45y) (Table 6).

Table 6. *Independent predictors associated with age groups of SLE patients*

		B	Wald	Sig.	Exp(B)	95% C.I.for EXP(B)	
						Lower	Upper
Step 7[a]	SLEDAI	-.700)	5.493	.019	.496	.276	.892
	CS+2 more Triple approach	-3.646)	8.722	.003	.026	.002	.293
	HTA	3.340	8.448	.004	28.223	2.968	268.421
	Family history	2.328	3.708	.054	10.253	.959	109.589
	EDVs	-.056)	5.074	.024	.946	.901	.993
	Constant	11.449	7.577	.006	93796.733		

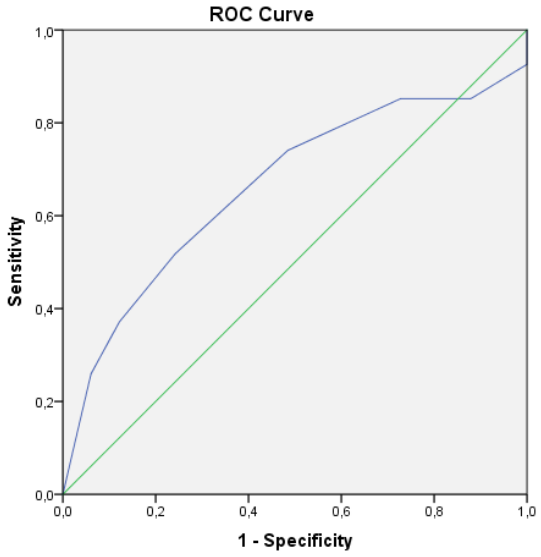

Figure 2. *ROC curve for SLEDAI index and Group I SLE patients*

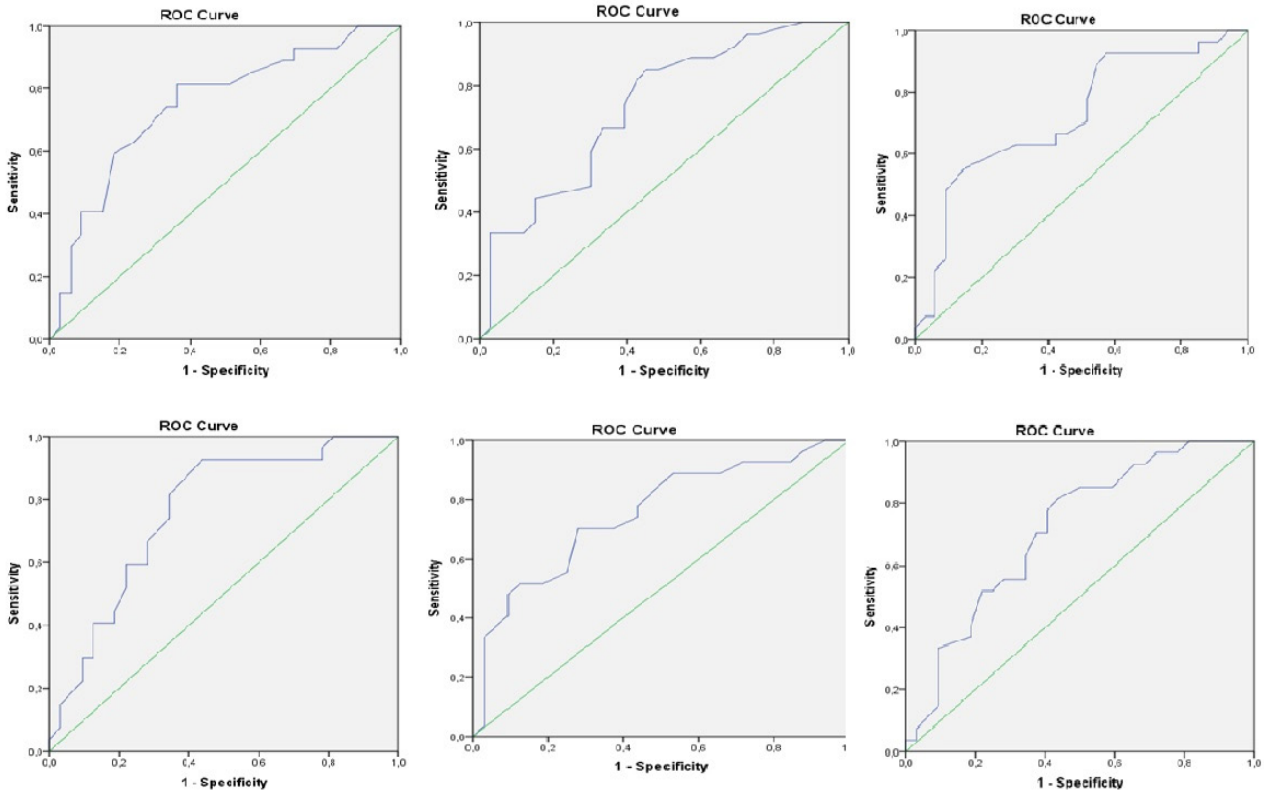

Figure 3. *ROC curve for LV end-diastolic, end-systolic and stroke volumes and Group I SLE patients*

As demonstrated, the ROC curve of SLEDAI index (Figure 2) has significant prediction capacity with area under the curve of ,663 (p=0,031), and 95% CI of ,519-,807.The same high statistical prediction power was demonstrated for all LV volumes (Figure 3). As demonstrated, the ROC curve of LV end-diastolic, end-systolic and stroke volumes in stress and rest are as follows: EDVs, area under the curve of ,748 (p=0,001), and 95% CI of ,622-,874; ESVs, area under the curve of ,732 (p=0,002), and 95% CI of ,605-,858; SVs, area under the curve of ,724 (p=0,003), and 95% CI of ,593-,856; EDVr, area under the curve of ,762 (p=0,001), and 95% CI of ,639-,886; ESVr, area under the curve of ,751 (p=0,001), and 95% CI of ,625-,878; SVr, area under the curve of ,715 (p=0,005), and 95% CI of ,585-,846.

DISCUSSION

The aim of our study was to evaluate the prevalence of myocardial perfusion abnormalities in patients with SLE, asymptomatic for coronary artery disease, in general and separately, in the subgroups of patients younger and older than 45 years. Having in mind the complex pathogenesis of atherosclerosis in SLE, we wanted to define the risk-profile for atherogenesis of the younger women with SLE and to identify SLE-related and the traditional risk factors for atherosclerosis, that in the routine rheumatologists' practice would help to stratify patients who are in risk of premature atherosclerosis and cardiac events, of which the most important would be premature myocardial infarction.

Considering risk profile of younger versus older SLE patients, as expected, older SLE patients had more severe risk-profile, with 2,3 OR for having hypertension, 4,1 OR family history for CAD, menopause, with more CAD risk factors, longer disease duration, as compared to their younger peers. There was no significant difference between the subgroups concerning the high values of hsCRP, as a biomarker of inflammation activity and high percent of patients with positive ANA,a-DNA, reflecting the high immunological activity of the disease. But, the overall disease activity measured through significantly higher SLEDAI score were observed in younger patients (p 0.047/0.028). The higher SLEDAI score in our young patients along with the higher values of hsCRP in sera and high

percent of patients with positive antibodies (although nonsignificant vs older patients) suggests a more accented immune- mediated inflammatory component within the SLE vasculopathy. These parameters in numerous studies have been recognized as significant SLE-related risk factors for atherogenesis [8, 9, 10, 11]. Moreover, an additional risk-factor in our young patients for atherosclerosis were identified – the higher percent of patients with positive aPhL antibodies and LAC, which may complicate the atherosclerosis increasing the risk of developing antiphospholipide syndrome, thrombogenesis, and thromboembolism. The latter is often confirmed in the literature as the SLE related risk factor for thrombogenesis superimposed with atherosclerosis [12, 13]. In the context of this, higher values of hsCRP, persistent immunological activity of the disease and accentuated procoagulant tendency stratified these young SLE patients to a group with high risk for myocardial infarct and other cardiac events. Such a risk profile in young patients requires more aggressive treatment of the underlying disease, which was proved in the study - unlike the older patient, the young patients more often were treated aggressively with more than 2 and/or 3 anti SLE medications, besides regular therapy with corticosteroids (CS). Overall, these SLE related factors of atherogenesis -high SLEDAI score and hsCRP, the type of anti SLE medications, less aggressive treatment with CS) alone, poor disease control, are distinguished in a number of studies as specific risk factors and promoters for atherosclerosis [8–13] in contrast to high-dose CS therapy, multidrug treatment of SLE, specifically chloroquine and hydrochloroquine, which give good control of the disease, especially the anti-inflammatory component, acting atheroprotective [14].

All the patients in our study were asymptomatic for CAD or with atypical chest discomfort, but taking into account their burdening with both types of risk factors, the pretest probability for having CAD stratified them into low to moderate risk for coronary atherosclerosis and myocardial perfusion abnormalities, indicating the evaluation of myocardial perfusion with 99mTc MIBI MPS SPECT.

The prevalence of myocardial perfusion abnormalities (abnormal MPS) in our study, both in the general group and in the subgroups of the younger and the older patients, is relatively high and coherent with other studies [15–27]. This prevalence is significantly higher than the calculated in the group of patients by gender and age, without SLE in the Framingham study [2, 5, 6], which confirms the fact that SLE is an independent strong, predictor of atherosclerosis.

Expected fact was the higher risk profile of older patients with SLE, as well as the higher number of proatherogenetic risk factors. But, it was surprising the prevalence of abnormal MPS in younger and older patient to be equal among the groups (44.4% vs 45.5%,ns), confirming unfavorable SLE-related risk factors rather than but along with traditional risk factors to participate in high prevalence of abnormal MPS in the younger patients. This percentage varies in the literature from 22,5-54,5%o [16, 17, 19, 23]. Similar to other studies, the dominant pattern of perfusion abnormalities in our patients, was the one-vessel affection, more frequently of LAD (with the significant extensity of the affected LAD region), in lesser percent of the RCA and rarely seen was the two-vessel damage which was in line with already published papers [18, 27].

Very similar to other studies were myocardial perfusion abnormalities - dominated mild and reversible perfusion defects [17, 18, 23, 27] with a lower incidence of moderate and fixed defects (in the absence of MI, they are associated with severe perfusion defects). We also separated the reverse redistribution defects with an unclear clinical significance, which in young patients are probably due to breast attenuation effects. What must be emphasized is that besides the fact that the MPS findings in young are equally represented as those in the older, they showed identical characteristics in terms of extent, severity and reversibility, expressed through the quantitative indicators (SSS, SRS, SDS) which confirm the premature and progressive atherosclerosis and myocardial perfusion alteration in young SLE patients. The only more representative ischemia in older patients was noticed in the RCA territory, with the borderline significance of the small specimen. Neither one of our patients did not meet the MPS criteria for coronary angiography, so it cannot be claimed whether the changes are due to the microcirculation dysfunction, or the presence of an obstructive CAD. Literature confirms the microcirculation damage over the obstructive coronary disease [16, 21, 26]. Nevertheless, Sella et al. [18] suggested to use myocardial scintigraphy for screening the patient with SLE and to perform coronary angiography in co-

existence of perfusion abnormalities plus at least four traditional risk factors.

Considering left ventricular (LV) functional parameters our study showed very interesting results. Namely, patients from younger group, had significantly higher end-diastolic, end-systolic and stroke volumes during stress and rest conditions, as compared to older patient group, although there were no differences in systolic function which was not affected in either of the groups as expressed threw ejection fraction. This type of findings is supported by the fact that SLE and other systemic diseases typically develop diastolic dysfunction due to increased stiffness of the myocardium, that over time results with decreasing of end-diastolic volumes, but for a long period of time the systolic function (expressed threw ejection fraction) is preserved. In this phenomenon of higher LV volumes in young patients participate also and more aggressive treatment with CS and volume preloading as well diastolic dysfunction in the older patients with the higher presentation of hypertension, which also increases the stiffness of the myocardial muscle of the LV.

The comparative analysis of some of the SLE-related risk factors for atherosclerosis and the traditional risk factors for CAD in the group of younger and older patients (Table 1, 2 and 3), was confirmed also with the correlation analysis (Table 4a and 4b) – significant positive correlation with the significance at the level of 0,01 was found for older group of patients and disease duration, hsCRP levels, presence of arterial hypertension, family history for CAD, menopause and number of CAD risk factors, while negative correlation for multidrug therapeutical approach (CS plus 2/3 more) highly and significantly correlates with the group of younger patients (Table 4a). Indeed, in the subgroup of younger patients with abnormal MPS, less aggressive dual therapy (CS plus 1 more) was applied and less often the patients were treated with aggressive therapy (CS plus 2 and/or 3 anti SLE drugs). It could explain the higher presentation of perfusion abnormalities in young patients, similar to those in older patients. One can only speculate that more aggressive medical treatment can predict preserved myocardial perfusion at the level of microcirculation [14]. Highly significant negative correlation was observed for LV volume variables with patients age, at the level of 0,01, as well (Table 4b). Our study aimed to define the predictors of the pathological MPS in the younger and the older patients with SLE (Table 5 and Table 6). With univariance regression analysis variables as SLEDAI score values and higher LV volumes, both in resting and in stress were identified as associated with the young SLE patient. Multivariate regression analysis identified five independent predictors of abnormal MPS SPECT: higher SLEDAI score, triple drug therapy (CS + 2 drugs) and higher EDV in stress. In different studies different predictors of pathologic MPS in patients with SLE are defined. Some of them are in agreement with our data [18, 22, 25] some of them are not [15, 17, 22] which mean that the conduction of more, preferably multicentric evidence-based studies with larger patients samples are needed and strongly recommended.

CONCLUSION

The study demonstrated relatively high prevalence of myocardial perfusion abnormalities in patients with SLE in general, especially and unexpected for the age – equaly high in younger and premenopausal patients with SLE compared with the older patients. SLE significantly participates in the development of premature accelerated atherosclerosis through its disease-related risk factors.

In the daily / routine practice of rheumatologists, there is a need for assessing the risk of atherogenesis and screening of atherosclerosis in SLE patients, by defining potential risk factors and biomarkers - surrogates of atherosclerosis, available from the clinical examination and laboratory tests in regular checkups – SLEDAI score, status of the immune system, procoagulant tendency, inflammatory activity followed through hsCRP as well as the presence of traditional risk factors for atherosclerosis. MPS can be used as a screening method for detection and qualification of myocardial perfusion abnormalities in young patients with SLE and in order for better stratification of the risk of these patients with heart disease, especially myocardial infarction. Timely and adequate treatment of high risk patients would contribute to the decreased mortality from early MI of the patients with SLE.

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Резиме

АБНОРМАЛНОСТИ ВО МИОКАРДНАТА ПЕРФУЗИЈА КАЈ МЛАДИ И ПРЕМЕНОПАУЗАЛНИ ЖЕНИ СО СИСТЕМСКИ ЛУПУС ЕРИТЕМАТОСУС, УТВРДЕНА СО 99MTC МІВІ МИОКАРДНА ПЕРФУЗИОНА СЦИНТИГРАФИЈА – ПРЕВАЛЕНЦА И КОРЕЛАЦИЈА СО ПРОТАЕРОГЕНЕЗНИ ФАКТОРИ

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Вовед: Атеросклерозата кај млади и кај пременопаузални жени со системски лупус еритематозус (СЛЕ) е честа, предвремена и прогресивна. Иако асимптоматски или со атипична клиничка презентација, пациентите се со висок ризик од кардијални настани. Целта на студијата е да го процени ризикот за атерогенезата и преваленцата на абнормалностите кај миокардната перфузија со 99mTc миокардна перфузиска сцинтиграфија (МПС) кај млади и пременопаузални жени.

Материјал и методи: Шеесет женски пациенти, на возраст од 30 до 72 години (поделени во две подгрупи: пациенти под 45-годишна возраст и група пациенти над 45-годишна возраст), дијагностицирани со СЛЕ во текот на пет години, во активната фаза на болеста се анализирани за активност на болеста (SLEDAI), имунолошки статус на болеста (ANA и a-DNA антитела во серумот), прокоагулантната тенденција (антифосфолипидни антитела – AFL и лупус-антикоагулант-LAC), активност на воспалителниот процес (hsCRP), терапевтски пристап против СЛЕ и присуство на традиционални фактори на ризик за атеросклероза (BMI, пушење, хипертензија, хиперлипидемија, дијабетес и фамилијарна историја за КАБ). Користејќи еднодневен дипиридамол – rest 99mTc SPECT Gated MPS SPECT, беа проценети степенот, тежината и реверзибилноста на абнормалностите на миокардната перфузија, заедно со резултатите при стрес, одмор, како и волуменот и ежекционата фракција на левата комора.

Резултати: Абнормални MPS SPECT беа откриени кај 27/60 или кај 45 % од пациентите со едносадовно зафаќање од 66,7 % (18/27 пац.) на LAD и 14,8 % (4/27 пац) на RCA и со двосадовно зафаќање на LAD/RCA кај 2/27 пациенти (7,4 %) и LAD/Cx кај 3/27 пациенти (11,1 %). Абнормалностите во миокардната перфузија подеднакво се распространети кај подгрупите на пациенти помлади од 45 години (44,4 %) и кај пациенти постари од 45 години (45,5 %) (нс). Нема значителна разлика кај подгрупите во однос на степенот на абнормалностите во перфузијата (9,8 ± 3,2 % од LV миокардна маса наспроти 9,8 ± 7,1 %, ns), тежината на дефектите (со доминација на благи перфузиски дефекти, 48,6 % vs 51,3 %, нс) и реверзибилност (реверзибилна кај 41,3 % и 58,6 %, ns). Разликите меѓу збирните резултати на тежината и степенот на исхемија во двете подгрупи беа

статистички незначајни. Помладите пациенти имаа значително повисоки енд-дијастолни, енд-систолни и ударни волумени во услови на стрес и одмор, во споредба со постари пациенти ($p < 0,01$), иако нема разлики во систолната функција, односно не е засегната ниту една од групите како што е изразено кај нивната ежекциона фракција.

Иако незначителни, помладите пациенти имаа повисоки вредности на hsCRP и повисоки прокоагулантни активности (позитивен aPhL, LAC) додека беа со поизразена активност на болеста, со повисоки SLEDAI скорови во споредба со постарите пациенти ($p = 0,028$). Повисоки SLEDAI скорови и волумените на ЛК, особено ЕДВ при стрес, се идентификувани како индикатор за абнормални МПС кај помладите групи и поагресивен третман со комбинација на повеќе лекови за СЛЕ како индикатор на нормален МПС.

Заклучок: Преваленцата и карактеристиките на абнормалностите на миокардната перфузија кај младите пациенти со СЛЕ се исти како кај постарите пациенти со СЛЕ, што укажува на присуство на предвремена, забрзана атеросклероза кај младата група на пациенти со СЛЕ. Помладите пациенти со СЛЕ со добра контрола на болеста (повисок SLEDAI скор, помалку агресивен третман, високи вредности на hsCRP и изразена прокоагулантна тенденција) треба да бидат подложени на скрининг за абнормалности на миокардијална перфузија со употреба на 99mTc MIBI MPS.

Клучни зборови: млади/пременопаузални пациенти со СЛЕ, предвремена атеросклероза, проатерогенезни фактори на ризик, миокардна перфузија, миокардна перфузиона сцинтиграфија