ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Carotid intima-media thickness and plaque as surrogate biomarkers of atherosclerosis among consecutive women with systemic lupus erythematosus

CODRUŢA BELIBOU[1,2], CODRINA ANCUŢA[1,3], E. ANCUŢA[4], CRISTINA FILOŞ[5], RODICA CHIRIEAC[1,3]

[1]*Department of Rheumatology, "Grigore T. Popa" University of Medicine and Pharmacy, Iassy*
[2]*Research Department*
[3]*Department of Rheumatology Rehabilitation Hospital, Iassy*
[4]*Research Department, "Cuza-Vodă" Hospital, Iassy*
[5]*Department of Neurology, Rehabilitation Hospital, Iassy*

Abstract

Background: In recent years, there has been a growing interest in understanding the pathogenic pathways of premature accelerated atherosclerosis (AS) in systemic lupus erythematosus (SLE). However, the role of both traditional and non-traditional, SLE-specific risk factors is still under debate. *Aim*: To assess surrogate biomarkers of subclinical AS in SLE and to evaluate potential relations with cardiovascular risk factors. *Patients and Methods*: Prospective observational study on 35 consecutive SLE women (ACR 1987 diagnostic criteria) evaluated according to a standard protocol including traditional cardiovascular risk factors (hypertension, obesity, diabetes mellitus, cigarette smoking, abnormal lipid metabolism), SLE-specific risk factors (renal disease, SLE activity and duration, corticosteroid therapy) and surrogate biomarkers of subclinical AS (carotid intima-media thickness, plaque) (B-mode color Doppler ultrasound, 7–10 MHz probe). Data were analyzed in SPSS 16 software, $p<0.05$. *Results*: Significant differences ($p<0.05$) among subgroups (with and without plaque, thickened and normal intima) have been registered; moreover, statistical significant correlations between cIMT and age ($r=0.476$), age at onset ($r=0.451$), VLDL ($r=0.382$), hsCRP ($r=0.436$), Framingham score ($r=0.421$) have been reported. In addition, significant association between homocysteine and SLE-duration ($r=0.460$), SLEDAI ($r=0.466$), SLICC/ACR ($r=0.846$) has been demonstrated, while hsCRP was associated with ESR ($r=0.472$), C3 ($r=0.396$), SLEDAI ($r=0.569$) and age ($r=-0.681$). Several predictors for increased cIMT have also been identified (ANOVA): hsCRP ($p=0.016$), VLDL ($p=0.037$), Framingham ($p=0.012$). *Conclusions*: Our data advocate for increased cardiovascular burden in SLE and support the value of cIMT and carotid plaque as surrogate AS biomarkers in women with SLE.

Keywords: systemic lupus erythematosus, atherosclerosis, surrogate biomarkers, carotid intima-media thickness, carotid plaque.

Introduction

Patients with systemic lupus erythematosus (SLE) have a significantly increased risk of cardiovascular morbidity and mortality, particularly related to premature atherosclerosis (AS) [1–6]. Since the first recognition of high cardiovascular disease and the bimodal pattern of mortality in patients with SLE [7], major advances in the comprehensive understanding of the pathways of AS have been made [1, 3, 6]. Nowadays is widely accepted that accelerated AS in SLE is attributed to traditional and non-traditional, SLE-specific, risk factors [1, 2, 3, 6]. Although traditional cardiac risk factors as defined by the Framingham Heart Studies [3], such as older age, high blood pressure (BP), high cholesterol and triglycerides, smoking, obesity, diabetes mellitus, appear to play a critical role in the determinism of AS, these factors alone cannot adequately explain the increased incidence of cardiovascular disease commonly reported in patients with SLE [1, 3]. Moreover, recent data definitely support that both inflammation and immune response are highly involved not only in the development but also in progression of AS plaques [3].

Accordingly, early accelerated AS in SLE is the result of a complex cross-talk between traditional cardiac risk factors and SLE-driven inflammation [1, 3, 4].

Non-invasive measures to assess and follow subclinical AS, as recommended by the *American Heart Association*, are based on two main parameters, intima-media thickness (cIMT) and plaque, assessed by B-mode ultrasound at the carotid artery level [1–5].

Despite recent achievements in defining risk factors for subclinical AS and for the progress of preclinical AS associated with SLE [1, 2, 4, 5], the role of individual traditional and non-traditional risk factor in SLE is still controversial.

The main outcomes of our study were to assess surrogate biomarkers of subclinical atherosclerosis in SLE and to evaluate potential relations with traditional and non-traditional cardiovascular risk factors.

Patients and Methods

We have performed a prospective observational study on 35 consecutive women with SLE (1987 *American College of Rheumatology* diagnostic criteria) seen at the Division of Rheumatology, Clinical Rehabilitation Hospital, Iassy, Romania, between July 2011 and January 2012.

Patients have been evaluated according to a standard protocol including (i) *traditional cardiovascular risk factors*: hypertension, obesity, diabetes mellitus, cigarette smoking, aberrant lipid metabolism based on abnormal total cholesterol (TC) and its fractions (high density and low density lipoproteins) (HDL- and LDL-cholesterol) (spectrophotometric enzymatic-colorimetric method), triglycerides (TG), very low density lipoproteins (VLDL), apolipoprotein A1 (apo-A1) (1.08–2.25 g/L, immunoturbidimetry), atherogenic index (AI) (calculated as log(TG/HDL-Cholesterol) [8] and familial history of cardiovascular disease; (ii) *non-traditional (SLE-specific) risk factors* including renal disease, SLE activity and duration, corticosteroid therapy; (iii) *surrogate biomarkers of subclinical atherosclerosis* (cIMT, plaque). *Novel biomarkers of AS* such as homocysteine (chemiluminescent immunoenzymatic method, 5–12 μM/L) and high sensitivity (hsCRP) (latex-immunoturbidimetric method: <1 mg/L low risk, 1–3 mg/L medium risk, and >3 mg/L high risk) have also been collected in all patients.

Duplex carotid-intima color Doppler ultrasound (Siemens Acuson X300, 7 MHz linear probe) has been performed by the same examiner; measurements have included the carotid intima-media thickness (cIMT) and carotid plaques. cIMT was assessed at three levels on each side: common carotid artery (10 mm before the bulb), bulb (5–10 mm cranially to the start of the bulb) and internal carotid artery (10 mm after the flow divider); mean cIMT (m-cIMT) was defined as the mean of the three cIMT measurements on each side, while the maximum cIMT, the highest cIMT value found among the six segments studied [9]. According to current sonographic criteria, we refer to "normal" cIMT when complex intima-media is $\leq$0.9 mm; the cIMT>0.9 mm was considered indicative of thickened intima, while >1.3 mm indicative of atherosclerotic plaque [4, 9]. In addition, the number and size of carotid AS plaques have also been assessed.

The study was approved by the local ethics committee; all patients gave written informed consent before enrollment in the study.

Statistical analysis was done in SPSS 16 software (non-parametric tests, univariate analysis, ANOVA), $p<0.05$.

Results

Basic characteristics of the patients

Clinical and biochemical parameters and cardiovascular risk factors of SLE patients are summarized in Table 1.

Table 1 – *Basic characteristics of SLE patients*

Parameter	Value
Demographics and SLE-related	
Age at entry [years]*	47.66±11.26 (20–68)
Age at diagnosis [years]*	41.66±11.53 (16–65)
SLE duration [years]*	6.43±4.70 (1–15)
Traditional cardiovascular risk factors	
BMI [kg/m^2]*	24.64±5.57 (18.4–47.2)
Hypertension [%]	40
Systolic BP [mmHg]*	137.29±24.53 (110–200)
Diabetes mellitus [%]	5
Total cholesterol [mg/dL]*	203.83±40.09 (132–308.01)
LDL cholesterol [mg/dL]	117.03±25.41 (80.07–174.24)
HDL cholesterol [mg/dL]	64.78±19.35 (29.39–113.90)
VLDL [mg/dL]	19.89±8.96 (9.54–49.43)
Triglycerides [mg/dL]	107.87±60.17 (47.73–314.80)
Apolipoprotein A1 [g/L]	1.68±0.32(0.98–2.72)
Homocysteine [μM/L]	16.70±11.75(8.4–50)
hsCRP [mg/L]	4.51±8.13 (0.53–32.60)
Non-traditional SLE-specific risk factors	
Renal disease – proteinuria [%]	14.3
SLE disease activity [SLEDAI]	7.71±7.01(0–28)
SLE duration	7.00±5.14 (1–15)
Corticosteroid therapy [years]	2.66±2.48 (0–10)
ESR [mm/hour]	22.45±10.86 (5–40)
C3 [mg/dL]	101.03±24.97 (56–176)
dsDNA ab [UI/mL]	26.07±49.80 (0–245)
ACL antibodies [GPL/mL]	5.48±9.87 (2-50)
Surrogate biomarkers for subclinical AS	
Intima-media thickness [mm]	0.89±0.16 (0.6–1.3)
Carotid plaque [%]	31.4

*Mean±SD.

Traditional risk factors

The study of traditional risk factors in our SLE patients has shown the presence of hypertension in 40%, obesity in 14.3% of cases, mixed dyslipidemia in 11.4% of cases, mainly based on hypercholesterolemia (48.6%) with high LDL (76.7%) and high VLDL levels (13.3%), but also on high triglycerides (17.1%) and apo-A1 (6.7%); the majority of SLE (85.7%) displayed a low cardiovascular risk as appreciated by the atherogenic index (values under 0.11). In addition, familial history of cardiovascular disease has been reported in more than half of patients (54.3%).

High levels of novel biomarkers for AS have been demonstrated in 60% cases for homocysteine (mean value of 16.70±11.75 μM/L) and in 56.7% cases for hsCRP (mean value of 4.51±8.13 mg/L); 26.7% of SLE presented with increased hsCRP (>3 mg/dL) meaning high cardiovascular risk, 30% moderate risk (hsCRP between 1 and 3 mg/dL), while 43.3% a low cardiovascular risk.

Both Framingham – general cardio-vascular disease score assessing the 10-years risk and SCORE (Systematic COronary Risk Evaluation, The European cardiovascular disease risk assessment model) were evaluated in all patients; the majority (91.4%) of our consecutive SLE presented low Framingham scores (<10%) (mean Framingham of 3.36±3.22), while only 8.6% scores between 10–20; no patient featured high cardiovascular risk according to Framingham score.

SLE-specific factors

Several non-traditional, SLE-specific risk factors

have also been identified comprising disease activity (mild – 31.4%, moderate – 28.6%, high – 17.1%, extremely high – 8.6% SLEDAI, with a mean value of 7.71±7.01) and damage scores (mean SLICC/ACR score of 1.51±1.14); proteinuria was reported in 14.3% cases, while high levels of double stranded DNA (dsDNA) antibodies in 37.1% (mean value 26.07±49.80 UI/mL) and low C3 levels in 43.1% of cases (mean values 101.03±24.97 mg/dL).

Surrogate biomarkers for subclinical AS

Carotid ultrasound has shown a thickened intima (Figures 1 and 2) in half of cases (51.4%, mean value for cIMT of 0.89±0.16 mm), while carotid plaques have been demonstrated in 31.4% of SLE (Figure 3). Additionally, one carotid plaque has been reported in up to 20% of women with SLE, while two plaques have been counted in 11.4% of cases.

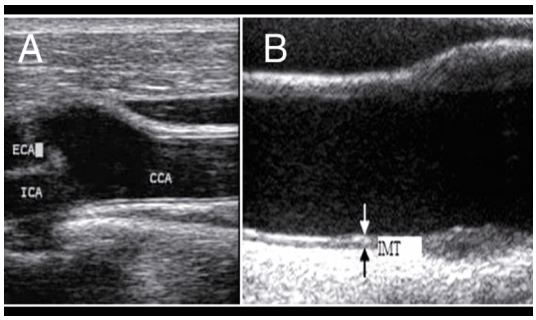

Figure 1 – ***Carotid ultrasound (Siemens Acuson X300, 7 MHz linear probe) in a SLE patient: (A) Sites of evaluation (common carotid artery – CCA, internal carotid artery – ICA, external carotid artery – ECA); (B) Normal cIMT.***

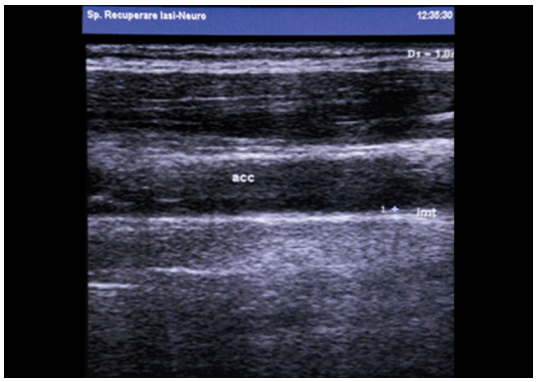

Figure 2 – ***Carotid ultrasound (Siemens Acuson X300, 7 MHz linear probe) in a SLE patient: thickened cIMT (1 mm).***

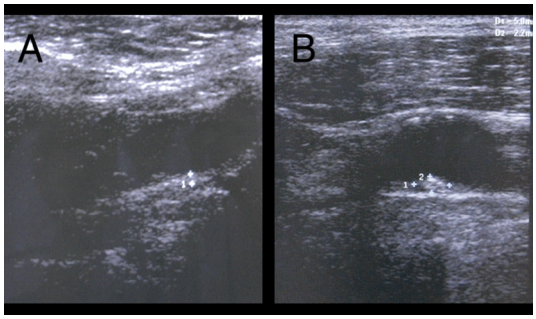

Figure 3 – ***(A and B) Carotid ultrasound (Siemens Acuson X300, 7 MHz linear probe) in a SLE patient: plaques.***

Analysis of risk factors

Subgroup analysis of various traditional and non-traditional risk factors has revealed their contribution to the development of accelerated AS in our SLE (Table 2).

Table 2 – ***Univariate analysis of risk factors for AS in consecutive women with SLE***

Risk factors	Thickened intima		Carotid plaque	
	Yes (0.9–1.3 mm) (n=18)	*No (≤0.9 mm) (n=17)*	*Yes (n=11)*	*No (n=24)*
Traditional factors*				
Age [years]	51.28 (10.16)	43.82 (11.37)	53.55 (9.45)	44.96 (11.15)
Age at SLE-onset [years]	43.39 (10.21)	39.82 (12.84)	48.82 (11.11)	38.38 (10.35)
Systolic BP [mmHg]	141.39 (24.18)	132.94 (24.87)	138.18 (27.77)	136.88 (23.53)
Total cholesterol [mg/dL]	206.21 (31.53)	201.31 (48.43)	197.86 (41.58)	206.56 (39.99)
HDL-cholesterol [mg/dL]	62.98 (14.99)	66.68 (23.44)	61.13 (18.92)	66.45 (19.71)
LDL-cholesterol [mg/dL]	119.20 (26.26)	115.12 (25.34)	109.71 (27.34)	120.68 (24.27)
Triglycerides [mg/dL]	119.34 (56.96)	95.72 (62.78)	131.93 (72.59)	96.84 (51.55)
VLDL [mg/dL]	23.89 (10.47)	16.40 (5.67)	22.88 (8.44)	18.40 (9.04)
Apolipoprotein A1 [g/L]	1.72 (0.15)	1.64 (0.43)	1.75 (0.38)	1.64 (0.30)
Atherogenic index (AI)	-0.09 (0.26)	-0.22 (0.25)	-0.06 (0.28)	-0.20 (0.24)
Homocysteine [μM/L]	12.31 (4.08)	19.63 (14.30)	13.05 (4.62)	18.27 (13.60)
hsCRP [mg/L]	2.20 (1.68)	6.54 (10.77)	2.03 (2.17)	5.75 (9.69)
SLE-specific factors*				
SLE duration [years]	7.17 (4.81)	5.65 (4.59)	4.00 (3.79)	7.54 (4.72)
SLEDAI	5.56 (3.48)	10.00 (9.00)	7.82 (8.17)	7.67 (6.61)
SLICC/ACR	1.67 (1.02)	1.35 (1.27)	1.82 (1.25)	1.38 (1.09)
C3 [mg/dL]	97.00 (28.25)	105.29 (20.96)	103.00 (30.16)	100.13 (22.88)
dsDNA ab [UI/mL]	20.51 (33.52)	31.95 (63.28)	28.50 (35.12)	24.95 (55.90)
ACL antibodies [GPL/mL]	3.72 (6.44)	7.01 (12.13)	2.00 (0.00)	7.22 (11.80)
Corticosteroid therapy [years]	3.50 (2.93)	1.76 (1.52)	2.55 (1.03)	2.71 (2.94)
Cardiovascular risk score*				
Framingham	4.33 (3.21)	2.94 (3.17)	4.27 (3.43)	3.38 (3.16)
SCORE	1.39 (1.85)	1.41 (2.67)	1.91 (1.92)	1.17 (2.39)

*Mean±SD.

Significant differences (p<0.05) among patients with and without plaque and with thickened and with normal intima have been registered: (i) age, systolic BP, TG, VLDL, atherogenic index, homocysteine and hsCRP, anticardiolipin (ACL) antibodies and anti-dsDNA antibodies, C3 levels, SLEDAI and corticosteroid therapy duration based on cIMT, and (ii) age at onset, TG, VLDL and atherogenic index, homocysteine and hsCRP, SLE duration, ACL and anti-dsDNA antibodies in subgroups based on plaque presence.

We have also demonstrated significant associations between plaque or thickened intima, respectively, and

certain CVD risk factors. Therefore, statistical significant correlations between *cIMT* and age (r=0.476, p=0.04), age at SLE onset (r=0.451, p=0.007), VLDL (r=0.382, p=0.37) and hsCRP (r=0.436, p=0.016) have been reported; the same direct correlation was reported with Framingham score (r=0.421, p=0.012). In addition, Framingham score was significantly associated with two traditional CVD risk factors, age at onset and systolic BP respectively (r=0.603 and r=0.610, respectively, p=0.000), but also with SCORE (r=0.821, p=0.000). Other two SLE-specific parameters have been associated with Framingham including disease duration (r=0.359, p=0.034) and corticosteroid duration (r=0.451, p=0.007).

Novel biomarkers of CVD risk in SLE patients have also been investigated, supporting the significant association between homocysteine level and SLE-duration (r=0.460, p=0.041), disease activity (SLEDAI) (r=0.466, p=0.038) and damage scores (SLICC/ACR) (r=0.846, p=0.00). Moreover, hsCRP was associated with ESR (r=0.472, p=0.008), C3 levels (r=0.396, p=0.03), SLEDAI (r=0.569, p=0.001) and age (r=-0.681, p=0.000).

Linear regression has demonstrated several *predictors for increased cIMT*, such as hsCRP (ANOVA, F=6.559, p=0.016), VLDL (p=0.037, F=4.794, t=2.190) and Framingham score (p=0.012, F=7.120, t=2.668). Conversely, no other traditional (apo-A1, TC, TG, HDL, AI, homocysteine) and non-traditional (SLEDAI, SLICC/ACR, corticosteroid duration, anti-double stranded DNA and C3 levels) risk factors have been demonstrated as predictors for thickened intima.

Discussion

Our study was designed to investigate the role of traditional (as defined by *Framingham Heart Studies*) and SLE-related risk factors, including novel inflammatory and immunological biomarkers, in the development of subclinical AS in a cohort of 35 consecutive SLE patients. As a surrogate measure of AS we have considered the carotid lesions assessed by B-mode ultrasound, comprising thickened intima found in half of cases, and plaque described in about one third of cases. Differences in the cut-off values and plaque definition may account for the literature variability (17–65%) [3, 5, 10].

Although they do not fully explain high levels of AS in SLE, both and SLE-specific risk factors have been identified [3–5, 10]. Moreover, their contribution to the development of AS is still under debate [3, 4], various prospective studies assessing the particular intervention of each factor. Nowadays it is widely accepted that several traditional risk factors including dyslipidemia [3, 11, 12], age [3, 12–20], high BP [3, 12, 14, 15, 21], diabetes mellitus [3, 14], cigarette smoking [3, 22], obesity [3, 12], menopausal status [3, 13] and homocysteine [3, 17, 23] are associated with AS in SLE [4]. While the majority of studies based on Framingham risk assessment model have suggested higher 10-year risk of a cardiac event, demonstrating at least one to three traditional risk factors as predictors [3, 4, 10, 15], few data have shown that the risk for coronary heart disease-related events did not significantly differ between patients with SLE and controls [4]. In our study, Framingham was significantly (p<0.05) associated with high BP (r=0.610), age and age at onset (r=0.603), but also correlates with SCORE (r=0.821), SLE-duration (r=0.359) and corticosteroid therapy duration (r=0.451).

On the other hand, non-traditional, disease specific risk factors have also been largely associated with AS in SLE patients, including renal disease [3, 4, 24], SLE activity and duration [3, 4, 23], corticosteroid therapy (doses, duration) [3, 4, 12, 16], even if the relation has been poorly understood to date. It seems that plaque characteristics (size, number) have been mainly related to SLE duration [4, 16, 23] and corticosteroid administration [4, 23]; while disease activity has been, surprisingly, inversely associated with plaque size [4, 11], high damage score (SLICC/ACR) has been considered an independent predictor of carotid plaque [4, 16]. Both high and low corticosteroid doses have been involved in plaque definition [4]. We have also reported several conflicting data about the intervention of classic (age, abnormal lipid levels and atherogenic index), novel biomarkers (hsCRP and homocysteine) and SLE-specific risk factors (disease duration, ACL levels) in plaque development.

cIMT, and particularly thickened intima has been commonly associated with both traditional and non-traditional risk factors, including age [5] and age of SLE diagnosis [3, 10], disease duration [5], C3 [5] and C4 levels [3, 10], homocysteine [5]. Accordingly, we have evaluated the intervention of risk factors in atherogenesis, and we have demonstrated a significant association between increased cIMT and age of patient, age at onset of the disease and hsCRP level; moreover, hsCRP and VLDL have been identified as independent predictors of thickened intima in SLE patients. In addition, our results have suggested that high cIMT has been commonly identified in relation with certain parameters such as age and age at onset, SLE duration, systolic BP, TG and VLDL levels, atherogenic index, low C3 and longer corticosteroid administration. Surprisingly, not only SLEDAI activity and anti-dsDNA antibodies titers, but also homocysteine and hsCRP have been inversely related to thickened intima in our study.

Whereas recent evidence have suggested that homocysteine may act as a predictor for AS in general population, the association of homocysteine level and AS in SLE patients is challenging [25–30]. Several papers have already illustrated the role of this novel biomarker in the pathogenesis of SLE and act as risk factor for premature AS in such patients [25–27], while other recent studies have clearly demonstrated no relation between the homocysteine and carotid plaque seen in ultrasound evaluation [16, 18, 23]. In addition, we have revealed the direct association between homocysteine levels and disease duration, activity and damage scores.

Although a small cohort of women with SLE has been included in this study, several pertinent data with potential impact on current daily practice have

been obtained. Further research, particularly dynamic assessment in a higher number of patients, should be done in order to validate and implement results.

Conclusions

Our data advocate for increased cardiovascular burden in SLE and support the value of cIMT and carotid plaque as surrogate AS biomarkers in women with SLE.

References

[1] Petri MA, Kiani AN, Post W, Christopher-Stine L, Magder LS, *Lupus Atherosclerosis Prevention Study (LAPS)*, Ann Rheum Dis, 2011, 70(5):760–765.

[2] Leonard D, Akhter T, Nordmark G, Rönnblom L, Nessen T, *Increased carotid intima thickness and decreased media thickness in premenopausal women with systemic lupus erythematosus: an investigation by non-invasive high-frequency ultrasound*, Scand J Rheumatol, 2011, 40(4):279–282.

[3] McMahon M, Hahn BH, Skaggs BJ, *Systemic lupus erythematosus and cardiovascular disease: prediction and potential for therapeutic intervention*, Expert Rev Clin Immunol, 2011, 7(2):227–241.

[4] Doria A, Shoenfeld Y, Wu R, Gambari PF, Puato M, Ghirardello A, Gilburd B, Corbanese S, Patnaik M, Zampieri S, Peter JB, Favaretto E, Iaccarino L, Sherer Y, Todesco S, Pauletto P, *Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus*, Ann Rheum Dis, 2003, 62(11):1071–1077.

[5] Rua-Figueroa I, Arencibia-Mireles O, Elvira M, Erausquin C, Ojeda S, Francisco F, Naranjo A, Rodríguez-Gallego C, Garcia-Laorden I, Rodríguez-Perez J, Rodríguez-Lozano C, *Factors involved in the progress of preclinical atherosclerosis associated with systemic lupus erythematosus: a 2-year longitudinal study*, Ann Rheum Dis, 2010, 69(6):1136–1139.

[6] López-Pedrera C, Aguirre MÁ, Barbarroja N, Cuadrado MJ, *Accelerated atherosclerosis in systemic lupus erythematosus: role of proinflammatory cytokines and therapeutic approaches*, J Biomed Biotechnol, 2010, 2010. pii:607084.

[7] Urowitz MB, Bookman AA, Koehler BE, Gordon DA, Smythe HA, Ogryzlo MA, *The bimodal mortality pattern of systemic lupus erythematosus*, Am J Med, 1976, 60(2):221–225.

[8] Dobiásová M, *Atherogenic index of plasma [log(triglycerides/HDL-cholesterol)]: theoretical and practical implication*, Clin Chem, 2004, 50(7):1113–1115.

[9] Borhani NO, Mercuri M, Borhani PA, Buckalew VM, Canossa-Terris M, Carr AA, Kappagoda T, Rocco MV, Schnaper HW, Sowers JR, Bond MG, *Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS). A randomized controlled trial*, JAMA, 1996, 276(10):785-791.

[10] Sazliyana S, Mohd Shahrir MS, Kong NC, Tan HJ, Hamidon BB, Azmi MT, *Thickened carotid intima media thickness and carotid atherosclerosis among lupus nephritis patients: the role of traditional and lupus-specific factors*, Int J Rheum Dis, 2011, 14(3):267–275.

[11] Manzi S, Selzer F, Sutton-Tyrrell K, Fitzgerald SG, Rairie JE, Tracy RP, Kuller LH, *Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus*, Arthritis Rheum, 1999, 42(1):51–60.

[12] McMahon M, Grossman J, Skaggs B, Fitzgerald J, Sahakian L, Ragavendra N, Charles-Schoeman C, Watson K, Wong WK, Volkmann E, Chen W, Gorn A, Karpouzas G, Weisman M, Wallace DJ, Hahn BH, *Dysfunctional pro-inflammatory high-density lipoproteins confer increased risk of atherosclerosis in women with systemic lupus erythematosus*, Arthritis Rheum, 2009, 60(8):2428–2437.

[13] Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, D'Agostino RB, Kuller LH, *Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study*, Am J Epidemiol, 1997, 145(5):408–415.

[14] Gladman DD, Urowitz MB, *Morbidity in systemic lupus erythematosus*, J Rheumatol Suppl, 1987, 14(Suppl 13): 223–226.

[15] Petri M, Perez-Gutthann S, Spence D, Hochberg MC, *Risk factors for coronary artery disease in patients with systemic lupus erythematosus*, Am J Med, 1992, 93(5):513–519.

[16] Roman MJ, Shanker BA, Davis A, Lockshin MD, Sammaritano L, Simantov R, Crow MK, Schwartz JE, Paget SA, Devereux RB, Salmon JE, *Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus*, N Engl J Med, 2003, 349(25):2399–2406.

[17] Roman MJ, Crow MK, Lockshin MD, Devereux RB, Paget SA, Sammaritano L, Levine DM, Davis A, Salmon JE, *Rate and determinants of progression of atherosclerosis in systemic lupus erythematosus*, Arthritis Rheum, 2007, 56(10):3412–3419.

[18] Asanuma Y, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, Linton MF, Raggi P, Stein CM, *Premature coronary-artery atherosclerosis in systemic lupus erythematosus*, N Engl J Med, 2003, 349(25):2407–2415.

[19] Wolak T, Todosoui E, Szendro G, Bolotin A, Jonathan BS, Flusser D, Buskila D, Sukenik S, Abu-Shakra M, *Duplex study of the carotid and femoral arteries of patients with systemic lupus erythematosus: a controlled study*, J Rheumatol, 2004, 31(5):909–914.

[20] Gustafsson J, Gunnarsson I, Börjesson O, Pettersson S, Möller S, Fei GZ, Elvin K, Simard JF, Hansson LO, Lundberg IE, Larsson A, Svenungsson E, *Predictors of the first cardiovascular event in patients with systemic lupus erythematosus – a prospective cohort study*, Arthritis Res Ther, 2009, 11(6):R186.

[21] El-Magadmi M, Bodill H, Ahmad Y, Durrington PN, Mackness M, Walker M, Bernstein RM, Bruce IN, *Systemic lupus erythematosus: an independent risk factor for endothelial dysfunction in women*, Circulation, 2004, 110(4):399–404.

[22] Selzer F, Sutton-Tyrrell K, Fitzgerald SG, Pratt JE, Tracy RP, Kuller LH, Manzi S, *Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus*, Arthritis Rheum, 2004, 50(1):151–159.

[23] Von Feldt JM, Scalzi LV, Cucchiara AJ, Morthala S, Kealey C, Flagg SD, Genin A, Van Dyke AL, Nackos E, Chander A, Gehrie E, Cron RQ, Whitehead AS, *Homocysteine levels and disease duration independently correlate with coronary artery calcification in patients with systemic lupus erythematosus*, Arthritis Rheum, 2006, 54(7):2220–2227.

[24] Schanberg LE, Sandborg C, Barnhart HX, Ardoin SP, Yow E, Evans GW, Mieszkalski KL, Ilowite NT, Eberhard A, Levy DM, Kimura Y, von Scheven E, Silverman E, Bowyer SL, Punaro L, Singer NG, Sherry DD, McCurdy D, Klein-Gitelman M, Wallace C, Silver R, Wagner-Weiner L, Higgins GC, Brunner HI, Jung L, Soep JB, Reed A; Atherosclerosis Prevention in Pediatric Lupus Erythematosus Investigators, *Premature atherosclerosis in pediatric systemic lupus erythematosus: risk factors for increased carotid intima-media thickness in the atherosclerosis prevention in pediatric lupus erythematosus cohort*, Arthritis Rheum, 2009, 60(5):1496–1507.

[25] Petri M, *Detection of coronary artery disease and the role of traditional risk factors in the Hopkins Lupus Cohort*, Lupus, 2000, 9(3):170–175.

[26] Svenungsson E, Jensen-Urstad K, Heimbürger M, Silveira A, Hamsten A, de Faire U, Witztum JL, Frostegård J, *Risk factors for cardiovascular disease in systemic lupus erythematosus*, Circulation, 2001, 104(16):1887–1893.

[27] Refai TM, Al-Salem IH, Nkansa-Dwamena D, Al-Salem MH, *Hyperhomocysteinaemia and risk of thrombosis in systemic lupus erythematosus patients*, Clin Rheumatol, 2002, 21(6): 457–461.

[28] Manger K, Kusus M, Forster C, Ropers D, Daniel WG, Kalden JR, Achenbach S, Manger B, *Factors associated with coronary artery calcification in young female patients with SLE*, Ann Rheum Dis, 2003, 62(9):846–850.

[29] Malinow MR, Nieto FJ, Szklo M, Chambless LE, Bond G, *Carotid artery intimal-medial wall thickening and plasma homocyst(e)ine in asymptomatic adults. The Atherosclerosis Risk in Communities Study*, Circulation, 1993, 87(4):1107–1113.

[30] McCully KS, *Homocysteine and vascular disease*, Nat Med, 1996, 2(4):386–389.

Corresponding author
Codrina Ancuța, Lecturer, MD, PhD, Department of Rheumatology, "Grigore T. Popa" University of Medicine and Pharmacy, Iassy, Romania; Phone +40740–036 387, Fax +40232–244 288, e-mail: alexia02ro@yahoo.com

Received: January 20th, 2012

Accepted: February 29th, 2012